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Article

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Design, Synthesis and Evaluation of a Novel Series of Oxadiazine Gamma Secretase Modulators for Familial Alzheimer's Disease

Matthew G. Bursavich,[†,*] Bryce A. Harrison, Raksha Acharya, Donald E. Costa, Emily A. Freeman, Hilliary E. Hodgdon, Lori A. Hrdlicka, Hong Jin, Sudarshan Kapadnis, Jeffrey S. Moffit, Deirdre A. Murphy, Scott Nolan, Holger Patzke, Cuyue Tang, Melody Wen, Gerhard Koenig, Jean-François Blain, Duane A. Burnett

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ABSTRACT: Herein we describe the design, synthesis and evaluation of a novel series of oxadiazine-based gamma secretase modulators obtained via isosteric amide replacement and critical consideration of conformational restriction. Oxadiazine lead **47** possesses good in vitro potency with excellent predicted CNS drug-like properties and desirable ADME/PK profile. This lead compound demonstrated robust $A\beta_{42}$ reductions and subsequent $A\beta_{37}$ increases in both rodent brain and CSF at 30 mg/kg dosed orally.

Introduction.

In the 100+ years since the German physician Alois Alzheimer first described Alzheimer's disease (AD), a vast amount of pharmaceutical research has been undertaken to address this devastating neurodegenerative disorder that leads to loss of cognition, loss of motor function and ultimately death. Currently, AD affects approximately 5.3 million people in the United States with estimated costs ex-

pected to grow to $1.1 trillion by 2050.[1] AD is the 6th leading cause of death in America and a significant burden to patients, caregivers and society as a whole. While current therapies including NMDA receptor antagonists and acetylcholinesterase inhibitors demonstrate temporary symptomatic treatment, they do not have an effect on disease progression. There is an urgent need for new therapies that will affect the course of the disease to prevent, or at least delay, the onset of cognitive decline and ultimate death due to this disease.

The amyloid hypothesis, formulated more than 20 years ago, ascribes a central role for beta-amyloid (Aβ) AD.[2,3] Several mutations in the amyloid precursor protein (APP) have been reported to be associated with familial AD (FAD)[4] while a specific mutation appears to protect against the disease[5], further supporting the central role of Aβ in the disease pathology. The Aβ peptides are produced by the sequential proteolysis of APP by beta amyloid cleavage enzyme 1 (BACE1) and gamma secretase (GS), resulting in peptides of various lengths of which the longer 42 amino acid $A\beta_{42}$ is believed to be the most toxic. Gamma secretase is an enzyme complex consisting of four different proteins, one of which is presenilin (PS). Presenilin has been described as the catalytic subunit of GS[6,7] and interestingly, mutations in the two presenilin genes have been associated with FAD.[8,9] The consequence of many FAD-causing PS mutations is a decreased catalytic activity of GS[10–13] with partial loss-of-function contributing to the increased $A\beta_{42}$:$A\beta_{40}$ ratio observed in FAD.[14,15]

Compounds that could modify GS activity to produce less $A\beta_{42}$ without affecting total Aβ levels were first described in 2001 by Weggen et al.[16] These compounds, termed gamma secretase modulators (GSMs), offered a new, potentially safer alternative to gamma secretase inhibitors (GSIs) to reduce toxic $A\beta_{42}$. Moreover, they have the opposite effect on GS kinetics than PS mutations,[13] suggesting they might have a profound impact on disease development in PS mutation carriers. Much research has been devoted to GSMs over the past 15 years to afford many examples of very potent compounds targeting

this unique intramembrane cleaving protease.[17–20] Unfortunately these very potent compounds typically possess poor CNS drug-like properties as measured by fraction sp^3 character (Fsp^3 values),[21] molecular weight (MW), lipophilicity (cLogP) and CNS multi-parameter optimization (MPO) scores.[22]

In our effort to discover novel, potent and efficacious GSMs that possess good CNS drug-like properties for proof-of-mechanism studies in human clinical trials, we focused our initial design efforts on E2012 (**1**)[23], the early GSM from the Eisai group (EC_{50} = 83 nM) that demonstrated dose-dependent plasma reductions of $A\beta_{40}$ and $A\beta_{42}$ in Phase 1 studies.[24] Based on a survey of the GSM literature, we hypothesized the importance of the central amide hydrogen bond acceptor, but also wanted to remove the cinnamide group, a potential Michael acceptor and undesirable structural feature.[25] These initial hypotheses led to our amide designs as shown in Figure 1. The key hydrogen bond acceptor is attached directly to the methoxyphenyl ring and the aminoether linker places the pendent phenyl in a similar location as the *p*-fluoro phenyl of **1**. Similar hypotheses and designs have been communicated independently from the Pfizer,[26] Janssen,[27] Amgen[28] and Dainippon Sumitomo[29] groups. From our initial amides **I**, we further investigated 1) heteroaryl replacements for the imidazole, 2) non-aromatic replacements for the methoxyphenyl ring and 3) cyclic amines to induce a conformational restriction into the amino ether linkage. Focused libraries afforded compound **II** which demonstrated good *in vitro* potency (EC_{50} = 35 nM) with greatly reduced aromaticity (increased Fsp^3 value to 0.50). Unfortunately, this compound also possesses high molecular weight (497), high cLogP (4.6) and a low calculated CNS MPO score (3.2).[30] Due to the non-optimal predicted CNS drug-like properties, as well as potential for amide hydrolysis, we designed a series of novel oxadiazines as described in Figure 2. The oxadiazine moiety mimics the required hydrogen bond acceptor of the amide[31,32] while also imparting a key conformational constraint into the pendant alkyl chain to potentially lock the compound into its putative bioactive conformation.

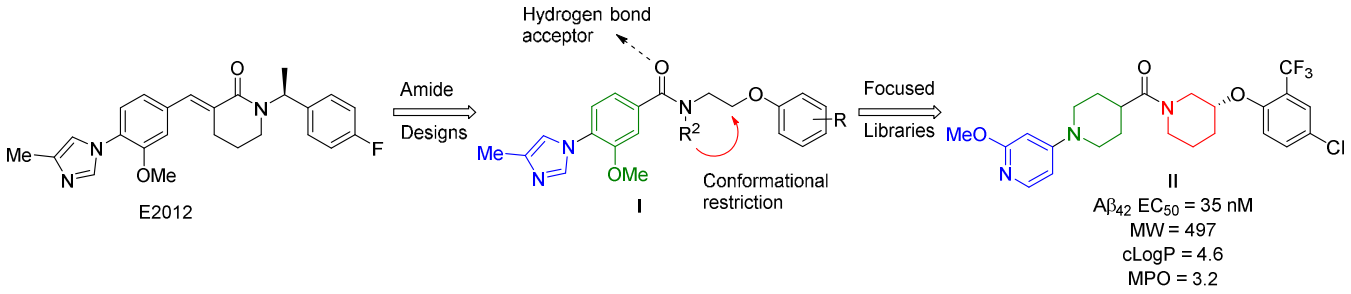


Figure 1. Initial amide design strategy

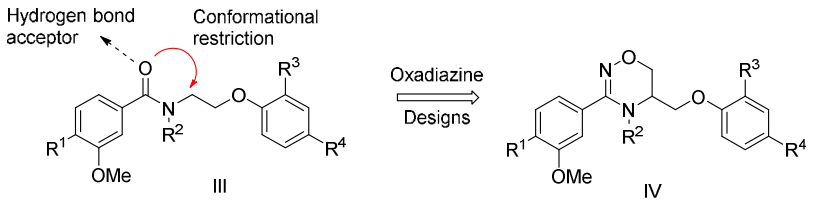


Figure 2. Initial oxadiazine design strategy

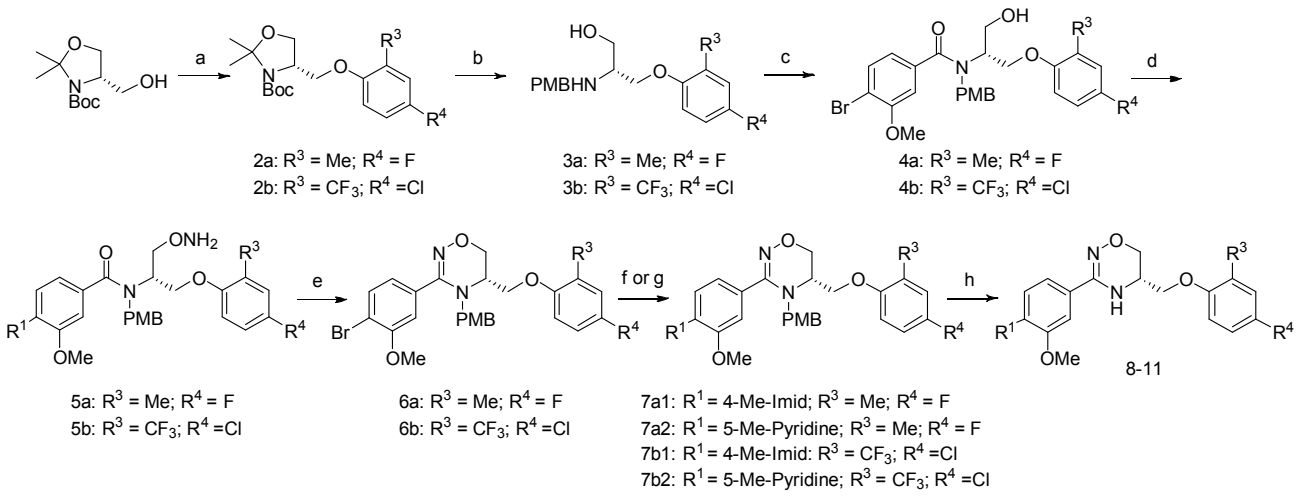
Results and discussion.

The synthesis of the initial oxadiazines **IV** began from commercially available *tert*-butyl (S)-4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate as described in Scheme 1.[33] We initially prepared both oxadiazine enantiomers starting from both R and S alcohols **1** (synthesis not shown with the R-alcohol). The commercially available primary alcohol derived from Garner's aldehyde was reacted with either 4-fluoro-2-methylphenol or 4-chloro-2-(trifluoromethyl)phenol in a Mitsunobu reaction to afford aryl ether **2** in good yields (70 and 77% respectively). The amino alcohol protecting groups were removed with trifluoroacetic acid in dichloromethane and the amine reprotected with the *p*-methoxyl benzyl group to afford **3** in good yields over two steps. Amine coupling with the *in situ* generated acid chlorides of 4-bromo-3-methoxybenzoic acid provided amides **4** in 59 and 95% yield respectively. Conversion of the primary hydroxyl to the alkoxylamines **5** was achieved via Mitsunobu reaction with *N*-hydroxyphthalimide and subsequent deprotection with hydrazine in high yields over two steps. The key

cyclization step in the synthesis to successfully form the oxadiazine was realized in moderate yields (45 and 55% respectively) with dehydrative P_2O_5 conditions in *i*-PrOH to afford oxadiazine **6**. Suzuki or Buchwald conditions successfully installed the R^1 heteroaryl groups to afford **7** and the *p*-methoxybenzyl protecting groups were removed with acidic conditions in a microwave reactor to afford the desired oxadiazines **8-11**.

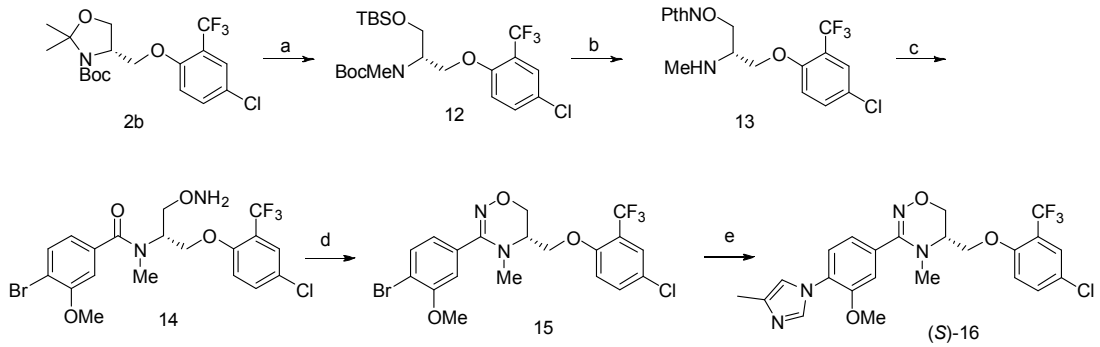
To investigate the importance of the oxadiazine N-H we embarked on the related synthesis in Scheme 2. Here ring opening of aryl ether **2** under *p*-toluenesulfonic acid conditions provided the Boc-protected amino alcohol which was protected with TBDMS-Cl and alkylated with methyl iodide to provide **12** in good yields over 3 steps. Compound **13** was realized in high yields via deprotection of the TBDMS group, Mitsunobu reaction with *N*-hydroxyphthalimide and subsequent N-Boc deprotection. Amine coupling with the *in situ* generated acid chloride of 4-bromo-3-methoxybenzoic acid followed by hydroxyphthalimide deprotection with hydrazine provided **14** in high yields over two steps. Dehydrative cyclization to successfully form the oxadiazine heterocycle **15** was accomplished in low yield (29%) with P_2O_5 in *i*-PrOH. Buchwald reaction conditions successfully installed the 4-methylimidazole to afford N-Methyl oxadiazine **(*S*)-16**.

Scheme 1. Synthesis of (S)-aryl ether oxadiazine GSMs



(a) 4-fluoro-2-methylphenol or 4-chloro-2-(trifluoromethyl)phenol, DIAD, PPh_3, THF, 70% and 77%; (b) a. TFA, DCM; b. TEA, $MgSO_4$, *p*-anisaldehyde, then $NaBH_4$, 71 and 68% over two steps (c) 4-bromo-3-methoxybenzoic acid, DMF/oxalyl chloride, DCM, 59% and 95%; (d) a. *N*-hydroxyphthalimide, DIAD, PPh_3, THF; b. hydrazine hydrate, EtOH, 85% and 91% over two steps; (e) P_2O_5, *i*-PrOH, 45% and 55%; (f) 4-methylimidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane, 67% and 57%; (g) (2-methylpyridin-4-yl)boronic acid, Cs_2CO_3, $PdCl_2(dppf)$, dioxane/H_2O, 68% and 60%; (h) TFA, DCE, 59-84%.

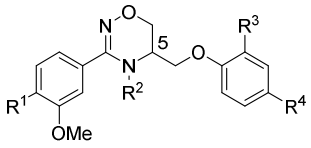
Scheme 2. Synthesis of N-methyl (*S*)-aryl ether oxadiazine analogs

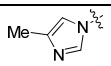
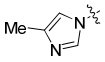
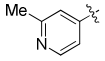
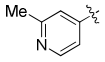
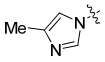
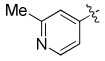
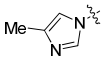


(a) a. p-TsOH-H_2O, MeOH; b. TBS-Cl, imidazole, DCM; c. MeI, KHMDS, THF/DMF, 63% over three steps; (b) a. HCl, MeOH/THF; b. *N*-hydroxyphthalimide, DIAD, PPh_3, THF; c. 4N HCl in dioxane, DCM, 72% over three steps; (c) a. 4-

bromo-3-methoxybenzoic acid DCM/DMF/oxalyl chloride, b. hydrazine hydrate, EtOH, 40% over two steps; (d) P_2O_5, *i*-PrOH, 29%; (e) 4-methylimidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane, 53%.

