The Synthesis and SAR Studies of Fused Oxadiazines as Gamma Secretase Modulators For Treatment of Alzheimer's Disease

Xianhai Huang,*[,1] Wei Zhou,[1] Xiaoxiang Liu,[1] Hongmei Li,[1] George Sun,[1] Mihirbaran Mandal,[1] Monica Vicarel,[1] Xiaohong Zhu;[1] Chad Bennett,[1] Troy McCraken,[1] Dmitri Pissarnitski,[1] Zhiqiang Zhao,[1] David Cole,[1] Gioconda Gallo,[1] Zhaoning Zhu,[1] Anandan Palani,[1] Robert Aslanian,[1] John Clader,[1] Michael Czarniecki,[1] William Greenlee,[1] Duane Burnett,[1] Mary Cohen-Williams,[2] Lynn Hyde,[2] Lixin Song,[3] Lili Zhang,[3] Inhou Chu,[4] Alexei Buevich[5]

[1]Department of Medicinal Chemistry; [2]Department of In Vitro Biology; [3]Department of In Vivo Biology; [4]Drug Metabolism; [5]Structual Elucidation, Merck Research Laboratory, 126 E. Lincoln Avenue, Rahway, New Jersey 07065, USA

* Corresponding author. Tel: +1 732 594 4734. E-mail address: xianhai.huang@merck.com

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Analytical methods: All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. ^{1}H NMR spectra were measured on a Varian Oxford 400 or Bruker 500 UltraShield spectrometer. Chemical shifts δ are reported relative to $CDCl_3$ at 7.26 ppm as an internal standard. Normal phase column chromatography was performed on prepacked silica gel columns using ISCO CombiFlash system. Reverse phase column chromatography was performed on Phenomenex Luna 10 μm C18 columns using Alltech 627 HPLC pump or Varian SD-1 HPLC system. Chiral columns were from Chiral Technologies. The purity of final compounds was analyzed on two independent reverse

phase HPLC systems with different gradient. LC−electrospray mass spectrometry with a C-18 column using a gradient of 5−95% MeCN in water as the mobile phase was used to determine the molecular mass and retention time. The purity of the samples was assessed using a mass detector and a UV detector at 254 nm. An additional analytical reverse phase HPLC system was used to assess the purity of final compounds using a UV detector monitored at both 219 and 254 nm and an ELSD detector.

1. Biological assay protocols

***In vitro* assay:**

Cell based assay. Human embryonic kidney (HEK) 293 cells stably transfected with APPsw-lon in pcDNA3.1 vector (Invitrogen) were treated with GSM compounds for 5 hours. Aβ in conditioned media was measured using MesoScale Discovery (MSD) technology based sandwich immunoassays. Aβ42 was measured using a pair of labeled antibodies TAG-G2-11 and biotin-4G8; Aβ40 was measured using antibody pair of TAG-G2-10 and biotin-4G8; total Aβ was measured using TAG-W02 and biotin-4G8.

***In vivo* assay:**

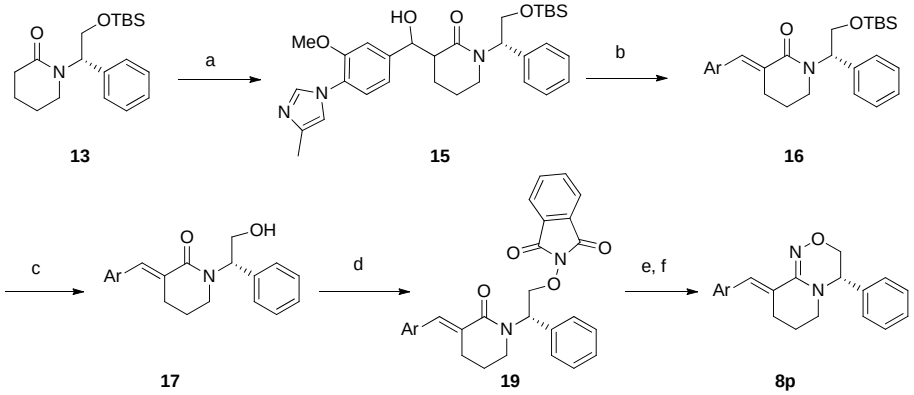
CSF and cortex Aβ assays. Rat CSF Aβ40 and Aβ42 were analyzed using AlphaLISA Amyloid Assay kits (PerkinElmer) according to manufacture's instruction. For brain cortex Ab42 analysis, half cortex was homogenized and extracted in 5 M guanidine-HCl/50 mM Tris-HCl, pH 8. The extracts were sonicated and partially purified using a solid phase extraction matrix in 96-well format, the HLB plate (Waters). The samples eluted from HLB plate were dried and resuspended in freshly prepared PBS/0.5% Tween 20. Aβ40 and Aβ were measured using AlphaLISA amyloid assay kits.

2. Chemistry Experimental Descriptions:

Two synthetic routes were developed to prepare the oxadiazine analogs. In the first route (Scheme 1), lactam **13** was treated with *t*-BuLi at -78 ^{o}C followed by addition of the imidazolophenyl aldehyde **14** to provide alcohol **15**. Alkene **16** was obtained upon dehydration of compound **15** with the Burgess' reagent[22-24] in a highly stereoselective fashion to give the desired *E*-isomer almost exclusively. The primary alcohol in **17** was

