Supporting information

Quinazolinone derivatives as orally available ghrelin receptor antagonists for the treatment of diabetes and obesity

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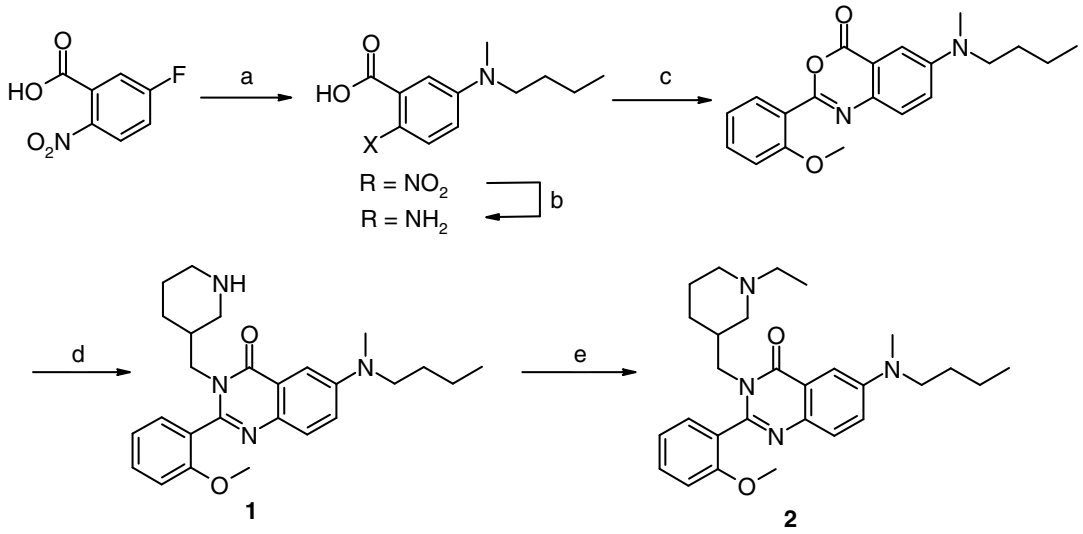
Synthetic procedures for the preparation of compounds 1 and 2 [a]



[a] Reagents and conditions: (a) *N*-methylbutylamine (2 eq.), Cs_2CO_3, DMF, 50 ^{0}C, 97%; (b) H_2, 10% Pd/C, EtOH, 86%; (c) o-anisoylchloride, Et_3N, CH_2Cl_2, 31%; (d) *tert*-butyl 3-aminomethyl)piperidine-1-carboxylate (2 eq.), $CHCl_3$, reflux; 1,2-ethanediol, NaOH, 130 ^{0}C; TFA, CH_2Cl_2, 23%; (e) CH_3CHO, CH_3COOH, 60 ^{0}C; CH_3CHO, $NaBH_3CN$, 11%.

Step 1. Preparation of 5-[butyl(methyl)amino]-2-nitrobenzoic acid. To a solution of 5-fluoro-2-nitrobenzoic acid (25.0 g, 135.1 mmol) and *N*-methylbutylamine (27.9 g, 310.6 mmol) in DMF (150 mL) was added cesium carbonate (92.41 g, 283.6 mmol), and the reaction mixture was stirred at 50 °C for 15 h. Water (500 mL) was added, and the mixture was extracted with ethyl acetate (3 x 300 mL). The combined extracts were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure to give the product as a light yellow solid (33.1 g, 97%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.01 (d, 1H), 6.77 (dd, 1H), 6.69 (dd, 1H), 3.28 (t, 2H), 3.09 (s, 3H), 1.57-1.67 (m, 2H), 1.31-1.48 (m, 2H), 0.98 (t, 3H); LC-MS method 2: *m/z* 252.9 (MH^+); RT (min) 2.77.

Step 2. Preparation of 2-amino-5-[butyl(methyl)amino]benzoic acid. A mixture of 2-nitro-5-[butyl(methyl)amino]benzoic acid (33.0 g, 130.8 mmol), 10% palladium on carbon (696.1 mg, 0.654 mmol), and ethanol (330 mL) was hydrogenated using a Parr

apparatus at 60 PSI for 4 h. The mixture was filtered through a pad of celite and concentrated under reduced pressure to afford 25.1 g (86%) of the product as a yellow solid. ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (dd, 1H), 7.45 (dd, 1H), 6.93 (d 1H), 3.49 (t, 2H), 3.22 (s, 3H), 1.28-1.58 (m, 4H), 0.92 (t, 3H); ES-MS *m/z* 223.1 (MH^+); HPLC RT (min) 0.29.