Table 1. In vitro activity of aryl ether oxadiazine GSMs



Cmpd	R^1	R^2	R^3	R^4	EC_{50} (nM)[a]
(*R*)-8		H	Me	F	2,888
(*S*)-8		H	Me	F	230
(*R*)-9		H	Me	F	6,446
(*S*)-9		H	Me	F	109
(*S*)-10		H	CF_3	Cl	109
(*S*)-11		H	CF_3	Cl	249
(*S*)-16		Me	CF_3	Cl	113

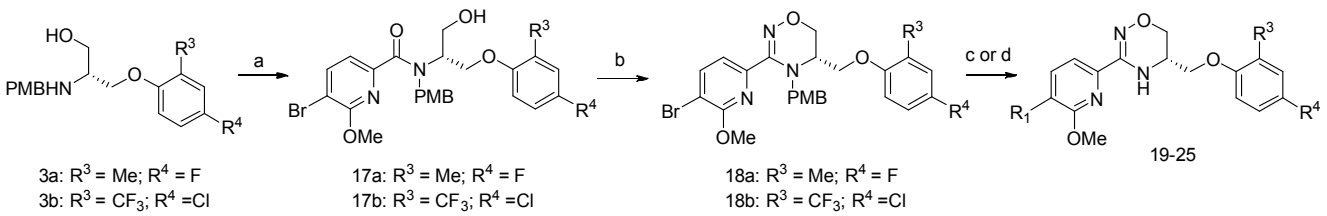
[a] $A\beta_{42}$ EC_{50} values were determined in H4 cells over expressing WT human APP751. $A\beta_{42}$ EC_{50} values shown here are the average of n > 2 assays run in duplicate.

Next we determined the $A\beta_{42}$ lowering potency (EC_{50}) in H4 cells over expressing WT human APP751. The initial compound **(*R*)-8** demonstrated only low micromolar potency, but its (S)-enantiomer **(*S*)-8** showed a 12-fold improvement ($A\beta_{42}$ EC_{50} = 230 nM) demonstrating a high eudysmic ratio. Re-

placement of the 4-methyl-imidazol-1-yl with 2-methylpyridin-4-yl demonstrated a similar preference for the S-enantiomer comparing **(*R*)-9** with **(*S*)-9** ($A\beta_{42}$ EC_{50} 6,446 vs. 109 nM). Incorporation of the more lipophilic 2-CF_3, 4-Cl phenyl in compound **(*S*)-10** improved the potency 2-fold relative to compound **(*S*)-8**. Replacing the 4-methyl-imidazol-1-yl with 2-methylpyridin-4-yl to afford compound **(*S*)-11** demonstrated a 2-fold reduction in potency relative to **(*S*)-10**. Addition of an N-Me to the more lipophilic **(*S*)-10** afforded an equipotent analog in **(*S*)-16** ($A\beta_{42}$ EC_{50} = 109 nM and 113 nM, respectively) albeit at an even higher cLogP (4.3 vs. 4.6). Unfortunately, none of these initial compounds demonstrated reduction of brain $A\beta_{42}$ in mice when dosed orally at 30 mg/kg.

In a strategic effort to lower the cLogP, restrict the rotation about the left hand side of the molecule via an intramolecular hydrogen bond and potentially improve the potency, we initiated the chemistry to replace the methoxyphenyl with a 2-methoxypyridine group first disclosed by the Eisai group (Scheme 3).[34] Here we only focused on the more potent (*S)*-oxadiazines. PMB-protected amino alcohols **3** were coupled with the *in situ* generated acid chloride of the commercially available 5-bromo-6-methoxypicolinic acid to provide amides **17** in moderate yields (78 and 59% respectively). Conversion of the primary hydroxyl to oxadiazine **18** was accomplished via Mitsunobu reaction with *N*-hydroxyphthalimide, deprotection with hydrazine and dehydration with P_2O_5 in *i*-PrOH over 3 steps with low yields again in the key cyclization step (17 and 21% respectively). Suzuki or Buchwald conditions successfully installed the R^1 heteroaryl groups and removal of the *p*-methoxybenzyl protecting group with TFA provided the desired oxadiazines **19-25** in moderate yields.

Scheme 3. Synthesis of (*S*)-2-methoxypyridine aryl ether oxadiazine GSMs



3a: R^3 = Me; R^4 = F
3b: R^3 = CF_3; R^4 =Cl

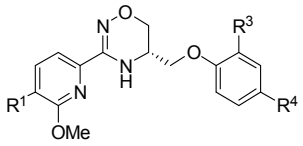
17a: R^3 = Me; R^4 = F
17b: R^3 = CF_3; R^4 =Cl

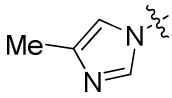
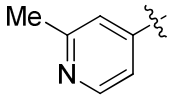
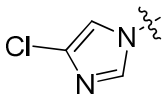
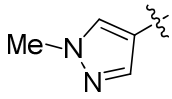
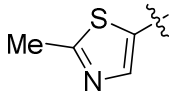
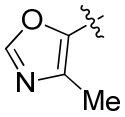
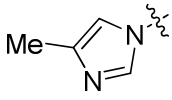
18a: R^3 = Me; R^4 = F
18b: R^3 = CF_3; R^4 =Cl

(a) 5-bromo-6-methoxypicolinic acid, DCM/DMF/oxalyl chloride, 78 and 59%; (b) a. *N*-hydroxyphthalimide, DIAD, PPh_3, THF; b. hydrazine hydrate, EtOH; c. P_2O_5, *i*-PrOH, 12 and 15% over 3 steps; (c) a. 4-methylimidazole or 4-chloroimidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane; b. TFA/DCE, 77-47% over two steps; (d) a. heteroarylboronic acid, Cs_2CO_3, $PdCl_2(dppf)$, dioxane/H_2O; b. TFA/DCE, 86-31% over two steps.

Rewardingly, the initial methoxypyridine compound **19** demonstrated in a 5-fold potency improvement ($A\beta_{42}$ EC_{50} = 51 nM) at a lower cLogP (3.2) relative to **(*S*)-8**. The SAR of the left hand side heterocycle was further explored with compounds **20-24**. Both compound **20** and **21** provided moderately potent analogs ($A\beta_{42}$ EC_{50} = 98 and 72 nM, respectively) but at the expense of significantly higher cLogP (3.9). All three of these potent analogs were further profiled for stability in rat hepatocytes and demonstrated very high turnover rates which appeared to correlate with increasing cLogP. Replacement of the methyl imidazole with other 5-member heterocycles provided compounds **22-24** which all demonstrated reduced cellular potency. Turning our attention back to the aryl ether, combining the more lipophilic 2-CF_3, 4-Cl phenyl with the more potent 4-methylimidazole provided compound **25** which demonstrated an approximate 10-fold potency improvement relative to compound **(*S*)-8** ($A\beta_{42}$ EC_{50} = 27 and 230 nM, respectively). This potency improvement comes with the expense of a higher cLogP (4.1) and demonstrated the expected high clearance in rat hepatocytes. Not surprisingly, orally dosing this relatively rat unstable compound (rat $CL_{int,\,u}$ = 3,830 ml min^{-1} kg^{-1}) at 30 mg/kg afforded only minimal exposure and demonstrated no brain $A\beta_{42}$ reduction in vivo.

Table 2. In vitro activity of aryl ether pyrimidine oxadiazine GSMs



Cmpd	R^1	R^3	R^4	cLogP	EC_{50} (nM)[a]	rat $CL_{int,\ u}$ ($mL\ min^{-1}\ kg^{-1}$)
19		Me	F	3.2	51	1906
20		Me	F	3.9	98	3259
21		Me	F	3.9	72	4105
22		Me	F	3.4	604	-
23		Me	F	3.8	1,271	-
24		Me	F	3.0	1,364	-
25		CF_3	Cl	4.1	27	3830

[a] $A\beta_{42}$ EC_{50} values were determined in H4 cells over expressing WT human APP751. $A\beta_{42}$ EC_{50} values shown here are the average of n > 2 assays run in duplicate.

In continuing to explore the alkyl-substituted aryl ether oxadiazines we engineered another conformational constraint to further restrict the rotation of the pendant aryl group as shown below in Figure 3. To mimic the potentially bioactive 3-dimentional presentation of the aryl motif in **V** we designed a series of piperidine aryl ethers **VI**. In this design there are only 5 rotatable bonds in the scaffold compared to the 7 rotatable bonds found in the initial amide designs. To mimic another possible bioactive 3-dimentional presentation of the aryl motif in **VII** we also designed a series of N-aryl substituted piperazines **VIII**. With the piperazine scaffold there are now only 4 rotatable bonds compared to the initial amides.

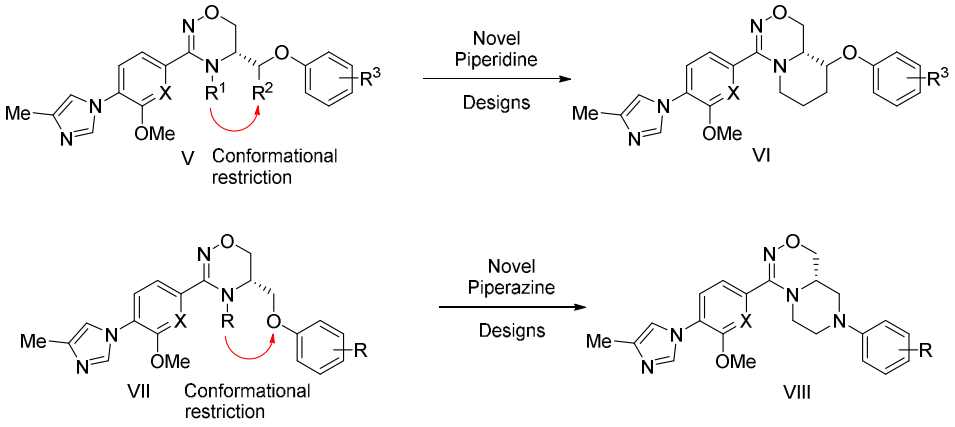
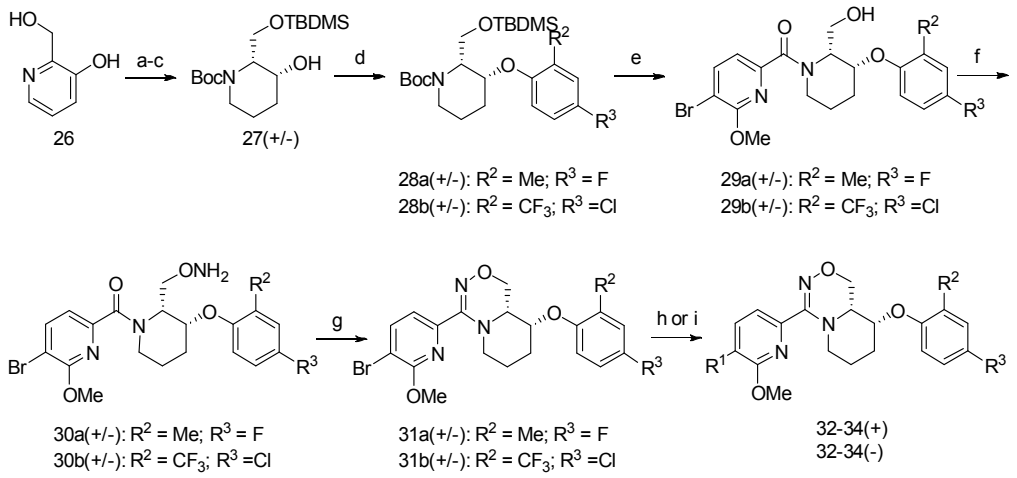


Figure 3. Design strategies incorporated into fused piperidine and piperazine scaffolds.

The racemic synthesis of piperidine ether oxadiazine GSMs began from commercially available 2-(hydroxymethyl)pyridin-3-ol is described in Scheme 4. The primary alcohol of pyrimidine **26** was protected with TBDMS-Cl, reduced to the piperidine with 60 psi of H_2 gas over PtO_2, then protected with Boc_2O to afford piperidinol **27** as a mixture of cis enantiomers. Piperidinol **27** was reacted with either 4-fluoro-2-methylphenol or 4-chloro-2-(trifluoromethyl)phenol in a Mitsunobu reaction to afford aryl

ether **28**. The silyl protecting group was removed with TBAF, the amine protecting group removed with TFA in DCM and the resulting amine coupled with the *in situ* generated acid chloride of 5-bromo-6-methoxypicolinic acid to provide amides **29**. Conversion of the primary hydroxyl to the alkoxyamine **30** was achieved via Mitsunobu reaction with *N*-hydroxyphthalimide and subsequent deprotection with hydrazine. Successful oxadiazine formation was realized with dehydrative P_2O_5 conditions in *i*-PrOH and further purification via preparative chiral HPLC afforded **31a(+), 31a(-), 31b(+) and 31b(-)**. Suzuki or Buchwald coupling conditions with each enantiomer successfully installed the R^1 heteroaryl groups to afford the desired oxadiazines **32-34(+)** and **32-34(-)**.

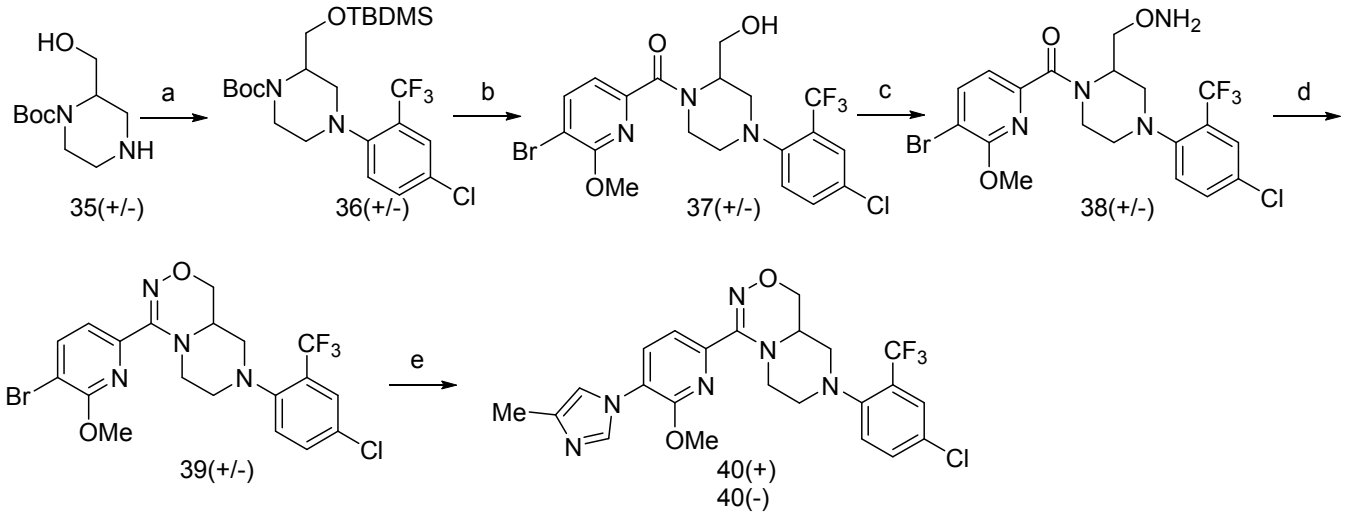
Scheme 4. Synthesis of piperidine oxadiazine GSMs



(a) TBDMS-Cl, imidazole, DMF, 48%; (b) H_2, PtO_2, EtOH, 87%; (c) Boc_2O, TEA, DCM, 63%; (d) 4-fluoro-2-methylphenol or 4-chloro-2-(trifluoromethyl)phenol, DIAD, PPh_3, DCM, 78 or 85% (e) a. TBAF, THF; b. TFA, DCM; c. 5-bromo-6-methoxypicolinic acid, DMF/oxalyl chloride, DCM then TEA, THF, 32 and 57% over three steps; (f) a. *N*-hydroxyphthalimide, DIAD, PPh_3, toluene; b. hydrazine hydrate, EtOH, 69 and 87% over two steps (g) $POCl_3$, *i*-PrOH, 35 and 56% (h) 4-methyl imidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane, 74-65% (i) (2-methylpyridin-4-yl)boronic acid, Cs_2CO_3, $PdCl_2(dppf)$, dioxane/H_2O, 61-56%.