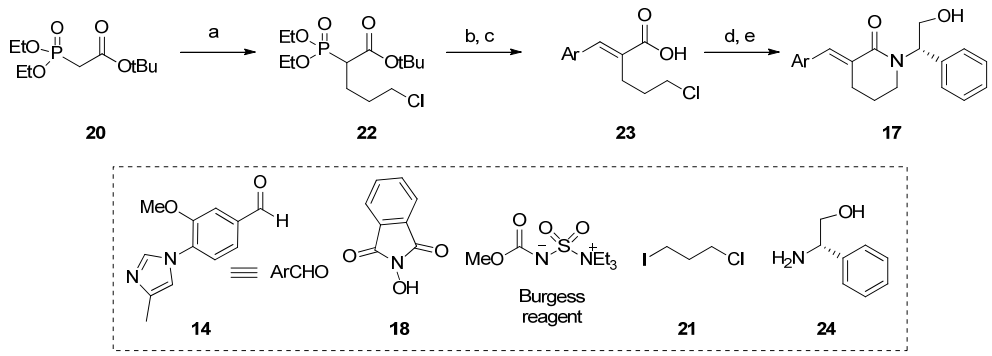
revealed by TBAF deprotection to set the stage for the introduction of N-O functional unit. Thus compound **17** was reacted with *N*-hydroxy phthalimide **18** under Mitsunobu reaction conditions[25] to furnish compound **19**. The phthalimide was deprotected with hydrazine hydrate to give alkoxyamine intermediate which was cyclized to the desired final product **8p** under acidic conditions. In the second route (Scheme 2), commercially available ester **20** was alkylated with iodide **21** under basic conditions to give chloride **22**. A Wittig reaction between **22** and aldehyde **14** proceeded smoothly under mild basic conditions to give an *E*-alkene which was deprotected with TFA to provide acid **23**. Compound **23** was then coupled with corresponding aminoalcohol **24** using EDCI/HOBt and subsequently cyclized in the presence of NaOMe to give primary alcohol **17** which was further converted to the desird oxadiazine as described in the first route (Scheme 1).

Scheme 1. First Synthetic Route Towards Fused Oxadiazine GSMs[a]



[a.] Reagents and conditions: (a). **14**, t-BuLi, THF, -78 ^{o}C, 86%; (b). Burgess reagent, THF, 80 ^{o}C, 76%; (c). TBAF, THF, 96%; (d). **18**, 1,1'-(azodicarbonyl)dipiperidine, PBu_3, THF, 80 ^{o}C, 66%; (e). $NH_2NH_2.xH_2O$, CH_3CN; (f) P_2O_5, EtOH, 80 ^{o}C, 61% over two steps.

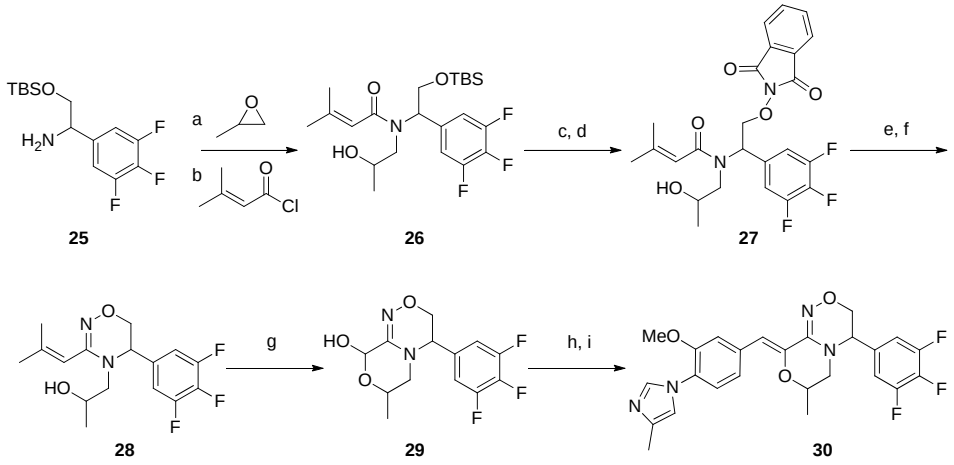
Scheme 2. Second Synthetic Route Towards Fused Oxadiazine GSMs[a]



[a.] Reagents and conditions: (a). **21**, NaH, THF; (b). **14**, LiOH, THF; (c). TFA, 57% over three steps; (d) **24**, EDCI/HOBt, DMF; (e). NaOMe, MeOH, 32% over two steps.

The fused morpholine oxadiazine analogs were prepared in a similar route to the preparation of the fused morpholine oxadiazolines.[20] TBS protected hydroxyamine **25** was reacted with 2-methyloxirane in the presence of $ZrCl_4$ at room temperature to give a secondary amine intermediate which was chemoselectively acylated with 3-methylbut-2-enoyl chloride to provide secondary alcohol **26**. The deprotection of the TBS group under basic conditions with TBAF was not very clean, instead **26** was deprotected cleanly with *in situ* generated HCl from 2-chloropropanoyl chloride in MeOH to give the diol intermediate. A chemoselective Mitsunobu reaction of the primary alcohol with *N*-hydroxyphthalimide gave compound **27**. Phthalimide derivative **27** was treated with hydrazine hydrate to give the alkoxyamine which was cyclized under acidic conditions in the presence of P_2O_5 to give oxadiazine **28**. Alkene **28** was cleaved by ozonolysis with an ozone generator to give hemiacetal **29**. Compound **29** was treated with PPh_3.HBr to generate a phosphonium salt intermediate[26] which was used as the crude product and converted to the desired product **30** upon treatment with NaH and aldehyde **14**. The desired *E*-isomer was isolated as the only major product with only trace amount of the *Z*-isomer observed. The diasteromers were separated with supercritical fluid chromatography (SFC) chiral purification system to give compounds **11** and **12**.

Scheme 3. The Synthesis of Fused Morpholine Oxadiazine GSMs[a]



[a.] Reagents and conditions: (a). $ZrCl_4$, rt, 72%; (b). NEt_3, CH_2Cl_2, 52%; (c). MeCHClCOCl, MeOH, 64%; (d) **18**, 1,1'-(azodicarbonyl)dipiperidine, PBu_3, THF, 80 ^oC, 60%; (e). $NH_2NH_2.xH_2O$, CH_3OH/CH_2Cl_2; (f). P_2O_5, EtOH, 80 ^oC, 72% over 2 steps; (g). O_3, MeOH, CH_2Cl_2, -78 ^oC, 51%; (h). $PPh_3.HBr$, $CH_3CN/ClCH_2CH_2Cl$, 80 ^oC; (i). **14**, LHMDS, THF/DMF, 0 ^oC-rt, 18% over two steps.