Step 3. Preparation of 6-[butyl(methyl)amino]-2-(2-methoxyphenyl)-4H-3,1-benzoxazin-4-one. A solution of 2-amino-5-[butyl(methyl)amino]benzoic acid (1.88 g, 8.46 mmol) and Et_3N (2.57 g, 25.37 mmol) in CH_2Cl_2 (20 mL) was cooled in an ice bath, and o-anisoyl chloride (1.73 g, 10.15 mmol) was added. The reaction mixture was stirred at 40 °C for 17 h. CH_2Cl_2 (20 mL) was added, and the solution was washed with ice-cold water, saturated aq Na_2CO_3 (3 x 10 mL), 1 N NaOH (3 x 10 mL), and brine (10 mL). The organic layer was concentrated under reduced pressure to give a dark green oily solid. This material was purified by silica gel flash chromatography (Biotage), eluting with a 20% EtOAc/hexane solvent system. Concentration of the product fractions under reduced pressure gave 0.9 g (31%) of the product as a yellow solid. ^{1}H NMR (300 MHz, CD_2Cl_2) δ 7.79 (d, 1H), 7.47-7.55 (m, 2H), 7.33 (d 1H), 7.22 (dd, 1H), 7.04-7.10 (m, 2H), 3.94 (s, 3H), 3.25 (t, 2H), 3.08 (s, 3H), 1.55-1.69 (m, 2H), 1.33-1.47 (m, 2H), 0.99 (t, 3H); LC-MS method 2: *m/z* 339.2 (MH^+); RT (min) 4.07.

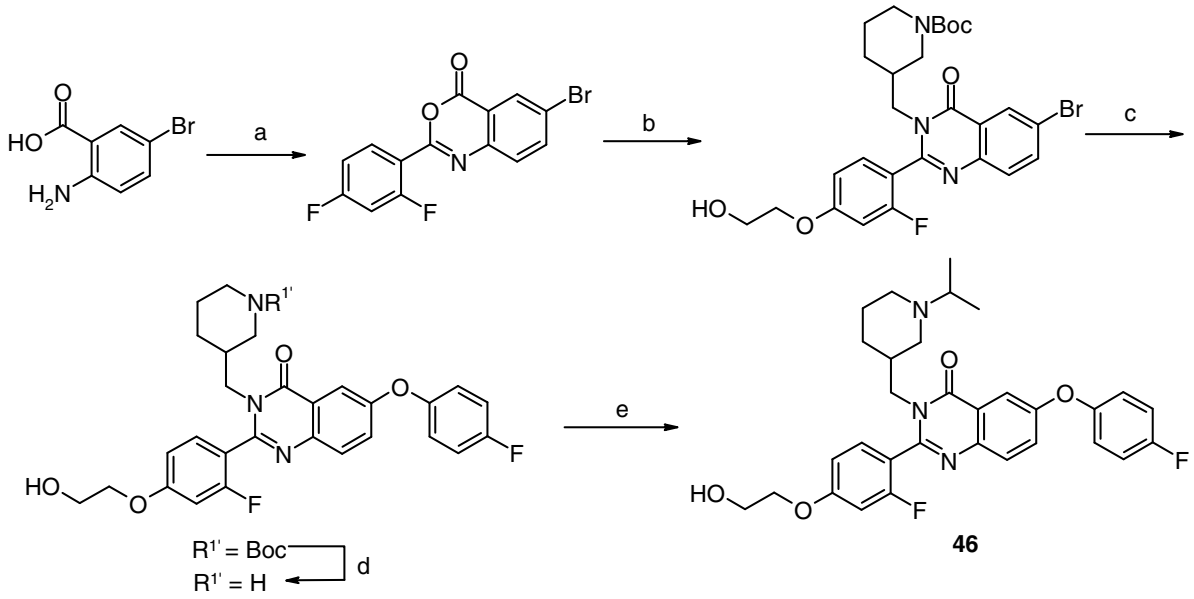
Step 4. Preparation of 6-[butyl(methyl)amino]-2-(2-methoxyphenyl)-3-(piperidin-3-ylmethyl)quinazolin-4(3H)-one trifluoroacetate (1). A solution of 6-[butyl(methyl)amino]-2-(2-methoxyphenyl)-4H-3,1-benzoxazin-4-one (200 mg, 0.59 mmol) (step 3) and *tert*-butyl 3-(aminomethyl)piperidine-1-carboxylate (152.0 mg, 0.71 mmol) in $CHCl_3$ (70 mL) was stirred at reflux for 2.5 d. *tert*-Butyl 3-(aminomethyl)