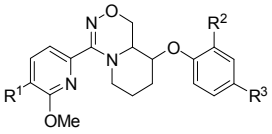
The racemic synthesis of N-aryl piperazine oxadiazine GSMs began from commercially available *tert*-butyl 2-(hydroxymethyl)piperazine-1-carboxylate as described in Scheme 5. The primary alcohol of piperazine **35** was protected with TBDMS-Cl then coupled with 2-bromo-5-chlorobenzotrifluoride using $Pd_2(dba)_3$ and DavePhos to afford N-aryl piperazine **36**. Both the amine and primary alcohol protecting groups were removed with HCl, and the resulting liberated amine was coupled with 5-bromo-6-methoxypicolinic acid under HATU conditions to provided amide **37**. Conversion of the primary hydroxyl to the alkoxyamine **38** was achieved via Mitsunobu reaction with *N*-hydroxyphthalimide and subsequent hydrazine deprotection. Successful oxadiazine formation was realized with $POCl_3$ in EtOH with catalytic addition of DMAP to afford **39**. Buchwald coupling successfully installed the 4-methyl imidazole to afford the desired oxadiazines which were purified via preparative chiral HPLC to provide both **40(+)** and **40(-)**.

Scheme 5. Synthesis of piperazine oxadiazine GSMs

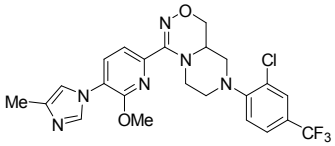


(a) a. TBDMS-Cl, imidazole, DCM; b. NaO*t*Bu, $Pd_2(dba)_3$, DavePhos, 2-bromo-5-chlorobenzotrifluoride, toluene, 70% over two steps; (b) a. HCl, MeOH/dioxane; b. 5-bromo-6-methoxypicolinic acid, DIEA, HATU, DMF; c. TBAF, DCM, 80% over three steps; (c) a. *N*-hydroxyphthalimide, DIAD, PPh_3, toluene; b. Hydrazine hydrate, EtOH; (d) $POCl_3$, DIEA, DMAP, EtOH; (f) 4-methyl imidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane

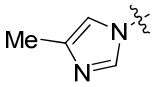
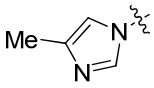
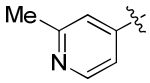
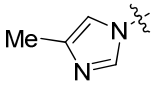
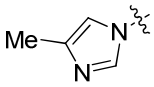
Table 4. In vitro activity of piperidine and piperazine oxadiazine GSMs

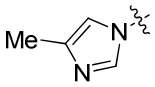


32-34



40

Cmpd	R^1	R^2	R^3	cLogP	EC_{50} (nM)[a]
32(+)		Me	F	4.0	197
32(-)		Me	F	4.0	>3,000
33(+)		Me	F	4.6	240
34(+)		CF_3	Cl	4.8	15
40(+)		CF_3	Cl	4.4	64

40(-)		CF_3	Cl	4.4	307

[a] $A\beta_{42}$ EC_{50} values were determined in H4 cells over expressing WT human APP751. $A\beta_{42}$ EC_{50} values shown here are the average of n > 2 assays run in duplicate.

Rewardingly the initial piperidine aryl ether afforded a modestly potent analog **32(+)** ($A\beta_{42}$ EC_{50} = 197 nM). Here again a high eudysmic ratio was observed as the enantiomeric **32(-)** demonstrated an $A\beta_{42}$ EC_{50} > 3,000 nM. Replacement of the methyl imidazole with methylpyridine provided compound **33(+)**. Once again the methylpyridine demonstrated less potency ($A\beta_{42}$ EC_{50} = 240 nM) with a significantly higher and less desirable cLogP (4.6). Incorporation of the more lipophilic 2-CF_3, 4-Cl phenyl in compound **34(+)** significantly improved the potency ($A\beta_{42}$ EC_{50} = 15 nM) relative to compound **32(+)** albeit at an even higher cLogP (4.8). Given this drastic improvement in potency we further profiled compound **34(+)** in both rat and human hepatocytes. While the stability in rat hepatocytes was considerably low (rat $CL_{int,u}$= 4251 mL min^{-1} kg^{-1}) the predicted human $CL_{int,u}$ was much better (human hep $CL_{int,u}$ = 167 mL min^{-1} kg^{-1}). We decided to determine the reduction of brain $A\beta_{42}$ in mice with this highly potent compound with promising human $CL_{int,u}$. Here, dosing compound **34(+)** at 90 mg/kg in mice provides a 32% $A\beta_{42}$ reduction in the brain at 6 hours post-dose with a total concentration of 36 μM of the compound observed in the brain and a B:P of 0.6. Unfortunately, the desired potency and modest efficacy comes at the expense of increasing the cLogP (4.8). The related N-aryl piperazine afforded modestly potent **40(+)** ($A\beta_{42}$ EC_{50} = 64 nM) which demonstrated a eudysmic ratio of 5 (**40(-)**: $A\beta_{42}$ EC_{50} = 307 nM), but further work on this high cLogP analog (4.4) was deprioritized due to the exciting results from our next set of designs.

To further explore the alkyl-substituted aryl ether pyrimidine oxadiazine GSMs, we engineered a different conformational constraint from the alkyl group to the aryl group restricting the rotation of the pendant aryl group as shown below in Figure 4. In this fashion the alkyl ether **V** was converted to heteroaryls **IX**. Here there are only 4 rotatable bonds in the newly designed scaffold compared to the 7 rotatable bonds found in the initial amide designs.

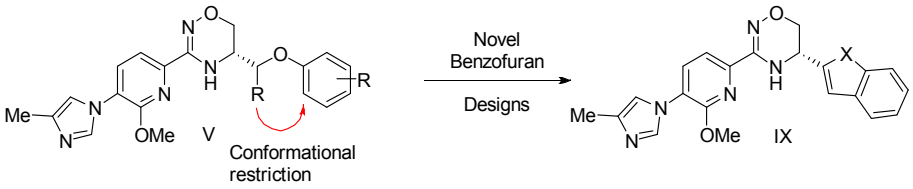
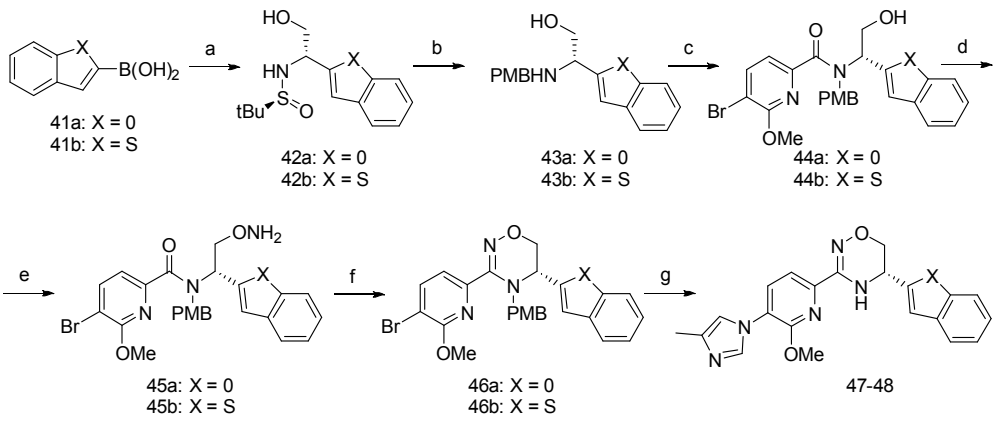


Figure 4. Design strategies incorporated into heteroaryl oxadiazine scaffold.

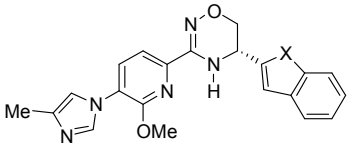
The heteroaryl oxadiazines were obtained via the stereoselective synthesis as described below in Scheme 6. The boronic acid **41** was converted into amino alcohol **42** via an asymmetric Petasis Borono–Mannich multicomponent reaction[35] and reduction of the resulting amino acid. Protecting group swap from the sulfinamide to the PMB-protected amine afforded **43**. The secondary amine was coupled with 5-bromo-6-methoxypicolinic acid to provided amide **44**. Mitsunobu reaction with *N*-hydroxyphthalimide and subsequent deprotection with hydrazine afforded the alkoxyamine **45**. Treatment with TEA in DCE effected acyl migration to the alkoxyamine which was then cyclized with $POCl_3$ in EtOH and catalytic addition of DMAP to provided oxadiazine **46**. Subsequent 4-methyl imidazole incorporation via Buchwald coupling afforded the key oxadiazines **47-48**.

Scheme 6. Asymmetric synthesis of heterocyclic oxadiazine GSMs



(a) a. glyoxylic acid monohydrate, (*S*)-2-methylpropane-2-sulfinamide, $InBr_3$, DCM; b. $LiAlH_4$, THF, 21 and 16% over two steps; (b) a. 4N HCl, dioxane; b. TEA, $MgSO_4$, p-anisaldehyde, then $NaBH_4$, MeOH,68 and 84% over two steps (c) NaOMe, 5-bromo-6-methoxypicolinic acid, MeOH, 78 and 82%; (e) a. *N*-hydroxyphthalimide, DIAD, PPh_3, toluene; b. Hydrazine hydrate, EtOH, 68 and 51% over two steps (f) a. TFA, DCE; b. $POCl_3$, DIEA, DMAP, EtOH, 37 and 32% over two steps; (g) a. 4-methyl imidazole, K_3PO_4, $Pd_2(dba)_3$, Me_4-di-t-BuXPhos, toluene/dioxane; b. TFA, DCE, 51 and 43% over two steps.

Table 5. In vitro activity of heterocyclic oxadiazines



Cmpd	X	EC_{50} (nM)[a]	cLogP/ MPO	LLE/ LELP	rat $CL_{int, u}$ (mL min^{-1} kg^{-1})	human $CL_{int, u}$ (mL min^{-1} kg^{-1})	[Brain] Total (uM)	[Brain] Free (nM)	Brain $A\beta_{42}$ low-ering[b]

47	O	35	2.8/5.0	4.7/7.6	84	44	29.8	427	43
48	S	8	3.7/4.1	4.4/9.4	430	322	30.2	76	34

[a] $A\beta_{42}$ EC_{50} values were determined in H4 cells over expressing WT human APP751. $A\beta_{42}$ EC_{50} values shown here are the average of n > 2 assays run in duplicate. [b] Brain $A\beta_{42}$ lowering was measured 6 hours post-dose.

Rewardingly the initial benzofuran afforded potent analog **47** ($A\beta_{42}$ EC_{50} = 35 nM) now with great predicted CNS drug-like properties based on a low cLogP (2.8) and high CNS-MPO score (5.0). The potency of this compound is achieved with very high efficiency as measured by both LLE (4.7) and LELP (7.6) scores.[19] Further profiling demonstrated greatly improved stability in rat hepatocytes ($CL_{int,u}$ = 84 mL min^{-1} kg^{-1}) and predicted human stability (human hep $CL_{int,u}$ = 44 mL min^{-1} kg^{-1}). We decided to immediately determine the reduction of brain $A\beta_{42}$ in mice with this potent, promising compound. Dosing compound **47** orally at 30 mg/kg in mice provides a 43% reduction of brain $A\beta_{42}$ at 6 hours with 30 μM (427 nM free) compound observed in the brain and a B:P of 1.5. Here, the free drug concentration in the brain exceeded the EC_{90} in the cellular assays, which predicates good in vivo activity in the CNS.[36] For the first time we had combined good potency and great predicted CNS drug-like properties with *in vivo* efficacy. Replacement of the benzofuran with the benzothiophene provided compound **48**, a more active analog ($A\beta_{42}$ EC_{50} = 8 nM) albeit with a higher cLogP (3.7) and lower CNS-MPO score (4.1). This analog is also highly efficient as measured by both LLE (4.4) and LELP (9.4) scores. Here the increase in lipophilicity leads to a reduction in both the rat and human hepatocyte stability (rat $CL_{int,u}$ = 430 mL min^{-1} kg^{-1} and human hep $CL_{int,u}$ = 322 mL min^{-1} kg^{-1}). We proceeded to determine the reduction of mouse brain $A\beta_{42}$ with this potent, promising compound. Dosing compound **48** at 30 mg/kg in our mouse model provided a 34% reduction of brain $A\beta_{42}$ at 6 hours with 30 μM total compound (76 nM free) observed in the brain and a B:P of 2.8.

Further profiling compound **47** demonstrated good aqueous solubility (84 μM) in a pH 7.4 buffer.[37] Permeability and Pg-P efflux potential were assessed via Caco-2 assay with compound **47** demonstrating good permeability ($P_{A\rightarrow B}$ = 10 x 10^{-6} cm/s) and minimal Pg-P efflux potential (Efflux ratio = 1.1). Compound **47** also demonstrated minimal cytotoxicity (TC_{50} > 72 μM) in HepG2 cells measuring ATP to assess viability as well as minimal hERG liability (IC_{50} = 15 μM) in a functional patch clamp assay. The cytochrome P450 profiling of compound **47** demonstrated minimal inhibition against CYP 3A4, 2C19 and 2C8 (IC_{50}s of 25, 17 and >25 μM respectively) and moderate inhibition of CYP 2C9, 2D6 and 1A2 (IC_{50}s of 8, 2 and 3 μM respectively). Profiling for CYP3A4 time dependent inhibition was shown to be negative as inhibition concentrations from 5 to 25 μM were consistent with vehicle. No genotoxicity with or without S9 metabolic activation was observed for compound **47** in a GreenScreen assessment.[38] Compound **47** was also shown to possess an excellent pharmacokinetic profile in both rat and monkey (Table 6).

Table 6. PK parameters of 47 in rat and monkey

Species[a]	AUC_{last}[b] (μM-h)	C_{max}[b] (μM)	%F[c]	$T_{1/2}$ (h)[d]	V_{ss} (L/kg)[d]	CL (mL min^{-1} kg^{-1})[d]
Wistar Rat	67.8	7.3	93	2.2	1.0	5.8
Cynomolgus monkey	8.1	11	136±34	1.5	0.9	5.6

[a]10 mg/kg for po; 1 mg/kg for iv. [b]AUC (area under the curve) and C_{max} (maximal drug concentration) obtained with p.o. administration. [c]%F: bioavailability. [d]$T_{1/2}$ (half-life), V_{ss} (volume of distribution), CL (in vivo clearance) obtained with i.v. administration.

Compound **47** demonstrates robust *in vivo* reduction of $A\beta_{42}$ and subsequent increase of $A\beta_{37}$ in rodents (Table 7).[36] Dosing **47** at 30 mg/kg in mice provides a 43% reduction of $A\beta_{42}$ and increases $A\beta_{37}$ 3.2-fold in mouse brain at 6 h. In order to assess these effects in both brain and CSF we dosed **47** at 30

mg/kg in rats. Here a 30% $A\beta_{42}$ reduction and 2.5-fold increase in $A\beta_{37}$ was observed in the rat brain at 6 hr. A greater effect size was noted in CSF, where compound **47** demonstrated a 58% reduction in $A\beta_{42}$ and a 20-fold increase in $A\beta_{37}$ also at 6 hr. To further characterize this compound a time course efficacy study (Figure 7) was conducted in mice dosed at 30 mg/kg. This study led to peak $A\beta_{42}$ reductions of 45% with a calculated $A\beta_{42}$ lowering $AUC_{1\rightarrow24}$ of 34%. Peak increases of 3.1-fold were observed for Aβ37.