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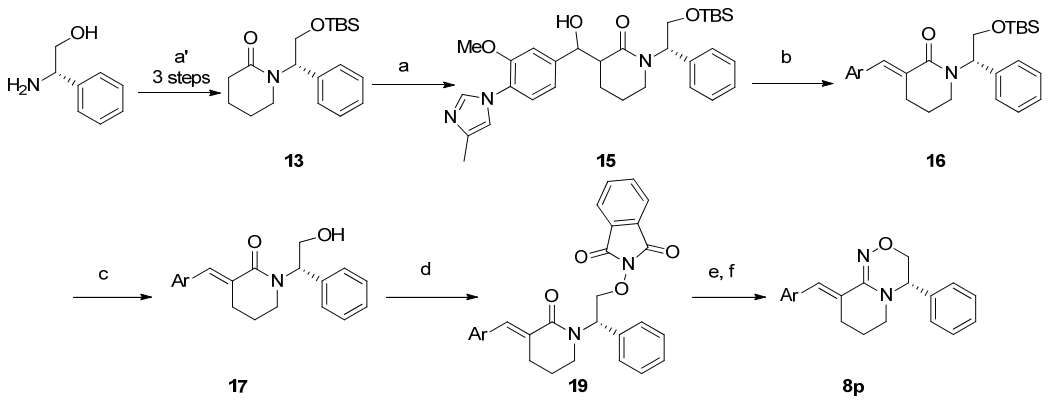
3. Chemistry Experimental Procedures:

General procedure for the preparation of fused oxadiazines (first route):



Step a':

TBSCl (5.6 g) in 10 mL CH_2Cl_2 was added dropwise to (*S*)-phenyl glycinol (5.1 g), NEt_3 (10.4 mL) and DMAP (catalytic amount) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature overnight. The mixture was quenched with addition of aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product. $Cl(CH_2)_4COCl$ (3.37 mL) was added dropwise to a solution of the crude TBS-(S)-phenyl glycinol (6.0 g) and NEt_3 in CH_2Cl_2 (50 mL). The mixture was quenched with addition of aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude chloride product. NaH (1.25 g, 60%) was added to crude chloride obtained above in DMF (50 mL) at room temperature. The mixture was heated at 60 ^oC overnight. The reaction mixture was cooled and diluted with EtOAc and saturated NH_4Cl aqueous solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **13** (5 g).

Step a:

t-BuLi (3.84 mL, 1.7 M in THF) was added to compound **13** (1.5 g) in THF (18 mL) at -78 ^oC. The mixture was stirred for 45 minutes at -78 ^oC before 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (1.24 g) in THF (12 mL) was added in fast drops. The reaction mixture was quenched with EtOAc and saturated NH_4Cl aqueous solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were

washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **15** (2.14 g).

Step b:

Burgess' reagent (43.4 mg) was added to a solution of compound **15** (50 mg) in THF (2.0 mL) at room temperature. The mixture was heated at 80 ^oC for 45 mins. The reaction mixture was quenched with EtOAc and saturated $NaHCO_3$ aqueous solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **16** (37 mg).

Step c:

TBAF (0.18 mL, 1.0 M in THF) was added to a solution of compound **16** (37 mg) in THF (1.5 mL) at room temperature. The mixture was stirred for 1 hour before it was quenched with EtOAc and saturated NH_4Cl aqueous solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **17** (28 mg).

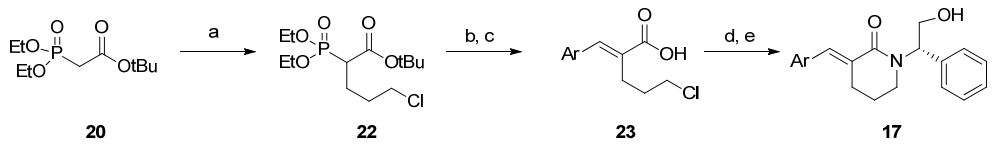
Step d:

Compound **17** (28 mg) in THF (1.0 mL) was treated with N-hydroxyphthalimide (14.1 mg), 1,1'-(azodicarbonyl)dipiperidine (23 m g) and PBu_3 (23 uL) at room temperature. The mixture was heated at 80 ^oC overnight. The mixture was cooled to room temperature and solid was filtered through a short celite pad. The filtrate was taken up in EtOAc and treated with aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **19** (25 mg).

Steps e and f:

Compound **19** (10 mg) in $MeOH/CH_2Cl_2$ (1.0 mL, v/v=1/1) was treated with $NH_2NH_2.xH_2O$ (2.6 uL) at room temperature. The mixture was stirred for 2 hours before it was diluted with CH_2Cl_2 and aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over MgSO4 and concentrated to give crude product which was dissolved in EtOH (1.0 mL) and treated with P_2O_5 (25.2 mg). The resulting mixture was stirred at 80 ^oC over night before it was cooled and concentrated under vacuum. The residue was diluted with EtOAc and NaOH solution (10%). The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **8p** (4.5 mg).

General procedure for the preparation of fused morpholine oxadiazines (second route):



20 **22** **23** **17**

Step a:

Compound **20** (10 g) was added dropwise to a mixture of NaH (1.73 g, 60% in mineral oil) in THF (80 mL) at 0 ^oC. The mixture was stirred for 1.5 hours before 3-chloropropanylbromide (12.5 g) was added. The reaction mixture was heated at 80 ^oC overnight before it was cooled to room temperature and diluted with EtOAc and saturated aqueous NH_4Cl solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was used directly for next step.

Steps b and c:

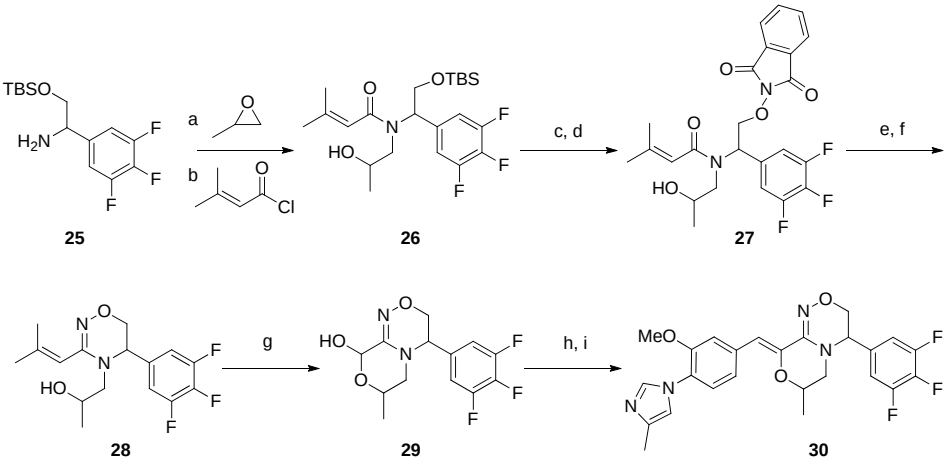
A mixture of compound **20** from previous step, 3-methoxy-4-(4-methyl-1H-imidazol-1-yl)benzaldehyde (7.79 g), and $LiOH.H_2O$ (4.53 g) in THF/EtOH (120 mL, v/v=3/1) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and water. The aqueous layer was extracted with EtOAC (3x). The combined organic layers

were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give tert-butyl ester intermediate (10.5 g). A solution of tert-butyl ester intermediate (10.5 g) in CH_2Cl_2 (40 mL) and TFA (20 mL) was stirred for 2 hours before solvent was removed. Small amount of EtOAc was added to crash out the solid which was collected with filtration to give product **23** as a TFA salt (10.2 g).

Steps d and e:

A mixture of compound **23** (1.5 g, TFA salt), phenyl glycinol (0.59 g), DIPEA (2.1 mL), HOBt (0.94 g) and EDCI (1.33 g) in DMF (15 mL) was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc and washed with water (4x). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated to give crude product hydroxyamide which was taken up in THF (12 mL) and treated with NaOMe in MeOH (1.88 mL, 25% weight). The mixture was stirred at room temperature for 3 hours before it was diluted with EtOAc and NH_4Cl solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **17** (0.46 g) which could be converted to **8p** as described in the first route.

General procedure for the preparation of fused morpholine oxadiazines:



Steps a and b:

A mixture of compound **25** (7g), propanepoxide (16 mL) and $ZrCl_4$ (0.27g) was stirred at room temperature overnight before it was filtered through a celite pad. Solvent was removed and the crude residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give hydroxy amine intermediate. NEt_3 was added to the above obtained hydroxyamine intermediate (6.77 g) in CH_2Cl_2 (150 mL) followed with addition of 3,3-dimethyl propenoyl chloride (2.5 mL) at 0 ^oC. The reaction was quenched in 2 hours with addition of aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **26**.

Step c and d:

MeCHClCOCl (0.26 mL) was added to a solution of compound **26** (2.1 g) in MeOH (15 mL) at room temperature. The reaction was worked up in 3 hours by removing solvent. The crude residue was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give diol intermediate (1.0 g). The diol (3.5 g) in THF (100 mL) was treated with N-hydroxyphthalimide (2.6 g), 1,1'-(azodicarbonyl)dipiperidine (5.33 g) and PBu_3 (5.1 mL) at room temperature. The mixture was heated at 80 ^oC overnight. The mixture was cooled to room temperature and solider was filtered through a short celite pad. The filtrate was taken up in EtOAc and treated with aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **27**.

Steps e and f:

Compound **27** (3.0 g) in MeOH/CH_2Cl_2 (60 mL, v/v=1/1) was treated with $NH_2NH_2.xH_2O$ (1.07 mL) at room temperature. The mixture was stirred for 2 hours before it was diluted with CH_2Cl_2 and aqueous $NaHCO_3$ solution. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine,

dried over MgSO4 and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give alkoxyamine intermediate (1.6 g) which was dissolved in EtOH (100 mL) and treated with P_2O_5 (13.1 g). The resulting mixture was stirred at 80 ^oC over night before it was cooled and concentrated to 20 mL. The residue was diluted with EtOAc and NaOH solution (10%). The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **28** (1.5 g).

Step g:

Compound **28** (1.9 g) in MeOH/CH_2Cl_2 (150 mL, v/v=2/3) was ozonized at -78 ^oC with an ozone generator for 1 hour. After purging away excess of O_3 with O_2, Me_2S (3.3 mL) was added to quench the reaction. Solvent was removed. The residue was diluted with EtOAc and NaOH solution (10%). The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **29** (0.9 g).

Steps h and i:

Compound **29** (0.46 g) in $ClCH_2CH_2Cl$/MeCN (20 mL, v/v=1/1) was treated with PPh_3.HBr (0.73 g) and heated for 5 hours before the solvent was removed. The residue was taken up in THF/DMF (27.5 mL, v/v=10/1) and 3-methoxy-4-(1-(4-methylinidazolyl))benzaldehyde (0.29 g) was added. The mixture was cooled to 0 ^oC and LHDMS (4.5 mL, 1.0 M in THF) was added dropwise. The mixture was stirred at 0 ^oC for 1 hour and then room temperature for 1 hour before aqueous NH_4Cl was added to quench the reaction. The mixture was diluted with EtOAc. The aqueous layer was extracted with EtOAC (3x). The combined organic layers were washed with water, brine, dried over $MgSO_4$ and concentrated to give crude product which was purified by column chromatography on silica gel eluting with EtOAc/hexanes to give compound **30** (0.13 g)

which could be separated by supercritical fluid chromatography system to give pure isomers **11** and **12**.

NMR and LCMS data of final compounds:

4: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.76 (s, 1 H), 7.54 (s, 1 H), 7.42 (dd, *J* = 5.2, 8.7 Hz, 2 H), 7.34 - 7.23 (m, 2 H), 7.19 - 6.92 (m, 4 H), 3.98 - 3.81 (m, 5 H), 3.12 - 2.89 (m, 3 H), 2.78 - 2.67 (m, 1 H), 2.36 (s, 3 H), 1.89 - 1.70 (m, 2 H), 1.82 (s, 3 H). Observed LCMS $[M+H]^+$ = 447.2.

5: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 9.31 (br. s., 1 H), 7.80 (s, 1 H), 7.44 - 7.26 (m, 4 H), 7.24 - 7.07 (m, 3 H), 7.01 (s, 1 H), 4.63 (d, *J* = 12.6 Hz, 1 H), 4.33 (d, *J* = 12.3 Hz, 1 H), 4.22 - 4.06 (m, 2 H), 3.92 (s, 3 H), 3.01 (d, *J* = 18.6 Hz, 2 H), 2.37 (s, 3 H), 2.11 (d, *J* = 2.8 Hz, 2 H), 1.39 - 1.25 (m, 2 H). Observed LCMS $[M+H]^+$ = 463.2.