Table 7. In vivo efficacy profile of 47 in rodents

Species	[Brain] Total (uM)	[Brain] Free (nM)	Brain Aβ42 reduction[a]	Brain Aβ37 increase[a]	CSF Aβ42 reduction[a]	CSF Aβ37 increase[a]
Mouse	29.8	427 nM	43%	3.2-fold	-	-
Rat	13.7	156 nM	30%	2.5-fold	58%	20-fold

[a]Expressed as % vehicle in CSF and brain 6 h post-dose

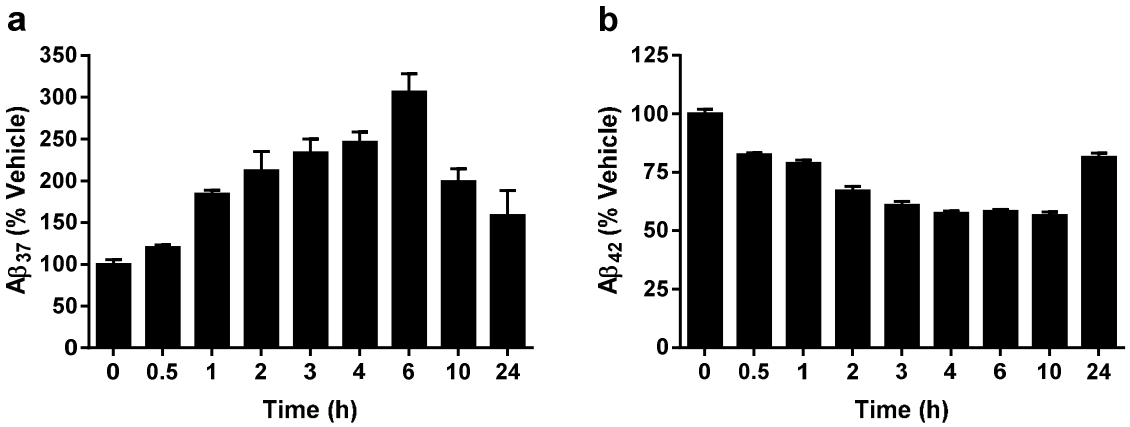


Figure 7. ***In vivo*** **time course profile of 47 in Mouse Brain.** $A\beta_{37}$ (left) and $A\beta_{42}$ (right) in the brain of mice treated acutely with a single oral dose of 47 (30 mg/kg). Data represent the mean ± SEM of 5-8 animals per group, expressed as % vehicle.

Conclusions.

From initial amide designs based on **1**, we have pursued molecules with the potential to alter the course of FAD in an effort to prevent, or at least delay, the impending cognitive decline. We have focused our efforts with a keen eye to overcome the shortcoming of previous GSMs - combining the desired in vitro potency and in vivo efficacy with good CNS drug-like properties.[20] Through the use of an

isosteric amide replacement and critical consideration of conformational restriction we have discovered a very exciting series of oxadiazines that address these critical issues. Oxadiazine **47** possesses very good potency and efficacy with excellent predicted CNS drug-like properties as measured by low MW (389), low lipophilicity (cLogP = 2.8), high CNS-MPO score (5.0) and high LLE (4.7) and LELP (7.6) binding efficiencies. This compound also demonstrates a desirable profile across various measurements including solubility, permeability, metabolic stability, CYP inhibition, hERG liability, P-gp efflux, genotoxicity and PK assays. This class of compounds has provided a new avenue to further develop the molecules required for proof-of-mechanism studies in the clinic. Our additional efforts to further improve potency and efficacy while maintaining this excellent CNS drug-like profile will be the subject of further discussion in due course.

Experimental Section.

General Methods

All reactions were carried out using commercial materials and reagents without further purification unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on silica gel plates (Keiselgel 60 F254, Merck), high-performance liquid chromatography (HPLC), liquid chromatography mass spectrometry (LCMS) or ultra-performance liquid chromatography (UPLC). All products were characterised by ^{1}H NMR and mass spectrometry. ^{1}H NMR data was recorded on a JEOL ECX400 MHz or Bruker Avance II Ultra shield 500 MHz spectrometer. Chemical shifts are expressed in parts per million values (ppm) and are designated as s (singlet); br s (broad singlet); d (doublet); t (triplet); q (quartet); quint (quintet) or m (multiplet). Coupling constants (*J*) are expressed as values in Hertz (Hz). Optical rotations were taken on a Rudolph Research Analytical; Autopol III automatic polarimeter; Model A21101 AIII/2W. Flash column chromatography was performed on silica gel using Fluorochem silica gel LC60A 40-63 micron and reagent grade solvents as eluent. All compounds submitted for in vitro testing were >95% purity (HPLC) and those for in vivo testing were >98% purity (HPLC). LCMS

analysis using LCMS A, standard conditions: XTerra RP18 column, 3.0 x 50 mm, 3.5 μm; Mobile phase A: H_2O, mobile phase B: CH_3CN with 0.1% formic acid (FA). 0-1 min. isocratic (5% B), 1-6 min. gradient (5-95% B), 6-7 min. isocratic (95% B); flow rate: 1 mL/min; LCMS analysis using LCMS B, standard conditions: Ascentis Express C-18 column, 50 × 3.0 mm, 2.7 μm; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B% 0.01/5, 0.5/5, 3/100, 5/100: flow rate: 1.2 mL/min. LCMS analysis using LCMS C, standard conditions: XBridge C18 column, 4.6 x 30 mm, 3.5 μm; Mobile phase A: H_2O (10.0 mM NH_4HCO_2), mobile phase B: CH_3CN. 0.0-0.2 min. isocratic (5% B), 0.2-2.0 min. gradient (5-100% B), 3.0-3.0 min. isocratic (100% B); flow rate: 3.0 mL/min.

(*S*)-*tert*-Butyl 4-((4-fluoro-2-methylphenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxy-late (2a): DIAD (1.70 mL, 8.68 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (2.28 g, 8.68 mmol, 1.2 equiv), (*S*)-*tert*-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (1.83 g, 7.89 mmol, 1.0 equiv) and 4-fluoro-2-methylphenol (1.09 g, 8.68 mmol, 1.2 equiv) in THF (20 mL) at RT. The resulting mixture was then stirred for 18 h at 80 °C. The reaction mixture was diluted with EtOAc and the organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-20% EtOAc / hexanes) to afford the desired product (1.90 g, 70%) as a colourless oil. LCMS (ES+) [M-Boc+H]+: 240.4.

(*S*)-*tert*-Butyl 4-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate (2b): DIAD (0.46 mL, 2.35 mmol, 1.1 equiv) was added to a solution of triphenylphosphine (616 mg, 2.35 mmol, 1.1 equiv), (*S*)-*tert*-butyl 4-(hydroxymethyl)-2,2-dimethyloxazolidine-3-carboxylate (495 mg, 2.14 mmol, 1.0 equiv) and 4-chloro-2-(trifluoromethyl)phenol (462 g, 2.35 mmol, 1.1 equiv) in THF (8 mL) at RT. The resulting mixture was then stirred for 18 h at 80 °C. The reaction mixture was diluted with EtOAc and the organic layer was

washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-20% EtOAc / hexanes) to afford the desired product (673 mg, 77%) as a colourless oil. LCMS (ES+) [M-Boc+H]+: 310.6/312.6.

(*R*)-3-(4-Fluoro-2-methylphenoxy)-2-(4-methoxybenzylamino)propan-1-ol (3a): A solution of (*S*)-*tert*-butyl 4-((4-fluoro-2-methylphenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate **(2a)** (787 mg, 2.32 mmol, 1.0 equiv) in DCM (10 mL) was treated with TFA (5 mL) at RT and the resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was then concentrated and the residue was dissolved in THF (10 mL). 1 N aqueous HCl (10 mL) was added and the mixture was stirred for 18 h at RT. The reaction mixture was diluted with Et_2O (50 mL) and extracted twice with 1 N aqueous HCl. The aqueous phases were combined, concentrated to dryness and co-evaporated twice with MeOH to give the desired ammonium salt (516 mg, 96%) as a white solid. LCMS (ES+) [M+H]+:200.3. A solution of (*R*)-2-amino-3-(4-fluoro-2-methylphenoxy)propan-1-ol hydrochloride (515 mg, 2.18 mol, 1.0 equiv) in DCM (12 mL) at ambient temperature was treated successively with triethylamine (0.61 mL, 4.36 mmol, 2.0 equiv), $MgSO_4$ (1.00 g) and *p*-anisaldehyde (0.27 mL, 2.18 mmol, 1.0 equiv). The resulting suspension was stirred for 16 h at ambient temperature and filtered through a pad of celite which was washed with EtOAc. The filtrate was concentrated under vacuum to afford the corresponding imine intermediate. This intermediate was dissolved in MeOH (15 mL) and cooled to 0 °C. $NaBH_4$ (249 mg, 3.54 mmol, 3.0 equiv) was added portion wise over 5 min. The resulting mixture was stirred for 30 min at 0 °C and then quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$. Water and DCM were added. The layers were separated, and the aqueous layer was extracted with DCM twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afforded a residue that was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to afford the desired amino-alcohol (516 mg, 74%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.27 – 7.24 (m,

2H), 6.88 – 6.85 (m, 3H), 6.81 (td, *J* = 8.3, 2.9 Hz, 1H), 6.70 (dd, *J* = 8.9, 4.5 Hz, 1H), 4.01 (dd, *J* = 9.4, 4.9 Hz, 1H), 3.95 (dd, *J* = 9.4, 6.1 Hz, 1H), 3.84 (s, 2H), 3.80 (s, 3H), 3.78 (dd, *J* = 10.9, 4.4 Hz, 1H), 3.59 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.14 (dt, *J* = 10.3, 5.0 Hz, 1H), 2.19 (s, 3H); LCMS (ES+) [M+H]+: 320.5.

(*R*)-3-(4-Chloro-2-(trifluoromethyl)phenoxy)-2-(4-methoxybenzylamino)propan-1-ol (3b): A solution of (*S*)-*tert*-butyl 4-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-2,2-dimethyloxazolidine-3-carboxylate **(2b)** (528 mg, 1.29 mmol, 1.0 equiv) in DCM (4 mL) was treated with TFA (2 mL) at RT and the resulting mixture was stirred for 1 h at the same temperature. The reaction mixture was then concentrated and the residue was dissolved in THF (4 mL). 1 N aqueous HCl (4 mL) was added and the mixture was stirred for 18 h at RT. The reaction mixture was diluted with Et_2O (30 mL) and extracted twice with 1 N aqueous HCl. The aqueous phases were combined, concentrated to dryness and co-evaporated twice with MeOH to give the desired ammonium salt (341 mg, 86%) as a white solid. LCMS (ES+) [M+H]+:270.4/272.4. A solution of (*R*)-2-amino-3-(4-chloro-2-(trifluoromethyl)phenoxy)propan-1-ol hydrochloride (339 mg, 1.01 mol, 1.0 equiv) in DCM (10 mL) at ambient temperature was treated successively with triethylamine (0.28 mL, 2.02 mmol, 2.0 equiv), $MgSO_4$ (1.00 g) and *p*-anisaldehyde (123 µL, 1.01 mmol, 1.0 equiv). The resulting suspension was stirred for 16 h at RT and filtered through a pad of celite which was washed with EtOAc. The filtrate was concentrated to afford the corresponding imine intermediate. This intermediate was dissolved in MeOH (8 mL) and cooled to 0 °C. $NaBH_4$ (112mg, 3.03 mmol, 3.0 equiv) was added portion wise over 5 min. The resulting mixture was stirred for 30 min at 0 °C and then quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$. Water and EtOAc were added. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afforded a residue that was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to af-

ford the desired amino-alcohol (312 mg, 79%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (d, J = 2.6 Hz, 1H), 7.43 (dd, J = 8.9, 2.6 Hz, 1H), 7.27 – 7.22 (m, 2H), 6.90 (d, J = 8.8 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.11 (dd, J = 9.2, 4.6 Hz, 1H), 4.04 (dd, J = 9.2, 6.3 Hz, 1H), 3.82 (s, 2H), 3.80 (s, 3H), 3.77 (dd, J = 11.1, 4.5 Hz, 1H), 3.59 (dd, J = 11.1, 4.9 Hz, 1H), 3.15 (dq, J = 6.1, 4.7 Hz, 1H); LCMS (ES+) [M+H]+: 390.5/392.5.

(*R*)-4-Bromo-N-(1-(4-fluoro-2-methylphenoxy)-3-hydroxypropan-2-yl)-3-methoxy-N-(4-methoxybenzyl)benzamide (4a): A solution of 4-bromo-3-methoxybenzoic acid (411 mg, 1.78 mmol, 1.1 equiv) in DCM (8 mL) at ambient temperature was treated with a catalytic amount of DMF (1 drop) and oxalyl chloride (0.53 mL, 4.86 mmol, 3.0 equiv). The resulting mixture was stirred at ambient temperature for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated to dryness, diluted with anhydrous THF (8 mL), concentrated again and dried under high vacuum for 1 h. The residue was diluted with anhydrous THF (8 ml), triethylamine (0.45 mL, 3.23mmol, 2.0 equiv) was added and the resulting mixture was cooled to 0 °C. A solution of (*R*)-3-(4-fluoro-2-methylphenoxy)-2-(4-methoxybenzylamino)propan-1-ol **(3a)** (516 mg, 1.62 mmol, 1.0 equiv) in THF (6 ml) was quickly added and the resulting mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-100% EtOAc / hexanes) to afford the desired amide (640 mg, 59%) as a white foam. LCMS (ES+) [M+H]+: 532.6/534.6.

(*R*)-4-Bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-hydroxypropan-2-yl)-3-methoxy-N-(4-methoxybenzyl)benzamide (4b): A solution of 4-bromo-3-methoxybenzoic acid (1.52 g, 6.58 mmol, 1.1 equiv) in DCM (30 mL) at RT was treated with a catalytic amount of DMF (1 drop) and oxalyl chlo-

ride (1.70 mL, 19.7 mmol, 3.3 equiv). The resulting mixture was stirred at RT for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated to dryness, diluted with anhydrous THF (15 mL), concentrated again and dried under high vacuum for 1 h. The residue was diluted with anhydrous THF (30 ml), triethylamine (2.50 mL, 17.9 mmol, 3.0 equiv) was added and the resulting mixture was cooled to 0 °C. A solution of (*R*)-3-(4-chloro-2-(trifluoromethyl)phenoxy)-2-(4-methoxybenzylami-no)propan-1-ol **(3b)** (2.33 g, 5.98 mmol, 1.0 equiv) in THF (15 ml) was quickly added and the resulting mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-100% EtOAc / hexanes) to afford the desired amide (3.44 g, 95%) as a white foam. LCMS (ES+) [M+H]+: 602.4/604.4/606.4.

(*S*)-*N*-(1-(Aminooxy)-3-(4-fluoro-2-methylphenoxy)propan-2-yl)-4-bromo-3-methoxy-N-(4-methoxybenzyl)benzamide (5a): DIAD (0.28 mL, 1.44 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (377 mg, 1.44 mmol, 1.2 equiv), (*R*)-4-bromo-*N*-(1-(4-fluoro-2-methylphenoxy)-3-hydroxypropan-2-yl)-3-methoxy-N-(4-methoxybenzyl)ben-zamide **(4a)** (640 mg, 1.20 mmol, 1.0 equiv) and *N*-hydroxyphtalimide (235 mg, 1.44 mmol, 1.2 equiv) in THF (10 mL) at 0 °C. The resulting mixture was kept at 0 °C for 1 h, then warmed to ambient temperature and stirred for 16 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with 1 N aqueous NaOH (twice), water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-50% EtOAc / hexanes) to afford the desired product (778 mg, 96%) as a white solid. LCMS (ES+) [M+H]+: 677.6/679.6. A suspension of (*S*)-4-bromo-N-(1-(1,3-dioxoisoindolin-2-yloxy)-3-(4-fluoro-2-methylphenoxy)propan-2-yl)-3-methoxy-*N*-(4-methoxybenzyl)benzamide (778 mg, 1.15mol, 1.0 equiv) in ethanol (90%, 12 mL) and THF (6 mL) at

ambient temperature was treated with hydrazine hydrate (50-60%, 1.2 mL). The resulting mixture was stirred for 30 min, then water was added. The mixture was extracted with EtOAc (three times) and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-100% EtOAc / DCM) to afford the desired product (560 mg, 89%) as a white solid. LCMS (ES+) [M+H]+: 547.6/549.6.