6: ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.20 (d, *J* = 1.6 Hz, 1 H), 7.69 - 7.58 (m, 2 H), 7.47 - 7.35 (m, 2 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 7.16 - 7.04 (m, 2 H), 6.96 (dd, *J* = 4.7, 8.8 Hz, 1 H), 4.63 (d, *J* = 12.0 Hz, 1 H), 4.45 - 4.33 (m, 1 H), 4.31 - 4.20 (m, 1 H), 4.14 (dd, *J* = 1.6, 12.0 Hz, 1 H), 3.99 (s, 3 H), 3.17 (ddd, *J* = 3.9, 7.9, 12.5 Hz, 1 H), 3.05 - 2.97 (m, 1 H), 2.90 - 2.84 (m, 2 H), 2.43 - 2.32 (m, 5 H), 2.04 - 1.82 (m, 2 H). Observed LCMS $[M+H]^+$ = 475.3.

7a: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (s, 1 H), 7.44 (s, 1 H), 7.32 - 7.18 (m, 1 H), 7.02 - 6.85 (m, 3 H), 4.01 - 3.70 (m, 3 H), 3.83 (s, 3 H), 3.41 (dd, *J* = 8.6, 11.6 Hz, 1 H), 3.31 - 3.09 (m, 3 H), 2.73 (t, *J* = 6.0 Hz, 2 H), 2.29 (s, 3 H), 1.88 (dd, *J* = 6.1, 8.8 Hz, 2 H). Observed LCMS $[M+H]^+$ = 369.2.

7b: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.73 - 7.61 (m, 5 H), 7.47 - 7.32 (m, 7 H), 7.20 (d, *J* = 7.7 Hz, 1 H), 6.98 - 6.86 (m, 3 H), 4.05 - 3.88 (m, 2 H), 3.82 (s, 3 H), 3.86 - 3.71 (m, 1 H), 3.39 (dd, *J* = 7.9, 11.4 Hz, 1 H), 3.30 - 3.09 (m, 3 H), 2.70 (t, *J* = 6.2 Hz, 2 H), 2.29 (s, 3 H), 1.95 - 1.73 (m, 2 H), 1.07 (s, 9 H). Observed LCMS $[M+H]^+$ = 607.3.

7c: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (s, 1 H), 7.43 (s, 1 H), 7.38 - 7.14 (m, 6 H), 7.01 - 6.84 (m, 3 H), 4.69 - 4.55 (m, 2 H), 4.10 - 3.99 (m, 1 H), 3.88 - 3.70 (m, 1 H), 3.82 (s, 1 H), 3.68 - 3.58 (m, 1 H), 3.45 - 3.08 (m, 5 H), 2.70 (m, 2 H), 2.29 (s, 3 H), 1.90 - 1.79 (m, 2 H). Observed LCMS $[M+H]^+$ = 459.2.

7d: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.71 (br. s., 1 H), 7.58 (s, 1 H), 7.39 - 7.21 (m, 4 H), 7.07 - 6.96 (m, 3 H), 6.90 (d, *J* = 8.3 Hz, 1 H), 4.51 (d, *J* = 4.2 Hz, 1 H), 4.34 - 4.14 (m, 2 H), 3.95 - 3.77 (m, 1 H), 3.88 (s, 3 H), 3.66 - 3.39 (m, 3 H), 2.94 - 2.81 (m, 1 H), 2.78 - 2.60 (m, 1 H), 2.45 (s, 3 H), 2.09 (m, 1 H), 1.98 (m, 1 H). Observed LCMS $[M+H]^+$ = 445.2.

7e: ^{1}H NMR (400MHz, CHLOROFORM-d, mixture of diasteromers) δ = 7.68 (br. s., 1 H), 7.41 (br. s., 1 H), 7.31 - 7.12 (m, 1 H), 7.03 - 6.85 (m, 5 H), 6.83 - 6.60 (m, 1 H), 5.02 (d, *J* = 4.4 Hz) and 4.75 (d, *J* = 7.2 Hz) (1 H), 4.13 - 3.70 (m, 2 H), 3.81 (s, 3 H), 3.52 (dd, *J* = 9.3, 11.3 Hz), 3.29 - 2.84 (m) (4 H), 2.77 - 2.52 (m, 2 H), 2.26 (s, 3 H), 1.92 - 1.68 (m, 2 H). Observed LCMS $[M+H]^+$ = 481.2.

7f: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.69 (br. s., 1 H), 7.60 (s, 1 H), 7.40 - 7.17 (m, 6 H), 7.14 - 6.99 (m, 3 H), 4.33 (d, *J* = 6.8 Hz, 1 H), 3.87 (s, 3 H), 3.56 - 3.15 (m, 5 H), 2.99 - 2.79 (m, 2 H), 2.64 (t, *J* = 10.9 Hz, 1 H), 2.45 (s, 3 H), 2.04 (m, 1 H), 1.94 (m, 1 H). Observed LCMS $[M+H]^+$ = 429.2.

7g: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.18 (br. s., 1 H), 7.47 (s, 1 H), 7.42 - 7.31 (m, 5 H), 7.25 (d, *J* = 7.7 Hz, 1 H), 7.04 - 6.90 (m, 4 H), 4.74 (dd, *J* = 2.4, 9.2 Hz, 1 H), 3.85 (s, 3 H), 3.55 (dd, *J* = 9.4, 11.7 Hz, 1 H), 3.39 - 3.27 (m, 2 H), 3.18 (m, 1 H), 2.74 (m, 2 H), 2.35 (s, 3 H), 1.92 (m, 2 H). Observed LCMS $[M+H]^+$ = 415.2.

7h: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.14 (d, *J* = 8.3 Hz, 1 H), 7.94 - 7.80 (m, 2 H), 7.74 - 7.45 (m, 6 H), 7.31 - 7.19 (d, 1 H), 7.05 - 6.89 (m, 3 H), 5.49 (dd, *J* = 2.6, 9.2 Hz, 1 H), 3.85 (s, 3 H), 3.72 (dd, *J* = 9.3, 11.8 Hz, 1 H), 3.59 - 3.44 (dd, 1 H), 3.39 - 3.17 (m, 2 H), 2.90 - 2.68 (m, 2 H), 2.30 (s, 3 H), 2.02 - 1.83 (m, 2 H). Observed LCMS $[M+H]^+$ = 465.3.

7i: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.73 (d, *J* = 0.9 Hz, 1 H), 7.48 (s, 1 H), 7.21 (d, 1 H), 7.09 - 6.89 (m, 5 H), 4.71 (dd, *J* = 3.1, 8.4 Hz, 1 H), 3.84 (s, 3 H), 3.40 (dd, 2 H), 3.30 (m, 1 H), 3.20 (m, 1 H), 2.86 - 2.59 (m, 2 H), 2.30 (s, 3 H), 1.94 - 1.76 (m, 2 H). Observed LCMS $[M+H]^+$ = 469.3.

7j: ^{1}H NMR (400MHz, METHANOL-d$_4$) δ = 8.83 (s, 1 H), 8.69 - 8.51 (m, 2 H), 7.80 (s, 1 H), 7.41 - 7.21 (m, 2 H), 7.19 - 6.90 (m, 3 H), 5.09 (dd, *J* = 2.9, 6.6 Hz, 1 H), 3.88 (s, 3 H), 3.81 (m, 1 H), 3.71 (m, 1), 3.30 (m, 2 H), 2.75 (t, *J* = 5.9 Hz, 2 H), 2.23 (s, 3 H), 2.02 - 1.76 (m, 2 H). Observed LCMS $[M+H]^+$ = 417.2.

7k: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.67 (br. s., 1 H), 7.52 - 7.23 (m, 3 H), 7.18 - 6.87 (m, 5 H), 5.42 (br. s., 1 H), 4.21 (d, *J* = 10.6 Hz, 1 H), 4.03 (s, 3 H), 3.98 (m, 2 H), 3.87 (s, 3 H), 3.62 (br. s., 1 H), 3.35 (m, 1 H), 2.70 - 2.63 (m, 1 H), 2.46 (s, 3 H), 2.09 - 1.80 (m, 2 H). Observed LCMS $[M+H]^+$ = 419.2.

7l: ^{1}H NMR (400MHz, METHANOL-d$_4$) δ = 9.23 - 9.04 (m, 1 H), 7.65 - 7.52 (m, 2 H), 7.37 - 7.16 (m, 2 H), 7.14 - 6.92 (m, 4 H), 5.53 (s, 1 H), 3.94 (s, 3 H), 3.84 (m, 1 H), 3.35 (m, 2 H), 2.87 (dt, *J* = 1.9, 6.5 Hz, 1 H), 2.43 (s, 3 H), 2.02 - 1.81 (m, 2 H). Observed LCMS $[M+H]^+$ = 465.2.

8a: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (d, *J* = 1.1 Hz, 1 H), 7.42 (s, 1 H), 7.18 (d, 1 H), 6.97 - 6.85 (m, 3 H), 4.07 (t, *J* = 4.7 Hz, 2 H), 3.81 (s, 3 H), 3.37 (t, *J* = 4.8 Hz, 2 H), 3.19 (t, *J* = 6.0 Hz, 2 H), 2.70 (dt, *J* = 1.5, 6.2 Hz, 2 H), 2.28 (s, 3 H), 1.86 (quin, *J* = 6.1 Hz, 2 H). Observed LCMS $[M+H]^+$ = 339.2.

8b: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.73 (s, 1 H), 7.53 (s, 1 H), 7.34 - 7.18 (m, 2 H), 7.09 - 6.85 (m, 3 H), 4.41 (s, 2 H), 3.86 (s, 3 H), 3.80 (m, 2 H), 2.92 - 2.71 (m, 2 H), 2.30 (s, 3 H), 1.92 (quin, *J* = 6.2 Hz, 2 H). Observed LCMS $[M+H]^+$ = 353.2. **8c:** Observed LCMS $[M+H]^+$ = 381.2.

8d: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 8.68 (d, *J* = 1.3 Hz, 1 H), 7.58 (s, 1 H), 7.0 (d, 1 H), 7.17 - 6.98 (m, 3 H), 4.25 (d, *J* = 11.4 Hz, 1 H), 3.97 (d, *J* = 11.2 Hz, 1 H), 3.88 (s, 3 H), 3.63 - 3.50 (m, 1 H), 3.44 - 3.26 (m, 2 H), 2.86 - 2.65 (m, 2 H), 2.47 (d, *J* = 0.6 Hz, 3 H), 2.11 - 1.89 (m, 2 H), 1.87 - 1.63 (m, 2 H), 1.60 - 1.42 (m, 1 H), 1.00 (dd, *J* = 6.4, 15.2 Hz, 6 H). Observed LCMS $[M+H]^+$ = 395.2.

8e: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (s, 1 H), 7.29 (s, 1 H), 7.20 (d, 1 H), 6.98 (s, 1 H), 6.96 (s, 1 H), 6.92 (s, 1 H), 4.43 (d, *J* = 11.4 Hz, 1 H), 3.83 (s, 3 H), 3.55 - 3.44 (m, 1 H), 3.31 (m, 1 H), 3.27 (m, 1 H), 2.92 - 2.79 (m, 1 H), 2.77 - 2.63 (m, 2 H), 2.29 (s, 3 H), 2.08 - 1.91 (m, 1 H), 1.90 - 1.63 (m, 1 H), 1.10 - 0.92 (m, 9 H). Observed LCMS $[M+H]^+$ = 395.2.

8f: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.75 (s, 1 H), 7.44 (s, 1 H), 7.26 (d, 1 H), 7.09 - 6.93 (m, 3 H), 4.34 (d, *J* = 11.0 Hz, 1 H), 4.08 (m, 2 H), 3.88 (s, 3 H), 3.62 (dd, *J* = 2.7, 11.2 Hz, 1 H), 3.51 - 3.39 (m, 2 H), 3.34 (dd, *J* = 5.4, 11.3 Hz, 1 H), 3.21 (ddd, *J* = 4.1, 8.0, 11.8 Hz, 1 H), 2.94 (m, 1 H), 2.85 (m, 1 H), 2.73 (m, 1 H), 2.35 (s, 3 H), 2.12 - 1.84 (m, 2 H), 1.81 - 1.67 (m, 2 H), 1.64 - 1.41 (m, 2 H). Observed LCMS $[M+H]^+$ = 423.2.