(*S*)-*N*-(1-(Aminooxy)-3-(4-chloro-2-(trifluoromethyl)phenoxy)propan-2-yl)-4-bromo-3-methoxy-N-(4-methoxybenzyl)benzamide (5b): DIAD (1.35 mL, 6.85 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (1.80 g, 6.85 mmol, 1.2 equiv), (*R*)-4-bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-hydroxypropan-2-yl)-3-methoxy-N-(4-methoxybenzyl)benzamide **(4b)** (3.44 g, 5.71 mmol, 1.0 equiv) and N-hydroxyphtalimide (1.12 g, 6.85 mmol, 1.2 equiv) in THF (30mL) at 0 °C. The resulting mixture was kept at 0 °C for 1 h, then warmed to RT and stirred for 16 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with 1 N aqueous NaOH (twice), water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-60% EtOAc / hexanes) to afford the desired product (3.94 g, 92%) as a white solid. LCMS (ES+) [M+H]+: 747.4/749.4/751.3. A suspension of (*S*)-4-bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-(1,3-dioxoisoindolin-2-yloxy)propan-2-yl)-3-methoxy-*N*-(4-methoxy-benzyl)benzamide (3.94 g, 5.27 mol, 1.0 equiv) in ethanol (90%, 20 mL) and THF (10 mL) at RT was treated with hydrazine hydrate (50-60%, 4.0 mL). The resulting mixture was stirred for 30 min and then water was added. The mixture was extracted with EtOAc (three times), the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product (3.25 g, 99%) as a white solid. LCMS (ES+) [M+H]+: 617.5/619.5/621.5.

(*S*)-3-(4-Bromo-3-methoxyphenyl)-5-((4-fluoro-2-methylphenoxy)methyl)-4-(4-methoxy-benzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (6a): A sealable vial was charged with (*S*)-*N*-(1-(aminooxy)-3-(4-fluoro-2-methylphenoxy)propan-2-yl)-4-bromo-3-methoxy-*N*-(4-methoxyben-zyl)benzamide **(5a)** (560 mg, 1.02 mmol, 1.0 equiv) and iPrOH (10.0 ml). P_2O_5 (1.45 g, 10.2 mmol, 10.0 equiv) was added at ambient temperature. The vial was sealed and the reaction was stirred at 80 °C for 16 h. The reaction mixture was cooled to ambient temperature and diluted with EtOAc. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-50% EtOAc / hexanes) to afford the desired product (241 mg, 45%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.58 (d, J = 8.1 Hz, 1H), 7.11 – 7.08 (m, 2H), 7.07 (d, J = 1.8 Hz, 1H), 7.03 (dd, J = 8.1, 1.9 Hz, 1H), 6.89 – 6.85 (m, 3H), 6.79 (td, J = 8.3, 2.7 Hz, 1H), 6.65 (dd, J = 8.9, 4.5 Hz, 1H), 4.39 – 4.35 (m, 2H), 4.23 – 4.20 (m, 1H), 4.09 – 4.00 (m , 2H), 3.89 (s, 3H), 3.81 (s, 3H), 3.74 – 3.70 (m, 1H), 3.58 (dd, J = 10.9, 2.5 Hz, 1H), 2.21 (s, 3H); LCMS (ES+) [M+H]+: 529.5/531.5.

(*S*)-3-(4-Bromo-3-methoxyphenyl)-5-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (6b): A sealable vial was charged with (*S*)-*N*-(1-(aminooxy)-3-(4-chloro-2-(trifluoromethyl)phenoxy)propan-2-yl)-4-bromo-3-methoxy-*N*-(4-methoxybenzyl)benzamide **(5b)** (1.00 g, 1.62 mmol, 1.0 equiv) and IPA (15 ml). P_2O_5 (2.30 g, 16.2 mmol, 10.0 equiv) was added at RT. The vial was sealed and the reaction was stirred at 100 °C for 30 h. The reaction mixture was cooled to RT and diluted with EtOAc. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous phase was extracted with EtOAc. The

organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-60% EtOAc / hexanes) to afford the desired product (530 mg, 55%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61 – 7.56 (m, 2H), 7.44 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.10 – 7.04 (m, 3H), 7.03 (dd, *J* = 8.1, 1.9 Hz, 1H), 6.89 (d, *J* = 8.9 Hz, 1H), 6.88 – 6.84 (m, 2H), 4.49 (d, *J* = 15.3 Hz, 1H), 4.28 (dd, *J* = 11.0, 1.4 Hz, 1H), 4.21 (d, *J* = 15.3 Hz, 1H), 4.17 – 4.11 (m, 2H), 3.89 (s, 3H), 3.80 (s, 3H), 3.79 – 3.74 (m, 1H), 3.48 (dd, *J* = 11.0, 2.5 Hz, 1H); LCMS (ES+) [M+H]+: 599.5/601.5/603.4.

(*S*)-5-((4-Fluoro-2-methylphenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (7a1): To a vial charged with (*S*)-3-(4-bromo-3-methoxyphenyl)-5-((4-fluoro-2-methylphenoxy)methyl)-4-(4-methoxy-benzyl)-5,6-dihydro-4H-1,2,4-oxadiazine **(6a)** (99 mg, 0.187 mmol, 1.0 equiv), 4(5)-methylimidazole (18 mg, 0.224 mmol, 1.2 equiv) and K_3PO_4 (79 mg, 0.374 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (0.9 mL). To a second vial charged with $Pd_2(dba)_3$ (8.6 mg, 0.009 mmol, 5.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 9.0 mg, 0.019 mmol, 10.0 mol%) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (0.9 mL). This mixture was stirred for 3 min at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 min and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated, and the residue was purified by normal phase chromatography on silica (0-7% MeOH / DCM) to afford the desired product (66 mg, 67%) as an off-white solid. LCMS (ES+) [M+H]+: 531.7.

(*S*)-5-((4-Chloro-2-(trifluoromethyl)phenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (7b1): To a vial charged with (*S*)-

3-(4-bromo-3-methoxyphenyl)-5-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine **(6b)** (127 mg, 0.212 mmol, 1.0 equiv), 4(5)-methylimidazole (26 mg, 0.318 mmol, 1.5 equiv) and K_3PO_4 (90 mg, 0.424 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (1.2 mL). To a second vial charged with $Pd_2(dba)_3$ (7.8 mg, 0.009 mmol, 4.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 8.2 mg, 0.017 mmol, 8.0 mol%) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (1.2 mL). This mixture was stirred for 3 min at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 minutes and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated, and the residue was purified by normal phase chromatography on silica (0-7% MeOH / DCM) to afford the desired product (74 mg, 58%) as an off-white solid. LCMS (ES+) [M+H]+: 601.6/603.6.

(*S*)-5-((4-Fluoro-2-methylphenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-5,6-dihydro-4H-1,2,4-oxadiazine ((*S*)-8): A solution of (*S*)-5-((4-Fluoro-2-methylphenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-4-(4-methoxy-benzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (66 mg, 0.124 mmol, 1.0 equiv) **(7a1)** in DCE (1.0 mL) at ambient temperature was treated with TFA (1.0 mL). The resulting mixture was stirred at 125 °C for 2 h in a microwave reactor. The reaction mixture was cooled to RT, concentrated and dissolved in EtOAc. The organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-10% MeOH / DCM) to afford the desired product (46 mg) as an off-white solid. The product was dissolved in DMF (1.5 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (43 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.73 (br s,

1H), 7.44 (d, *J* = 1.7 Hz, 1H), 7.28 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.94 (br s, 1H), 6.88 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.84 (td, *J* = 8.4, 3.1 Hz, 1H), 6.77 (dd, *J* = 8.9, 4.5 Hz, 1H), 5.22 (br s, 1H), 4.16 – 4.06 (m, 5H), 3.89 (s, 3H), 2.29 (s, 3H), 2.23 (s, 3H); LCMS analysis using LCMS A, standard conditions: T_R = 3.62 min, LCMS (ES+) [M+H]+: 411.5; $[\alpha]_D$ = +66.1 (c = 0.18, MeCN).

(*S*)-5-((4-Chloro-2-(trifluoromethyl)phenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-5,6-dihydro-4H-1,2,4-oxadiazine ((*S*)-10): A solution of (*S*)-5-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-3-(3-methoxy-4-(4-methyl-1H-imidazol-1-yl)phenyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine **(7b1)** (72 mg, 0.119 mmol, 1.0 equiv) in DCE (1.0 mL) at RT was treated with TFA (1.0 mL). The resulting mixture was stirred at 125 °C for 2 h in a microwave reactor. The reaction mixture was cooled to RT, concentrated and dissolved in EtOAc. The organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-8% MeOH / DCM) to afford the desired product (43 mg) as an off-white solid. The product was dissolved in DMF (1.5 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (34 mg, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.78 (s, 1H), 7.58 (d, *J* = 2.6 Hz, 1H), 7.49 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.40 (d, *J* = 1.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.94 (s, 1H), 5.27 (s, 1H), 4.32 – 4.24 (m, 1H), 4.20 – 4.10 (m, 3H), 4.08 – 4.02 (m, 1H), 3.89 (s, 3H), 2.30 (d, *J* = 0.9 Hz, 3H); LCMS analysis using LCMS A, standard conditions: T_R = 4.00 min, LCMS (ES+) [M+H]+: 481.5/483.5; $[\alpha]_D$ = +57.1 (c = 0.34, MeOH).

(*R*)-5-Bromo-*N*-(1-(4-fluoro-2-methylphenoxy)-3-hydroxypropan-2-yl)-6-methoxy-N-(4-methoxybenzyl)picolinamide (17a): A solution of 5-bromo-6-methoxypicolinic acid (2.17 g,

9.36 mmol, 1.0 equiv) in DCM (50 mL) at RT was treated with a catalytic amount of DMF (1 drop) and oxalyl chloride (2.50 ml, 28.1 mmol, 3.0 equiv). The resulting mixture was stirred at RT for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated to dryness, diluted with anhydrous THF (30 mL), concentrated again and dried under high vacuum for 1 h. The residue was diluted with anhydrous THF (40 ml), triethylamine (3.90 mL, 28.1 mmol, 3.0 equiv) was added and the resulting mixture was cooled to 0 °C. A solution of (*R*)-3-(4-fluoro-2-methylphenoxy)-2-(4-methoxybenzylamino)propan-1-ol (**3a**) (2.99 g, 9.36 mmol, 1.0 equiv) in THF (25 ml) was quickly added and the resulting mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-50% EtOAc / DCM) to afford the desired amide (3.90g, 78%) as a white foam. LCMS (ES+) [M+H]+: 533.6/535.6.

(*R*)-5-Bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-hydroxypropan-2-yl)-6-methoxy-*N*-(4-methoxybenzyl)picolinamide (17b): A solution of 5-bromo-6-methoxypicolinic acid (800 mg, 3.45 mmol, 1.1 equiv) in DCM (15 mL) at ambient temperature was treated with a catalytic amount of DMF (1 drop) and oxalyl chloride (0.90 ml, 10.3 mmol, 3.0 equiv). The resulting mixture was stirred at ambient temperature for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated to dryness, diluted with anhydrous THF (10 mL), concentrated again and dried under high vacuum for 1 h. The residue was diluted with anhydrous THF (15 ml), triethylamine (1.43 mL, 10.3 mmol, 3.0 equiv) was added and the resulting mixture was cooled to 0 °C. A solution of (*R*)-3-(4-chloro-2-(trifluoromethyl)phenoxy)-2-(4-methoxybenzylamino)propan-1-ol (**3b**) (1.22 g, 3.14 mmol, 1.0 equiv) in THF (10 ml) was quickly added and the resulting mixture was stirred at 0 °C for 30 min. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were sepa-

rated and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-100% EtOAc / hexanes) to afford the desired amide (1.13 g, 59%) as a white foam. LCMS (ES+) [M+H]+: 603.4/605.4/607.4.

(*S*)-3-(5-Bromo-6-methoxypyridin-2-yl)-5-((4-fluoro-2-methylphenoxy)methyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (18a): DIAD (1.73 mL, 8.77 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (2.30 g, 8.77 mmol, 1.2 equiv), (*R*)-5-bromo-N-(1-(4-fluoro-2-methylphenoxy)-3-hydroxypropan-2-yl)-6-methoxy-N-(4-methoxybenzyl)picolinamide (**17a**) (3.90 g, 7.31 mmol, 1.0 equiv) and N-hydroxyphtalimide (1.43 g, 8.77 mmol, 1.2 equiv) in THF (30 mL) at 0 °C. The resulting mixture was kept at 0 °C for 1 h, allowed to warm to RT and stirred for 16 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with 1 N aqueous NaOH twice, water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-20% EtOAc DCM) to afford the desired product (4.14 g, 83%) as a light brown foam. LCMS (ES+) [M+H]+: 678.2/680.2. A suspension of (*S*)-5-bromo-*N*-(1-(1,3-dioxoisoindolin-2-yloxy)-3-(4-fluoro-2-methylphenoxy)propan-2-yl)-6-methoxy-*N*-(4-methoxybenzyl)picolinamide (4.14 g, 6.10 mol, 1.0 equiv) in ethanol (90%, 20 mL) and THF (10 mL) at 0 °C was treated with hydrazine hydrate (50-60%, 3.0 mL). The resulting mixture was stirred for 1 h and then water was added. The mixture was extracted with EtOAc (three times) and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-70% EtOAc / DCM) to afford the desired product (2.88 mg, 86%) as a white foam. LCMS (ES+) [M+H]+: 548.2/550.2. A sealable vial was charged with (*S*)-*N*-(1-(aminooxy)-3-(4-fluoro-2-methylphenoxy)propan-2-yl)-5-bromo-6-methoxy-*N*-(4-methoxyben-zyl)picolinamide (2.76 g, 5.03 mmol, 1.0 equiv) and IPA (40 ml). P_2O_5 (7.14 g, 50.3

mmol, 10.0 equiv) was added at RT. The vial was sealed and the reaction was stirred at 90 °C for 16 h. The reaction mixture was cooled to RT and diluted with EtOAc. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-100% EtOAc / hexanes) to afford the desired product (461 mg, 17%) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.86 (d, J = 7.8 Hz, 1H), 7.26 – 7.23 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 6.89 – 6.82 (m, 3H), 6.77 (td, J = 8.3, 2.9 Hz, 1H), 6.61 (dd, J = 8.9, 4.5 Hz, 1H), 4.52 (d, J = 15.4 Hz, 1H), 4.45 – 4.36 (m, 2H), 4.12 – 4.06 (m, 1H), 4.05 – 3.98 (m, 1H), 3.92 (s, 3H), 3.80 (s, J = 2.4 Hz, 3H), 3.72 – 3.62 (m, 2H), 2.19 (s, 3H); LCMS (ES+) [M+H]+: 530.2/532.2.