8g: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.82 (s, 1 H), 7.54 (br. s., 1 H), 7.32 (d, 1 H), 7.15 - 6.99 (m, 3 H), 4.45 (d, *J* = 11.2 Hz, 1 H), 4.03 (m, 1 H), 3.95 (s, 3 H), 3.66 - 3.50 (m, 2 H), 3.44 (br. s., 1 H), 3.37 - 3.24 (m, 1 H), 3.02 - 2.70 (m, 2 H), 2.41 (s, 3 H), 2.02 (t, *J* = 5.6 Hz, 2 H), 1.46 - 1.28 (m, 2 H). Observed LCMS $[M+H]^+$ = 369.2.

8h: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.79 (s, 1 H), 7.52 (s, 1 H), 7.50 - 7.36 (m, 5 H), 7.35 (d, 1 H), 7.10 - 6.97 (m, 3 H), 4.74 - 4.58 (m, 2 H), 4.38 (d, *J* = 11.2 Hz, 1 H), 3.92 (s, 3 H), 3.85 - 3.71 (m, 3 H), 3.61 - 3.46 (m, 2 H), 3.26 (td, *J* = 5.8, 11.6 Hz, 1 H), 2.95 - 2.68 (m, 2 H), 2.39 (s, 3 H), 1.95 (t, *J* = 5.9 Hz, 2 H). Observed LCMS $[M+H]^+$ = 459.2.

8i: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.49 - 7.32 (m, 5 H), 7.21 (d, 2 H), 7.04 - 6.89 (m, 3 H), 4.99 (d, *J* = 6.8 Hz, 1 H), 4.05 (d, J = 11.4 Hz, 1 H), 3.84 (s, 3 H), 3.57 (dd, *J* = 2.4, 11.4 Hz, 1 H), 3.39 - 3.24 (m, 2 H), 3.10 (ddd, *J* = 4.0, 8.2, 11.8 Hz, 1 H), 2.81 (m, 1 H), 2.70 (m, 1 H) , 2.31 (s, 3 H), 1.91 - 1.72 (m, 2 H). Observed LCMS $[M+H]^+$ = 479.3.

8j: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.68 (d, *J* = 1.1 Hz, 1 H), 7.45 (s, 1 H), 7.36 - 7.14 (m, 6 H), 7.02 - 6.80 (m, 3 H), 4.05 (d, *J* = 11.2 Hz, 1 H), 3.81 (s, 3 H), 3.60 (dd, *J* = 2.0, 11.0 Hz, 1 H), 3.32 (t, *J* = 6.6 Hz, 1 H), 3.20 - 2.83 (m, 4 H), 2.78 - 2.60 (m, 2 H), 2.28 (s, 3 H), 1.80 (m, 2 H). Observed LCMS $[M+H]^+$ = 429.2.

8k: ^{1}H NMR (400MHz, METHANOL-d$_4$) δ = 9.09 (d, *J* = 1.1 Hz, 1 H), 7.53 (s, 1 H), 7.43 (d, *J* = 8.1 Hz, 1 H), 7.24 - 7.09 (m, 2 H), 7.01 (d, *J* = 8.4 Hz, 1 H), 6.19 (t, *J* = 4.2 Hz, 1 H), 4.21 (d, *J* = 11.4 Hz, 1 H), 3.90 (s, 3 H), 3.86 - 3.80 (m, 1 H), 3.72 - 3.59 (m, 4 H), 3.37 (d, *J* = 6.6 Hz, 2 H), 2.78 (q, *J* = 7.6 Hz, 2 H), 2.42 (s, 3 H), 2.35 - 2.24 (m, 2 H), 1.28 (t, *J* = 7.7 Hz, 3 H). Observed LCMS $[M+H]^+$ =464.3.

8l: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.70 (s, 1 H), 7.40 (s, 1 H), 7.31 - 7.16 (d, 1 H), 7.02 - 6.83 (m, 3 H), 4.35 (d, *J* = 11.4 Hz, 1 H), 4.01 - 3.91 (m, 1 H), 3.82 (s, 3 H), 3.79 (m, 1 H), 3.55 - 3.39 (m, 2 H), 3.32 (dd, *J* = 4.4, 13.9 Hz, 1 H), 3.18 (td, *J* = 6.1, 11.6 Hz, 1 H), 3.01 (s, 3 H), 2.79 - 2.63 (m, 2 H), 2.28 (s, 3 H), 1.88 (quin, *J* = 6.1 Hz, 2 H). Observed LCMS $[M+H]^+$ = 431.2. **8m:** Observed LCMS $[M+H]^+$ = 506.3.

8n: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.76 (d, *J* = 0.9 Hz, 1 H), 7.43 (s, 1 H), 7.20 (d, 1 H), 7.04 - 6.84 (m, 3 H), 4.31 (d, *J* = 10.8 Hz, 1 H), 3.82 (s, 3 H), 3.71 - 3.59 (m, 5 H), 3.45 (td, *J* = 5.5, 11.4 Hz, 1 H), 3.26 (m, 1 H), 3.19 - 3.06 (m, 1 H), 2.85 - 2.65 (m, 3 H), 2.61 (s, 3H), 2.53 (m, 5 H), 1.96 - 1.71 (m, 2 H). Observed LCMS $[M+H]^+$ = 438.2.

8o: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.67 (s, 1 H), 7.41 (s, 1 H), 7.19 (d, *J* = 7.7 Hz, 1 H), 7.00 - 6.85 (m, 3 H), 4.13 (d, *J* = 11.0 Hz, 1 H), 3.90 - 3.82 (m, 1 H), 3.80 (s, 3 H), 3.76 (d, J = 11.0 Hz, 1 H), 3.64 - 3.26 (m, 5 H), 3.20 - 3.02 (m, 1 H), 2.83 (dd, *J* = 8.8, 15.7 Hz, 1 H), 2.74 - 2.65 (m, 2 H), 2.57 (dd, *J* = 3.7, 15.7 Hz, 1 H), 2.27 (s, 3 H), 1.91 - 1.76 (m, 2 H), 1.63 (m, 2 H), 1.60 - 1.44 (m, 4 H). Observed LCMS $[M+H]^+$ = 464.3.