(*S*)-3-(5-Bromo-6-methoxypyridin-2-yl)-5-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (18b): DIAD (0.44 mL, 2.25 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (590 mg, 2.25 mmol, 1.2 equiv), (*R*)-5-bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-hydroxypropan-2-yl)-6-methoxy-*N*-(4-methoxybenzyl)picolinamide (**17b**) (1.13 g, 1.87 mmol, 1.0 equiv) and *N*-hydroxyphthalimide (366 mg, 2.25 mmol, 1.2 equiv) in THF (10 mL) at 0 °C. The resulting mixture was kept at 0 °C for 1 h. The reaction mixture was diluted with EtOAc and the organic layer was washed with 1 N aqueous NaOH (twice), water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-50% EtOAc / hexanes) to afford the desired product (1.09 g, 78%) as a white solid. LCMS (ES+) [M+H]+: 748.5/750.5/752.5. A suspension of (*S*)-5-bromo-*N*-(1-(4-chloro-2-(trifluoromethyl)phenoxy)-3-(1,3-dioxoisoindolin-2-yloxy)propan-2-yl)-6-methoxy-*N*-(4-methoxy-benzyl)picolinamide (1.09 g, 1.46 mol, 1.0 equiv) in ethanol (90%, 10 mL) and THF (5 mL) at RT was treated with hydrazine hydrate (50-60%, 1.0 mL). The resulting mixture was stirred for 30 min

and then water was added. The mixture was extracted with EtOAc three times, the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-3% MeOH / DCM) to afford the desired product (810 mg, 90%) as a white solid. LCMS (ES+) [M+H]+: 618.5/620.5/622.5. A sealable vial was charged with (*S*)-*N*-(1-(aminooxy)-3-(4-chloro-2-(trifluoromethyl)phenoxy)propan-2-yl)-5-bromo-6-methoxy-*N*-(4-methoxybenzyl)picolinamide (810, 1.31 mmol, 1.0 equiv) and IPA (15 ml). P_2O_5 (1.86 g, 13.1 mmol, 10.0 equiv) was added at RT. The vial was sealed and the reaction was stirred at 85 °C for 16 h. The reaction mixture was cooled to ambient temperature and diluted with EtOAc. A saturated aqueous solution of $NaHCO_3$ was added, the layers were separated and the aqueous phase was extracted with EtOAc. The organic phases were combined, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-60% EtOAc / hexanes) to afford the desired product (180 mg, 21%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.86 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.41 (dd, J = 8.8, 2.6 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 6.89 – 6.82 (m, 3H), 4.58 (d, J = 15.5 Hz, 1H), 4.41 – 4.34 (m, 2H), 4.13 (qd, J = 9.0, 7.2 Hz, 2H), 3.92 (s, 3H), 3.80 (s, J = 5.3 Hz, 3H), 3.73 (tdd, J = 7.5, 2.1, 1.2 Hz, 1H), 3.61 (dd, J = 11.1, 2.3 Hz, 1H); LCMS (ES+) [M+H]+: 600.5/602.5/604.5.

(*S*)-5-((4-Fluoro-2-methylphenoxy)methyl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazine (19): To a vial charged with (*S*)-3-(5-bromo-6-methoxypyridin-2-yl)-5-((4-fluoro-2-methylphenoxy)methyl)-4-(4-methoxy-benzyl)-5,6-dihydro-4H-1,2,4-oxadiazine **(18a)** (315 mg, 0.593 mmol, 1.0 equiv), 4(5)-methylimidazole (98 mg, 1.19 mmol, 2.0 equiv) and K_3PO_4 (252 mg, 1.19 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (3.0 mL). To a second vial charged with $Pd_2(dba)_3$ (22.0 mg, 0.024 mmol, 4.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 23.0 mg, 0.047 mmol, 8.0 mol%) under N_2 atmosphere was added

degassed 4:1 PhMe:dioxane solvent mixture (3.0 mL). This mixture was stirred for 3 min at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 min and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated and the residue was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to afford the desired product (216 mg, 69%) as an off-white solid. LCMS (ES+) [M+H]+: 532.4/534.4. A solution of (*S*)-5-((4-fluoro-2-methylphenoxy)methyl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-4-(4-methoxy-benzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (214 mg, 0.403 mmol, 1.0 equiv) in DCE (5.0 mL) at RT was treated with TFA (5.0 mL). The resulting mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT, concentrated and dissolved in EtOAc. The organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to afford the desired product (165 mg, 99%) as an off-white solid. 69 mg of this material was dissolved in DMF (1.5 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (55 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.84 (br s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.64 – 7.59 (m, 1H), 6.98 (br s, 1H), 6.88 (dd, J = 8.9, 3.1 Hz, 1H), 6.83 (td, J = 8.4, 3.1 Hz, 1H), 6.76 (dd, J = 8.9, 4.5 Hz, 1H), 6.67 (br s, 1H), 4.19 – 4.12 (m, 3H), 4.07 – 4.00 (m, 5H), 2.30 (d, J = 0.8 Hz, 3H), 2.25 (s, 3H); LCMS analysis using LCMS A, standard conditions: T_R = 3.85 min, LCMS (ES+) [M+H]+: 412.3; $[\alpha]_D$ = +91.9 (c = 0.52, MeOH).

(*S*)-5-((4-Chloro-2-(trifluoromethyl)phenoxy)methyl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazine (25): To a vial charged with (*S*)-3-(5-bromo-6-methoxypyridin-2-yl)-5-((4-chloro-2-(trifluoromethyl)phenoxy)me-thyl)-4-(4-methoxybenzyl)-5,6-

dihydro-4H-1,2,4-oxadiazine **(18b)** (179 mg, 0.298 mmol, 1.0 equiv), 4(5)-methylimidazole (49 mg, 0.596 mmol, 2.0 equiv) and K_3PO_4 (127 mg, 0.596 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (2.4 mL). To a second vial charged with $Pd_2(dba)_3$ (11.0 mg, 0.012 mmol, 4.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 11.5 mg, 0.024 mmol, 8.0 mol%) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (2.4 mL). This mixture was stirred for 3 min at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 min and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated and the residue was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to afford the desired product (94 mg, 53%) as an off-white solid. LCMS (ES+) [M+H]+: 602.6/604.6. A solution of (*S*)-5-((4-chloro-2-(trifluoromethyl)phenoxy)methyl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyri-din-2-yl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (93 mg, 0.155 mmol, 1.0 equiv) in DCE (2.0 mL) at RT was treated with TFA (2.0 mL). The resulting mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled to RT, concentrated and dissolved in EtOAc. The organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-6% MeOH / DCM) to afford the desired product (65 mg, 88%) as an off-white solid. The product was dissolved in DMF (1.5 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (57 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.18 (s, 1H), 7.85 (s, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 2.6 Hz, 1H), 7.47 (dd, J = 8.8, 2.6 Hz, 1H), 6.98 (s, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.76 (s, 1H), 4.27 – 4.14 (m, 4H), 4.06 (s, 3H), 3.97 (dd, J = 11.1, 2.6 Hz, 1H), 2.31 (s, 3H); LCMS analysis using LCMS A, standard conditions: T_R = 4.13 min, LCMS (ES+) [M+H]+: 482.5/484.5; $[\alpha]_D$ = +72.8 (c = 0.35, MeOH).

(rac)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxypiperidine-1-carboxylate (27(+/-)): A solution of 2-(hydroxymethyl)pyridin-3-ol hydrochloride **(26)** (6.0 g, 37.26 mmol, 1.0 equiv), imidazole (7.61 g, 112 mmol, 3.0 equiv) and tertbutyldimethylsilane (6.74 g, 44.7 mmol, 1.2 equiv) in anhydrous DMF (185 mL) was stirred for 16 h at 60 °C. Water and EtOAc were then successively added. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-20% EtOAc / hexanes) to afford the desired pyridine (4.30 g, 48%). LCMS (ES+) [M+H]+: 240.1. A suspension of 2-((*tert*-butyldimethylsilyloxy)methyl)pyridin-3-ol (4.3 g, 18.0 mmol, 1.0 equiv) in degassed EtOH (40.0 mL) and water (20.0 mL) was treated with PtO_2 (850 mg). The reaction mixture was put on Parr Shaker apparatus at 60 psi of H_2 for 16 h at RT. The reaction was filtered through a pad of celite which was washed thoroughly with MeOH and DCM. The filtrate was concentrated to afford the desired piperidine (3.82 g, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) □□□ 5.08 (s, 1H), 3.84 (s, 1H), 3.81 – 3.72 (m, 2H), 3.16 – 3.10 (m, 1H), 2.73 – 2.63 (m, 2H), 1.95 – 1.88 (m, 2H), 1.87 – 1.79 (m, 1H), 1.56 – 1.40 (m, 2H), 0.92 – 0.89 (m, 9H), 0.09 – 0.07 (m, 6H). A solution of (rac)-2-((*tert*-butyldimethylsilyloxy)methyl)piperidin-3-ol (3.80 g, 15.5 mmol, 1.0 equiv) triethylamine (6.47 mL, 46.5 mmol, 3.0 equiv) and BOC_2O (3.72 g, 17.0 mmol, 1.1 equiv) in anhydrous DCM (55.0 mL) was stirred for 16 h at RT. Water and DCM were then successively added. The layers were separated, and the aqueous layer was extracted with DCM twice. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (5-35% EtOAc / hexanes) to afford the desired product (3.37 g, 63%). LCMS (ES+) [M+H]+: 346.3.

(rac)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-chloro-2-(trifluoromethyl) phenoxy)piperidine-1-carboxylate (28b(+/-)): DIAD (1.96 mL, 9.95 mmol, 1.5 equiv) was added to a so-

lution of PPh_3 (2.61 g, 9.95 mmol, 1.5 equiv), (rac)-*tert*-butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-hydroxypiperidine-1-carboxylate **(27(+/-))** (2.29 g, 6.63 mmol, 1.0 equiv) and 4-chloro-2-(trifluoromethyl)phenol (6.51 g, 33.1 mmol, 5.0 equiv) in DCM (8.30 mL) at 0 °C. The resulting mixture was stirred at this temperature for 5 min, warmed to RT and then heated to 60 °C for 2.5 h in a microwave reactor. An aqueous solution of NaOH 1 N was added and the aqueous layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-15% EtOAc / 1:1 DCM/hexanes) to afford the desired product (2.95 g, 85%). LCMS (ES+) [M-BOC+H]+: 424.6/426.6.

(rac)(5-Bromo-6-methoxypyridin-2-yl)(3-(4-chloro-2-(trifluoromethyl)phenoxy)-2-(hydroxymethyl)piperidin-1-yl)methanone (29b(+/-)): A solution of (rac)-*tert*-Butyl 2-((*tert*-butyldimethylsilyloxy)methyl)-3-(4-chloro-2-(trifluoromethyl)phenoxy)piperidine-1-carboxylate **((28b(+/-))** (2.95 g, 5.63 mmol, 1.0 equiv) and TBAF 1 M solution in THF (6.19 mL, 6.19 mmol, 1.1 equiv) in anhydrous THF (28.0 mL) was stirred for 16 h at RT. An aqueous solution of NaOH 1 N and EtOAc were then successively added. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with aqueous NaOH 1 N, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-5% MeOH / DCM) to afford the desired alcohol (2.09 g, 90%). LCMS (ES+) [M-BOC+H]+: 310.4/312.4. A solution of ((rac)-*tert*-butyl 3-(4-chloro-2-(trifluoromethyl)phenoxy)-2-(hydroxymethyl)piperidine-1-carboxylate (2.1 g, 5.09 mmol, 1.0 equiv) and TFA (1.95 mL, 25.4 mmol, 5.0 equiv) in anhydrous DCM (25.5 mL) was stirred for 16 h at RT. An aqueous solution of HCl 1 N and DCM were then successively added. The layers were separated, and the organic layer was extracted with aqueous HCl 1N. The combined aqueous layers were basified with aqueous NaOH 1 N and extracted with DCM (4 times). The combined organic layer were dried over $MgSO_4$, filtered and concen-

trated to afford the desired amino alcohol (1.19 g, 76%) that was used directly in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.56 (d, J = 2.6 Hz, 1H), 7.44 (dd, J = 8.8, 2.6 Hz, 1H), 6.96 (d, J = 8.9 Hz, 1H), 4.64 – 4.59 (m, 1H), 3.75 (dd, J = 11.2, 8.0 Hz, 1H), 3.67 (dd, J = 11.2, 5.5 Hz, 1H), 3.27 – 3.17 (m, 2H), 2.87 – 2.78 (m, 1H), 2.22 – 2.13 (m, 1H), 1.76 – 1.66 (m, 2H), 1.58 – 1.48 (m, 1H). LCMS (ES+) [M+H]+: 310.5/312.5. A solution of 5-bromo-6-methoxypicolinic acid (898 mg, 3.87 mmol, 1.1 equiv) in DCM (17.6 mL) at ambient temperature was treated with a catalytic amount of DMF (4 drops) and oxalyl chloride (921 uL, 10.6 mmol, 3.0 equiv). The resulting mixture was stirred at ambient temperature for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated, diluted with anhydrous THF (30.0 mL), concentrated again and dried under high vacuum for 1 hour. The residue was diluted in anhydrous THF (13.5 ml), treated with triethylamine (979 uL, 7.04 mmol, 2.0 equiv) and cooled to 0 °C. A solution of ((rac)-3-(4-chloro-2-(trifluoromethyl)phenoxy)piperidin-2-yl)methanol (794 mg, 3.32 mmol, 1.0 equiv) in THF (10.0 ml) was quickly added and the resulting mixture was stirred at 0 °C for 1 h. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-5% MeOH / DCM) to afford the desired amide (1.53 g, 83%). LCMS (ES+) [M+H]+: 523.4/525.4/527.4.

(rac)-2-(Aminooxymethyl)-3-(4-chloro-2-(trifluoromethyl)phenoxy)piperidin-1-yl)(5-bromo-6-methoxypyridin-2-yl)methanone (30b(+/-)): A solution of DIAD (862 uL, 4.38 mmol, 1.5 equiv) and PPh_3 (1.15 g, 4.38 mmol, 1.5 equiv) in DCM (10.0 mL) were stirred at ambient temperature for 20 min. To this mixture was added *N*-hydroxylphtalimide (715 mg, 4.38 mmol, 1.5 equiv) at 0 °C, followed by (5-bromo-6-methoxypyridin-2-yl)((rac)-3-(4-chloro-2-(trifluoromethyl)phenoxy)-2-(hydroxymethyl)piperidin-1-yl)methanone **(29b(+/-))** (1.53 g, 2.92 mmol, 1.0 equiv) in DCM (10.0

mL). The resulting mixture was kept at 0 °C for 5 min, then warmed to ambient temperature and stirred for 1 h. An aqueous solution of NaOH 1 N and DCM were then successively added. The layers were separated, and the aqueous layer was extracted with DCM twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (3-20% EtOAc / 1:1 DCM/Hexanes) to afford the desired product (2.15 g). The final product is contaminated with reduced DIAD and was used directly in the next step. LCMS (ES+) [M+H]+: 668.4/670.4/672.4. A suspension of 2-(((rac)-1-(5-bromo-6-methoxypicolinoyl)-3-(4-chloro-2-(trifluoromethyl)phenoxy)piperidin-2-yl)methoxy)isoindoline-1,3-dione (1.00 g, 1.50 mmol, 1.0 equiv) in ethanol (90%, 15.0 mL) at -20 °C was treated with hydrazine hydrate (50-60%, 2.00 mL). The resulting mixture was stirred for 30 minutes, then water was added. The mixture was extracted with EtOAc (three times), and the combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (1-3% MeOH / DCM) to afford the desired product (700 mg, 87%). LCMS (ES+) [M+H]+: 538.5/540.5/542.5.