8p: ^{1}H NMR (500MHz, METHANOL-d$_4$) δ = 9.22 (s, 1 H), 7.72 - 7.60 (dd, 2 H), 7.58 - 7.38 (m, 7 H), 7.37 - 7.22 (m, 1 H), 4.51 - 4.36 (m, 2 H), 4.01 (s, 3 H), 3.54 (m, 1 H), 3.46 (m, 1 H), 3.01 (m, 1 H), 2.93 (m, 1 H), 2.47 (s, 3 H), 2.09 (m, 1 H), 1.96 (m, 1 H). Observed LCMS $[M+H]^+$ = 415.2.

8q: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.76 (s, 1 H), 7.58 (s, 1 H), 7.37 (t, J = 8.5 Hz, 2 H), 7.28 (d, 1 H), 7.13 (t, *J* = 8.5 Hz, 2 H), 7.03 (m, 2 H), 6.98 (s, 1 H), 4.40 (t, *J* = 3.2 Hz, 1 H), 4.16 (d, 1 H), 4.06 (d, 1 H), 3.90 (s, 3 H), 3.19 (m, 1 H), 3.10 (m, 1 H), 2.86 (m, 1 H), 2.79 (m, 1 H), 2.36 (s, 3 H), 1.91 (m, 1 H), 1.84 (m, 1 H). Observed LCMS $[M+H]^+$ = 433.2.

8r: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.77 (s, 1 H), 7.59 (s, 1 H), 7.34 (m, 1 H), 7.19 (s, 1 H), 7.14 (d, 1 H), 7.05 (m, 3 H), 6.99 (s, 1 H), 4.37 (br. s., 1 H), 4.20 - 4.02 (m, 2 H), 3.91 (s, 3 H), 3.23 (m, 1 H), 3.14 (m, 1 H), 2.89 (m, 1 H), 2.79 (m, 1 H), 2.36 (s, 3 H), 2.01 - 1.81 (m, 2 H). Observed LCMS $[M+H]^+$ = 467.3.

8s: ^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.69 (s, 1 H), 7.51 (s, 1 H), 7.22 (d, 1 H), 6.96 (m, 4 H), 6.91 (s, 1 H), 4.25 (t, *J* = 2.6 Hz, 1 H), 4.02 (d, *J* = 2.8 Hz, 2 H), 3.83 (s, 3 H), 3.17 - 2.99 (m, 2 H), 2.82 (m, 1 H), 2.73 (m, 1 H), 2.28 (s, 3 H), 1.95 - 1.78 (m, 2 H). Observed LCMS $[M+H]^+$ = 469.3.

8t: ^{1}H NMR (500MHz, METHANOL-d4) δ = 9.20 (d, *J* = 1.6 Hz, 1 H), 7.69 - 7.59 (m, 2 H), 7.51 (s, 1 H), 7.38 (s, 1 H), 7.28 (d, *J* = 8.2 Hz, 1 H), 7.10 (d, *J* = 8.8 Hz, 2 H), 4.74 (br. s., 1 H), 4.33 (dd, 1 H), 4.26 (dd, 1 H), 4.01 (s, 3 H), 4.00 (s, 3 H), 3.52 - 3.37 (m, 2 H), 2.98 (m, 1 H), 2.89 (m, 1 H), 2.46 (s, 3 H), 2.06 (m, 1 H), 1.93 (m, 1 H). . Observed LCMS $[M+H]^+$ = 481.3.

9: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.77 (s, 1 H), 7.54 (s, 1 H), 7.36 (d, 1 H), 7.25 (d, 1 H), 7.04 - 6.79 (m, 3 H), 6.87 (m, 1 H), 6.69 (s, 1 H), 4.42 (br. s, 1 H), 4.38 (m, 1 H), 4.16 (dd, 1 H), 4.06 (dd, 1 H), 3.82 (s, 3 H), 3.32 (t, *J* = 11.0 Hz, 1 H), 3.15 (dd, *J* = 2.5, 12.0 Hz, 1 H), 2.35 (s, 3 H), 1.49 (d, *J* = 6.3 Hz, 3 H). Observed LCMS $[M+H]^+$ = 467.3.

10: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.77 (br. s., 1 H), 7.54 (br. s., 1 H), 7.36 (d, 1 H), 7.24 (d, 1 H), 6.98 (s, 1 H), 6.91 (m, 3 H), 6.66 (d, *J* = 2.5 Hz, 1 H), 4.49 (m, 2 H), 4.22 (d, 1 H), 4.10 (dd, 1 H), 3.90 (s, 3 H), 3.31 (m, 1 H), 3.06 (d, *J* = 12.6 Hz, 1 H), 2.35 (s, 3 H), 1.48 (d, *J* = 6.3, 3 H). Observed LCMS $[M+H]^+$ = 467.3.

11: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.74 (s, 1 H), 7.51 (s, 1 H), 7.32 (d, *J* = 8.2 Hz, 1), 7.22 (d, *J* = 8.2 Hz, 1 H), 7.05 (t, *J* = 6.9 Hz, 2 H), 6.96 (s, 1 H), 6.66 (s, 1 H), 4.39 - 4.24 (m, 2 H), 4.10 (dd, 1 H), 3.99 (dd, *J* = 3.2, 11.3 Hz, 1 H), 3.87 (s, 3 H), 3.29 (dd, 1 H), 3.09 (dd, *J* = 2.5, 12.0 Hz, 1 H), 2.32 (s, 3 H), 1.46 (d, *J* = 6.3 Hz, 3 H). Observed LCMS $[M+H]^+$ = 485.3.

12: ^{1}H NMR (500MHz, CHLOROFORM-d) δ = 7.73 (s, 1 H), 7.50 (s, 1 H), 7.31 (d, 1 H), 7.20 (d, 1 H), 6.98 (m, 2 H), 6.94 (s, 1 H), 6.61 (s, 1 H), 4.46 (m, 1 H), 4.40 (br. s, 1 H), 4.15 (dd, 1 H), 4.05 (dd, 1 H), 3.86 (s, 3 H), 3.25 (dd, *J* = 9.9, 12.1 Hz, 1 H), 3.02 (dd, *J* = 2.2, 12.3 Hz, 1 H), 2.31 (s, 3 H), 1.44 (d, *J* = 6.0 Hz, 3 H). Observed LCMS $[M+H]^+$ = 485.3.