(cis)-4-(5-Bromo-6-methoxypyridin-2-yl)-9-(4-chloro-2-(trifluoromethyl)phenoxy)-1,6,7,8,9,9a-hexahydropyrido[1,2-d][1,2,4]oxadiazine (31b1 and **31b2):** A solution of ((rac)-2-(aminooxymethyl)-3-(4-chloro-2-(trifluoromethyl)phenoxy)piperidin-1-yl)(5-bromo-6-methoxypyridin-2-yl)methanone **(30b(+/-))** (700 mg, 1.30 mmol, 1.0 equiv) in anhydrous DCE (13.0 mL) treated with $POCl_3$ (302 uL, 3.25 mmol, 2.5 equiv). The vial was sealed and heated at 100 °C for 1 h. Reaction profile show slow conversion to desired product, therefore, the temperature was increased by 10 °C every hour until 120 °C was reached (Total of 3h, 64% conversion to desired product observed). An aqueous solution NaOH 1 N and DCM were then successively added. The layers were separated, and the aqueous layer was extracted with DCM twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afford the desired product (360 mg, 53%). The racemates were separated using semi preparative

HPLC (Chiralpak IA column, 5 uM, 20x250 mm, 15 mL/min, 76% Hexanes/12% MeOH/12% DCM) to afford cis-enantiomer **31b1** (117 mg, 17%, t_r = 9.60 min) and cis-enantiomer **31b2** (113 mg, 17%, t_r = 13.56 min). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 7.86 (d, *J* = 7.7 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.44 (dd, *J* = 8.9, 2.4 Hz, 1H), 7.17 (d, *J* = 7.8 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 1H), 4.62 (s, 1H), 4.24 (dd, *J* = 11.5, 4.8 Hz, 1H), 4.18 – 4.09 (m, 1H), 4.02 (s, 3H), 3.91 (dd, *J* = 8.4, 4.7 Hz, 1H), 3.76 (d, *J* = 12.7 Hz, 1H), 2.89 (td, *J* = 12.8, 2.2 Hz, 1H), 2.29 (d, *J* = 12.5 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.72 (t, *J* = 13.0 Hz, 1H), 1.47 (d, *J* = 13.0 Hz, 1H). LCMS (ES+) [M+H]+: 520.1/522.1/524.1

(cis)-9-(4-Chloro-2-(trifluoromethyl)phenoxy)-4-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-1,6,7,8,9,9a-hexahydropyrido[1,2-d][1,2,4]oxadiazine (34(+)): To a vial charged with (cis)-4-(5-bromo-6-methoxypyridin-2-yl)-9-(4-chloro-2-(trifluoromethyl)phenoxy)-1,6,7,8,9,9a-hexahydropyrido[1,2-d][1,2,4]oxadiazine (cis-enantiomer **31b1**, 90.0 mg, 0.17 mmol, 1.0 equiv), 4(5)-methylimidazole (28.4 mg, 0.35 mmol, 2.0 equiv), and K_3PO_4 (73.4 mg, 0.35 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (1.0 mL). To a second vial charged with $Pd_2(dba)_3$ (6.30 mg, 0.007 mmol, 4.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 6.65 mg, 0.01 mmol, 8.0 mol%) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (0.80 mL). This mixture was stirred for 3 minutes at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 minutes and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated, and the residue was purified by normal phase chromatography on silica (0-5% MeOH / DCM) to afford the desired product. This material was dissolved in DMF (1.50 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (58.7 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$) δ= 8.11 (s,

1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 2.6 Hz, 1H), 7.45 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.03 (s, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 4.63 (s, 1H), 4.25 (dd, *J* = 11.5, 5.0 Hz, 1H), 4.14 (dd, *J* = 11.5, 9.1 Hz, 1H), 4.05 (s, 3H), 3.95 – 3.89 (m, 1H), 3.82 (d, *J* = 13.1 Hz, 1H), 2.93 (td, *J* = 12.8, 2.5 Hz, 1H), 2.39 (s, 3H), 2.32 (d, *J* = 14.3 Hz, 1H), 2.17 – 2.08 (m, 1H), 1.75 (tdd, *J* = 14.1, 4.0, 2.1 Hz, 1H), 1.54 – 1.47 (m, 1H); LCMS analysis using LCMS A, standard conditions: t_r = 4.03 min, LCMS (ES+) [M+H]+: 522.4/524.2.

***Tert*-butyl 2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazine-1-carboxylate (36(+/-)).** To a stirred solution of *tert*-butyl 2-(hydroxymethyl) piperazine-1-carboxylate (**35**) (3 g, 14 mmol) in CH_2Cl_2 (30 mL) under an argon atmosphere were added imidazole (2.1 g, 29 mmol) and TBDMS-chloride (4.05 g, 28 mmol) at 0 ^oC. The reaction mixture was stirred at room temperature for 12 h. After consumption of starting material (by TLC), the reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain *tert*-butyl 2-(((*tert*-butyldimethylsilyl) oxy) methyl) piperazine-1-carboxylate (4 g, 87%) as a colorless syrup used in the next step without further purification. TLC: 50% EtOAc/ Hexane (R_f: 0.1). To a stirred solution of *tert*-butyl 2-(((*tert*-butyldimethylsilyl) oxy) methyl) piperazine-1-carboxylate (3 g, 9 mmol) in toluene (30 mL) under an argon atmosphere were added 1-bromo-4-chloro-2-(trifluoromethyl) benzene (4.7 g, 18 mmol), (±) BINAP (560 mg, 1 mmol), $Pd(OAc)_2$ (203 mg, 1 mmol) and cesium carbonate (8.8 g, 3 mmol) at room temperature and purged under an argon atmosphere for 10 min. The reaction mixture was stirred at 110 ^oC for 12 h in a sealed tube. After consumption of starting material (by TLC), the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography using 10% EtOAc/ Hexane to afford *tert*-butyl 2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazine-1-carboxylate (3.7 g, 80%) as a brown syrup. ^1H NMR (DMSO-d_6, 400 MHz): δ= 7.76-7.69 (m, 2H), 7.64 (d, 1H), 4.08 (br s, 1H), 3.91-3.71

(m, 3H), 3.00-2.93 (m, 3H), 2.84 (d, 1H), 2.74-2.66 (m, 1H), 1.42 (s, 9H), 0.85 (s, 9H), 0.05-0.04 (m, 6H); LCMS analysis using LCMS B, standard conditions: t_r = 4.42 min, LCMS (ES+) [M+H]+: 409 (M-Boc); TLC: 50% EtOAc/ Hexane (R_f: 0.7).

(5-Bromo-6-methoxypyridin-2-yl) (4-(4-chloro-2-(trifluoromethyl) phenyl)-2-(hydroxymethyl) piperazin-1-yl) methanone (37(+/-)). To a stirred solution of *tert*-butyl 2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazine-1-carboxylate **(36(+/-))** (700 mg, 1 mmol) in CH_2Cl_2 (7 mL) under an argon atmosphere was added trifluoroacetic acid (3.5 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 1 h. After consumption of starting material (by TLC), the reaction mixture was diluted with a saturated sodium bicarbonate solution (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 3-(((*tert*-butyldimethylsilyl) oxy) methyl)-1-(4-chloro-2-(trifluoromethyl) phenyl) piperazine (560 mg, 99%) as a colorless syrup which was used in the next step without further purification. LCMS: 409 (M+); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 µm); RT 2.46 min; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B% 0.01/5, 0.5/5, 3/100, 5/100: flow rate: 1.2 mL/min) (Gradient); TLC: 40% EtOAc/ Hexane (R_f: 0.4). To a stirred solution of 5-bromo-6-methoxypicolinic acid (350 mg, 1 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere were added oxalyl chloride (347 mg, 2 mmol) and DMF (catalytic amount) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h. After consumption of acid (by TLC), the volatiles were evaporated *in vacuo* to give 5-bromo-6-methoxypicolinoyl chloride. To a stirred solution of 3-(((*tert*-butyldimethylsilyl) oxy) methyl)-1-(4-chloro-2-(trifluoromethyl) phenyl) piperazine (560 mg, 1 mmol) in CH_2Cl_2 (2 mL) under an argon atmosphere were added diisopropylethylamine (0.73 mL, 4 mmol) and the above acid chloride in CH_2Cl_2 (1.6 mL) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 h. After consumption of acid (by TLC), the reaction mixture was quenched with water (20

mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extract was washed with water (20 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain (5-bromo-6-methoxypyridin-2-yl) (2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) methanone (600 mg, crude) as a pale yellow liquid used in the next step without further purification. LCMS: 623.9 (M+); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 µm); RT 3.98 min; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B% 0.01/5, 0.5/5, 3/100, 5/100: flow rate: 1.2 mL/min) (Gradient); TLC: 50% EtOAc/ Hexanes (R_f: 0.7). To a stirred solution of (5-bromo-6-methoxypyridin-2-yl) (2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) methanone (600 mg, 1 mmol) in CH_2Cl_2 (6 mL) under an argon atmosphere was added tetrabutylammonium fluoride (2 mL, 1 M in THF solution) at room temperature. The reaction mixture was stirred at room temperature for 12 h. After consumption of starting material (by TLC), the reaction mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo.* The crude material was purified by column chromatography using 20% EtOAc/ Hexane to afford (5-bromo-6-methoxypyridin-2-yl) (4-(4-chloro-2-(trifluoromethyl) phenyl)-2-(hydroxymethyl) piperazin-1-yl) methanone (400 mg, 81%) as a white solid. LCMS analysis using LCMS B, standard conditions: t_r = 2.84 min, LCMS (ES+) [M+H]+: 509.8; TLC: 20% EtOAc/ Hexane (R_f: 0.4).

(2-((Aminooxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) (5-bromo-6-methoxypyridin-2-yl) methanone (38(+/-)). To a stirred solution of (5-bromo-6-methoxypyridin-2-yl) (2-(((*tert*-butyldimethylsilyl) oxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) methanone **(37(+/-))** (700 mg, 1 mmol) in dry THF (7 mL) under an argon atmosphere were added molecular sieves (1 g), diisopropylazodicarboxylate (415 mg, 2 mmol), triphenylphosphine (541 mg, 2

mml) and *N*-hydroxypthalimide (269 mg, 1 mmol) at 0 ^{o}C. The reaction mixture was warmed to room temperature and stirred for 2 h. After consumption of starting material (by TLC), the reaction mixture was diluted with water (20 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo.* The crude material was purified by preparative HPLC (YMC Actus Triart C-18 (250 x 20 mm, 5µ (155 mg loading; CH_3CN: 0.05% TFA (0.1/90, 2/80, 10/60, 20/30, 25/10, 35/10)) to afford 2-((1-(5-bromo-6-methoxypicolinoyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-2-yl) methoxy) isoindoline-1, 3-dione (350 mg, 39%) as a white solid. LCMS: 654.6 (M+); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 µm); RT 3.21 min; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B% 0.01/5, 0.5/5, 3/100, 5/100: flow rate: 1.2 mL/min) (Gradient); TLC: 50% EtOAc/ Hexane (R_f: 0.7). To a stirred solution of 2-((1-(5-bromo-6-methoxypicolinoyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-2-yl) methoxy) isoindoline-1, 3-dione (320 mg, 0.49 mmol) in EtOH: THF (2: 1, 7.36 mL) under an argon atmosphere was added hydrazinehydrate (0.48 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h. After consumption of starting material (by TLC), the volatiles were evaporated *in vacuo*. The residue was dissoloved in ether and the obtained solid was filtered. The filtrate was washed with water (30 mL) and extracted with EtOAc (2 x 20 mL). The combined oganic extracts were dried over sodium sulphate, filtered and concentrated *in vacuo* to obtain (2-((aminooxy) methyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) (5-bromo-6-methoxypyridin-2-yl) methanone (300 mg, crude) as a white solid which was used in the next step without further purification. LCMS analysis using LCMS B, standard conditions: t_r = 2.20 min, LCMS (ES+) [M+H]+: 524.7 (M+); TLC: 50% EtOAc/ Hexane (R_f: 0.7).

4-(5-Bromo-6-methoxypyridin-2-yl)-8-(4-chloro-2-(trifluoromethyl) phenyl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine (39(+/-)). To a stirred solution of (2-((aminooxy) me-

thyl)-4-(4-chloro-2-(trifluoromethyl) phenyl) piperazin-1-yl) (5-bromo-6-methoxypyridin-2-yl) methanone **(38(+/-))** (300 mg, 0.56 mmol) in $POCl_3$ (3 mL) under an argon atmosphere was stirred at 120 ^oC for 12 h in a sealed tube. After consumption of starting material (by TLC), the reaction mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to obtain 4-(5-bromo-6-methoxypyridin-2-yl)-8-(4-chloro-2-(trifluoromethyl) phenyl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine (350 mg, crude) as a white solid. LCMS: 506.8 (M+2); (column; Ascentis Express C-18 (50 × 3.0 mm, 2.7 µm); RT 3.15 min; mobile phase: 0.025% Aq TFA+5% ACN: ACN+5% 0.025% Aq TFA; T/B% 0.01/5, 0.5/5, 3/100, 5/100: flow rate: 1.2 mL/min) (Gradient); TLC: 50% EtOAc/ Hexane (R_f: 0.7). To a stirred solution of 4-(5-bromo-6-methoxypyridin-2-yl)-8-(4-chloro-2-(trifluoromethyl) phenyl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine (350 mg, 0.64 mmol) in toluene : EtOH (2: 1, 3 mL) under an argon atmosphere were added triethylamine (0.88 mL, 6.40 mmol) and dimethylaminopyridine (78 mg, 0.64 mmol) at 0 ^oC. The reaction mixture was stirred at 70 ^oC for 1 h. After consumption of starting material (by TLC), the reaction mixture was diluted with saturated sodium bicarbonate solution (20 mL) and extracted with EtOAc (2 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to afford 4-(5-bromo-6-methoxypyridin-2-yl)-8-(4-chloro-2-(trifluoromethyl) phenyl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine (90 mg, 28%) as a white solid. LCMS analysis using LCMS B, standard conditions: t_r = 3.06 min, LCMS (ES+) [M+H]+: 506.8 (M+2); TLC: 50% EtOAc/ Hexane (R_f: 0.7).

8-(4-Chloro-2-(trifluoromethyl) phenyl)-4-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl) pyridin-2-yl)-1, 6, 7, 8, 9, 9a-hexahydropyrazino [1, 2-d] [1, 2, 4] oxadiazine (40(+) and **40(-)).** To a dry vial

was added a suspension of $Pd_2(dba)_3$ (8 mg, 0.008 mmol) and *tert*-butyl tetra methyl X-phos (8.5 mg, 0.02 mmol) in toluene: 1, 4-dioxane (2: 1, 0.67 mL) at room temperature. The suspension was degassed with argon, heated to 120 ^oC, and stirred at 120 ^oC for 3 min. A mixture of 4-(5-bromo-6-methoxypyridin-2-yl)-8-(4-chloro-2-(trifluoromethyl) phenyl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine **(39(+/-))** (90 mg, 0.17 mmol), 4-methyl-1*H*-imidazole (17 mg, 0.21 mmol) and potassium phosphate (76 mg, 0.35 mmol) in toluene: 1, 4-dioxane (2: 1, 0.67 mL) was degassed and the catalyst premix was added. The resulting mixture was stirred at 110 ^oC for 12 h in a sealed tube. After consumption of the starting material (monitored by TLC and LCMS), the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by column chromatography using 5%MeOH/ CH_2Cl_2 to afford 8-(4-chloro-2-(trifluoromethyl) phenyl)-4-(6-methoxy-5-(4-methyl-1*H*-imidazol-1-yl) pyridin-2-yl)-1, 6, 7, 8, 9, 9*a*-hexahydropyrazino [1, 2-*d*] [1, 2, 4] oxadiazine (50 mg, 55%) as a pale yellow thick syrup which was separated using a Chiralpak-ADH column (250 x 20 mm, 5µm) (20 mg loading; 0.1 % DEA in *n*-Hexane: EtOH (A: B: 85: 15) as mobile phase) to afford **40(+),** ^1H NMR (CD_3OD, 400 MHz): δ= 7.99 (s, 1H), 7.89 (d, 1H), 7.68-7.60 (m, 2H), 7.57 (d, 1H), 7.32 (d, 1H), 7.21 (s, 1H), 4.19-4.13 (m, 1H), 4.07 (s, 3H), 4.95-4.80 (m, 2H), 4.75-4.71 (m, 1H), 3.10-2.90 (m, 5H), 2.23 (s, 3H); Mass (ESI): 507.6 [M+1]; HPLC: RT 8.34 min; Chiral HPLC: RT = 15.47 min and **40(-)**, Mass (ESI): 507.7 [M+1]; HPLC: RT 8.34 min; Chiral HPLC: RT = 23.98 min. Analytical conditions for **40(+)** and **40(-)**: HPLC: (column; Eclipse XDB C-18, 150 × 4.6 mm, 5.0 µm); mobile phase: ACN: 0.05% Aq TFA; flow rate: 1.0 mL/min; Gradient programe: T/B% 0.01/90, 2/90, 8/10, 15/10: Diluent: CH_3CN: Water: Chiral HPLC: (Chiralpak-ADH (250 x 4.6 mm, 5µm; mobile phase (A) 0.1 % DEA in *n*-Hexane (B) EtOH (A: B; 85:15); flow Rate: 1.0 mL/min).

(*S*)-*N*-((*R*)-1-(Benzofuran-2-yl)-2-hydroxyethyl)-2-methylpropane-2-sulfinamide (42a): A suspension of benzofuran-2-ylboronic acid (**41a**) (5.0 g, 30.9 mmol, 1.0 equiv), glyoxylic acid monohydrate

(3.16 g, 34.3 mmol, 1.1 equiv) and (*S*)-2-methylpropane-2-sulfinamide (4.16 g, 34.3 mmol, 1.1 equiv) in anhydrous DCM (100 mL) at ambient temperature was treated with $InBr_3$ (1.22 g, 3.43 mmol, 0.11 equiv). The resulting mixture was stirred for 16 h at ambient temperature. To the mixture was added $MgSO_4$ (3 g), the suspension was stirred for 5 minutes and filtered through a pad of celite, which was washed with EtOAc. The filtrate was concentrated under vacuum to afford the corresponding intermediate as an orange solid that was used directly in the next step. LCMS (ES+) [M+H]+: 296.1. A THF (80 mL) solution of crude (*S*)-2-(benzofuran-2-yl)-2-((*S*)-1,1-dimethylethylsulfinamido)acetic acid from the previous reaction was slowly added to a cooled (0 °C) suspension of $LiAlH_4$ (5.86 g, 154 mmol, 5.0 equiv) in THF (120 mL). The resulting mixture was stirred for 1 h at 0 °C before being diluted with Et_2O (300 mL). While maintained at 0 °C the reaction mixture was quenched by sequential addition of water (5.60 mL), sodium hydroxide (2 N, 5.60 mL) and water (16.8 mL). The mixture was allowed to warm to RT, stirred for 1 hour and $MgSO_4$ was added. The mixture was stirred for 10 minutes, and the solids were filtered and rinsed thoroughly with 10% MeOH / DCM (500 mL). The filtrate was concentrated and the residue was purified by normal phase chromatography on silica (0-5% MeOH / DCM) to afford the alcohol as pale yellow oil (1.85 g, 21%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.54 (ddd, J = 7.6, 1.4, 0.7 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.30 – 7.26 (m, 1H), 7.25 – 7.21 (m, 1H), 6.65 (t, J = 0.9 Hz, 1H), 4.69 – 4.64 (m, 1H), 4.14 (dd, J = 11.9, 3.6 Hz, 1H), 3.95 – 3.88 (m, 2H), 1.29 (s, 9H); LCMS (ES+) [M+H]+: 282.0.

(*R*)-2-(Benzofuran-2-yl)-2-(4-methoxybenzylamino)ethanol (43a): (*S*)-*N*-((*R*)-1-(benzofuran-2-yl)-2-hydroxyethyl)-2-methylpropane-2-sulfinamide (**42a**) (1.85 g, 6.58 mmol, 1.0 equiv) was dissolved in a 4 N solution of HCl in 1,4-dioxane (40.0 mL) at ambient temperature. The resulting mixture was stirred at ambient temperature for 30 minutes and concentrated to dryness to afford the desired hydrochloride salt which was used directly in the next step. LCMS (ES+) [M-H_2O]+: 161.0. A solution of crude (*R*)-1-

(benzofuran-2-yl)-2-hydroxyethanaminium chloride from previous step in DCM (40.0 mL) at ambient temperature was treated successively with triethylamine (1.83 mL, 13.2 mmol, 2.0 equiv), $MgSO_4$ (5.6 g) and anisaldehyde (800 µL, 6.58 mmol, 1.0 equiv). The resulting suspension was stirred for 16 hours at ambient temperature and filtered through a pad of celite which was washed with EtOAc. The filtrate was concentrated under vacuum to afford the corresponding imine intermediate. This intermediate was dissolved in MeOH (50.0 mL) and cooled to 0 °C. Solid $NaBH_4$ (730 mg, 19.7 mmol, 3.0 equiv) was added portion wise over 5 minutes. The resulting mixture was stirred for 30 minutes at 0 °C, then quenched by the slow addition of a saturated aqueous solution of $NaHCO_3$. Water and DCM were added. The layers were separated, and the aqueous layer was extracted with DCM twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to afforded a residue that was purified by normal phase chromatography on silica (0-10% MeOH/DCM) to afford the desired amino-alcohol (1.96 g, 68%) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.55 (ddd, J = 7.5, 1.4, 0.7 Hz, 1H), 7.49 – 7.43 (m, 1H), 7.31 – 7.26 (m, 1H), 7.25 – 7.21 (m, 3H), 6.88 – 6.82 (m, 2H), 6.63 – 6.62 (m, 1H), 3.97 (dd, J = 8.4, 4.4 Hz, 1H), 3.89 – 3.73 (m, 6H), 3.70 – 3.61 (m, 1H); LCMS (ES+) [M+H]+: 298.1.

(*R*)-*N*-(1-(Benzofuran-2-yl)-2-hydroxyethyl)-5-bromo-6-methoxy-N-(4-methoxybenzyl) picolinamide (44a): A solution of 5-bromo-6-methoxypicolinic acid (1.08 g, 4.45 mmol, 1.05 equiv) in DCM (40.0 mL) at ambient temperature was treated with a catalytic amount of DMF (4 drops) and oxalyl chloride (1.17 mL, 13.4 mmol, 3.0 equiv). The resulting mixture was stirred at ambient temperature for 1 h at which point LCMS monitoring showed completion of the reaction. The mixture was concentrated, diluted with anhydrous THF (20.0 mL), concentrated again and dried under high vacuum for 1 hour. The residue was diluted in anhydrous THF (20.0 ml), treated with triethylamine (1.86 mL, 13.4 mmol, 3.0 equiv) and cooled to 0 °C. A solution of (*R*)-2-(benzofuran-2-yl)-2-(4-methoxybenzylamino)ethanol (**43a**) (1.32 g, 4.45 mmol, 1.0 equiv) in THF (20.0 ml) was quickly added

and the resulting mixture was stirred at 0 °C for 30 minutes. A saturated aqueous solution of $NaHCO_3$ and EtOAc were then successively added. The layers were separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-40% EtOAc / hexanes) to afford the desired amide as white foam (1.78 g, 78%). LCMS (ES+) [M+H]+: 511.2/513.2.

(*R*)-*N*-(2-(Aminooxy)-1-(benzofuran-2-yl)ethyl)-5-bromo-6-methoxy-N-(4-methoxybenzyl) picolinamide (45a): DIAD (828 uL, 4.18 mmol, 1.2 equiv) was added to a solution of triphenylphosphine (PPh_3) (1.10 g, 4.18 mmol, 1.2 equiv), (*R*)-N-(1-(benzofuran-2-yl)-2-hydroxyethyl)-5-bromo-6-methoxy-N-(4-methoxybenzyl)picolinamide (**44a**) (1.78 g, 3.48 mmol, 1.0 equiv) and *N*-hydroxylphtalimide (681 mg, 4.18 mmol, 1.2 equiv) in THF (20.0 mL) at 0 °C. The resulting mixture was kept at 0 °C for 1 h, then warmed to ambient temperature and stirred for 16 h. EtOAc was added, and the organic layer was washed with 1 N aqueous NaOH (twice), water, and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-40% EtOAc / hexanes) to afford the desired product as beige foam (1.61 g, 71%). LCMS (ES+) [M+H]+: 656.2/658.2. A suspension of (*R*)-*N*-(1-(benzofuran-2-yl)-2-(1,3-dioxoisoindolin-2-yloxy)ethyl)-5-bromo-6-methoxy-*N*-(4-methoxybenzyl)picolinamide (1.61 g, 2.45 mmol, 1.0 equiv) in ethanol (90%, 15.0 mL) and THF (2.25 mL) at ambient temperature was treated with hydrazine hydrate (50-60%, 2.50 mL). The resulting mixture was stirred for 30 minutes, then water was added. The mixture was extracted with EtOAc (three times), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford the desired product (1.24 g, 96%) as off-white foam that was used directly in the next step. LCMS (ES+) [M+H]+: 526.0/528.0.

(*R*)-5-(Benzofuran-2-yl)-3-(5-bromo-6-methoxypyridin-2-yl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (46a): A solution of (*R*)-*N*-(2-(aminooxy)-1-(benzofuran-2-yl)ethyl)-5-bromo-6-methoxy-N-(4-methoxybenzyl)picolinamide (**45a**) (1.24 g, 2.34 mmol, 1.0 equiv) in DCE (20.0 mL) was treated with TFA (1.00 mL). The resulting mixture was stirred at 80 °C for 1 h, then cooled to ambient temperature and concentrated to dryness. The residue was diluted with EtOAc, washed with saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated to afford the desired product (1.21 g, 98%) as pale yellow oil that was used directly in the next step. LCMS (ES+) [M+H]+: 526.1/528.0. A solution of (*S*)-*N*-(2-(benzofuran-2-yl)-2-(4-methoxybenzylamino)ethoxy)-5-bromo-6-methoxypicolinamide (1.20 g, 2.28 mmol, 1.0 equiv) in anhydrous DCE (20.0 ml) at ambient temperature was treated with $POCl_3$ (3.2 mL, 34.3 mmol, 15.0 equiv). The vial was sealed and heated at 115 °C for 6 h. The reaction mixture was evaporated, dried under high vacuum for 10 minutes, dissolved in EtOH (15.0 mL) and treated with DIPEA (2.0 mL, 11.5 mmol, 5.0 equiv) and DMAP (140 mg, 1.15 mmol, 0.5 equiv). The resulting mixture was heated to 115 °C for 16 h. The reaction mixture was cooled to ambient temperature and diluted with EtOAc. The organic layer was washed with 1 N aqueous NaOH, water (twice) and brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by normal phase chromatography on silica (0-30% EtOAc / hexanes) to afford the desired product (442 mg, 38%) as a pale orange foam. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.88 (d, J = 7.8 Hz, 1H), 7.56 (ddd, J = 7.5, 1.4, 0.6 Hz, 1H), 7.46 (dd, J = 8.1, 0.8 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.25 – 7.22 (m, 2H), 7.21 – 7.17 (m, 2H), 6.86 – 6.82 (m, 2H), 6.79 (t, J = 0.8 Hz, 1H), 4.70 (d, J = 15.6 Hz, 1H), 4.62 (t, J = 2.9 Hz, 1H), 4.46 (dd, J = 11.1, 3.1 Hz, 1H), 4.14 (d, J = 15.6 Hz, 1H), 4.04 (dd, J = 11.1, 3.2 Hz, 1H), 3.94 (s, J = 5.3 Hz, 3H), 3.79 (s, 3H); LCMS (ES+) [M+H]+: 508.1/510.0.

(*R*)-5-(Benzofuran-2-yl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-5,6-dihydro-4H-1,2,4-oxadiazine (47): To a vial charged with (*R*)-5-(benzofuran-2-yl)-3-(5-bromo-6-

methoxypyridin-2-yl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (**46a**) (442 mg, 0.87 mmol, 1.0 equiv), 4(5)-methylimidazole (143 mg, 1.74 mmol, 2.0 equiv), and K_3PO_4 (369 mg, 1.74 mmol, 2.0 equiv) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (4.00 mL). To a second vial charged with $Pd_2(dba)_3$ (31.8 mg, 0.035 mmol, 4.0 mol%) and Me_4-di-t-BuXPhos (CAS# 857356-94-6, 33.4 mg, 0.07 mmol, 8.0 mol%) under N_2 atmosphere was added degassed 4:1 PhMe:dioxane solvent mixture (2.00 mL). This mixture was stirred for 3 minutes at 120 °C to give a dark red solution which was cooled to RT and transferred to the first vial. The reaction was degassed by bubbling with N_2 for 5 minutes and then sealed. The reaction mixture was stirred at 120 °C for 16 h. The reaction was cooled to RT and filtered through a pad of celite which was washed thoroughly with EtOAc. The filtrate was concentrated, and the residue was purified by normal phase chromatography on silica (0-5% MeOH / DCM) to afford the desired product (322 mg, 73%) as an off-white solid. LCMS (ES+) [M+H]+: 510.4. A solution of (*R*)-5-(benzofuran-2-yl)-3-(6-methoxy-5-(4-methyl-1H-imidazol-1-yl)pyridin-2-yl)-4-(4-methoxybenzyl)-5,6-dihydro-4H-1,2,4-oxadiazine (320 mg, 0.63 mmol, 1.0 equiv) in DCE (4.00 mL) at ambient temperature was treated with TFA (4.00 mL). The resulting mixture was stirred at 95 °C for 1.5 h in a microwave reactor. The reaction mixture was cooled to RT, concentrated and dissolved in EtOAc. The organic layer was washed with 1 N aqueous NaOH and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by normal phase chromatography on silica (0-10% MeOH / DCM) to afford the desired product (225 mg) as an off-white solid. A portion (100 mg) of this material was dissolved in DMF (1.50 mL) and further purified using reverse phase chromatography on C18 resin (5-100% MeCN / H_2O + 0.1% HCOOH) to give the desired product, after lyophilisation, as a white solid (70.0 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.82 (d, J = 1.3 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.56 (ddd, J = 7.7, 1.3, 0.7 Hz, 1H), 7.48 (dd, J = 8.2, 0.8 Hz, 1H), 7.30 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 7.24 (dd, J = 7.4, 1.0 Hz, 1H), 7.00 – 6.98 (m, 1H), 6.75 (t, J = 0.8 Hz, 1H), 6.70 (d, J = 2.5 Hz, 1H), 5.04 (dt, J = 5.6, 2.9 Hz, 1H), 4.33

(dd, J = 10.9, 3.7 Hz, 1H), 4.21 (dd, J = 11.0, 5.3 Hz, 1H), 4.05 (s, 3H), 2.30 (d, J = 0.9 Hz, 3H); LCMS analysis using LCMS A, standard conditions: t_r = 3.78 min, LCMS (ES+) [M+H]+: 390.3; $[\alpha]_D$ = +435 (c = 0.11, MeOH).

SUPPORTING INFORMATION

Full experimental procedures and characterization of compounds **9**, **11**, **16**, **20-24**, **32**, **33** and **48** as well as biological assay protocols are available free of charge via the Internet at http://pubs.acs.org.

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Notes

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ABBREVIATIONS

AD, Alzheimer's disease; ADMET, Absorption, Distribution, Metabolism, Elimination, and Toxicity; Aβ, amyloid β peptide; amyloid precursor protein intracellular domains; APP, amyloid precursor protein; AUC, area under the curve; BACE1, β-amyloid cleavage enzyme 1; brain to plasma ratio, B:P; cLogP, calculated logarithm of octanol/water partition coefficient; CNS, central nervous system; CSF,

cerebrospinal fluid; CYP, cytochrome P450; Fsp^3, fraction sp^3 character; FAD, familial Alzheimer's disease; GS, γ-secretase; GSM, γ-secretase modulator; hERG, human ether-a-go-go-related gene; LLE, lipophilic ligand efficiency; LELP, ligand efficiency dependent lipophilicity, MPO, multi-parameter optimization; MW, molecular weight; NMDA, N-methyl-D-aspartic acid; NSAID, nonsteroidal anti-inflammatory drug; P-gp, P-glycoprotein; PK, pharmacokinetic; POM, proof-of-mechanism; PS, presenilin; Pen-2, presenilin enhancer protein 2; PSEN, presenilin gene.

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(38) GreenScreen Human Cells [GADD45alpha] (growth arrest and DNA damage gene)-Green Fluorescent Protein (GFP)] assay from Gentronix, conducted at BioReliance Corporation.

Table of Contents Graphic