piperidine-1-carboxylate (50 mg, 0.51 mmol) was added, and the mixture was heated under reflux for 10 h to form the uncyclized intermediate. 1,2-Ethanediol (2 mL) and NaOH (5.5 mg, 0.14 mmol) were added, chloroform was removed in vacuo, and the resulting mixture was stirred at 130 °C for 3 h. More NaOH (15 mg, 0.38 mmol) was added, and the resulting mixture was stirred at 130 °C for 15 h. To remove the BOC protecting group from the cyclized material, CH_2Cl_2 (2 mL) was added, followed by TFA (1.35 g, 11.8 mmol). The mixture was stirred at rt for 3 h. The volatile solvents were removed, MeOH (2 mL) was added, and the mixture was purified on a Gilson HPLC reversed-phase system eluting with the gradient 2-60% MeCN/water (containing 0.1 % TFA) to afford 78 mg (23%) of the product as a clear, colorless oil. ^{1}H NMR (300 MHz, CD_3OD) δ 7.71 (d, 1H), 8.18 (dd, 1H), 7.86-7.87 (m, 1H), 7.67 (dd, 1H), 7.53-7.61 (m, 1H), 7.20 (d, 1H), 7.05-7.12 (m, 1H), 4.11 (s, 3H), 3.56-3.64 (m, 2H), 3.33-3.51 (m, 4H), 3.28 (s, 3H), 2.85-2.97 (m, 1H), 2.73-2.84 (m, 1H), 2.06-2.22 (br m, 1H), 1.87-2.04 (m, 2H), 1.65-1.83 (m, 1H), 1.46-1.60 (m, 2H), 1.29-1.45 (m, 3H), 0.93 (t, 3H); LC-MS method 2: *m/z* 435.3 (MH^+); RT (min) 2.76.

6-[Butyl(methyl)amino]-3-[(1-ethylpiperidin-3-yl)methyl]-2-(2-methoxyphenyl)quinazolin-(3H)-one trifluoroacetate (2). A mixture of 6-[butyl(methyl)amino]-2-(2-methoxyphenyl)-3-(piperidin-3-ylmethyl) quinazolin-4(3H)-one (23.0 mg, 0.05 mmol) (**1**), acetaldehyde (4.7 mg, 0.11 mmol), acetic acid (11.4 mg, 0.19 mmol), and methanol (0.7 mL) was stirred at 60 °C for 2 h. The reaction mixture was cooled to rt, and acetaldehyde (4.7 mg, 0.11 mmol) was added, followed by $NaBH_3CN$ (4.0 mg, 0.06 mmol), and the mixture was stirred at rt for 15 h. The solvent

was removed, and the crude mixture was purified on a Gilson reversed-phase HPLC system eluting with the gradient 2-60% MeCN/water (containing 0.1 % TFA) to afford 3 mg (11%) of the product as a clear, light yellow oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.62-7.71 (m, 1H), 7.53-7.61 (m, 2H), 7.40-7.45 (m, 2H), 7.18-7.32 (m, 2H), 4.32 (dd, 0.6 H), 4.15 (dd, 0.4H), 3.91 (s, 3H), 3.85 (dd, 0.4H), 3.53 (dd, 0.6H), 3.52 (t, 2H), 3.41-3.50 (m, 2H), 3.05-3.17 (m, 5H), 2.65-2.69 (m, 1.6 H), 2.50 (t, 0.4H), 2.06-2.26 (br m, 1H), 1.84-1.96 (m, 1H), 1.52-1.75 (m, 4H), 1.25-1.51 (m, 5H), 1.05-1.20 (m, 1H), 1.01 (t, 3H); LC-MS method 2: *m/z* 463.4 (MH^+); RT (min) 2.30.

Synthetic procedure for the preparation of compound 46



[a] Reagents and conditions: (a) NEt_3, $CHCl_3$, 2,4-difluorobenzoylchloride; Ac_2O, 50 ^{0}C, 97%; (b) *tert*-butyl 3-aminomethyl)piperidine-1-carboxylate, toluene, reflux; 1,2-ethanediol, K_2CO_3, 140 ^{0}C, 18%; (c) 4-fluorophenol, Cs_2CO_3, CuCl, TMHD, NMP, 115 ^{0}C, 47%; (d) TFA, CH_2Cl_2, 22%; (e) 2-iodopropane, K_2CO_3, CH_3CN, 80 ^{0}C, 25%.

2-[2-Fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-3-[(1-isopropylpiperidin-3-yl)methyl]quinazolin-4(3H)-one (46).

Step 1. Preparation of 6-bromo-2-(2,4-difluorophenyl)-4H-3,1-benzoxazin-4-one. To a solution of 2-amino-5-bromobenzoic acid (10 g, 46 mmol) and triethylamine (19 mL, 139 mmol) in chloroform (100 mL) was added 2,4-difluorobenzoylchloride (6.8 mL, 55 mmol) dropwise at rt to form a precipitate. After the solution was stirred for 2 h, the solvent was removed under reduced pressure, and the residue was heated in acetic acid anhydride (90 mL) at 50 ^{0}C for 2 h. The resulting precipitate was collected by filtration, washed with MeOH and dried under vacuum for 15 h to afford 15 g (97% yield) of the product as a light yellow solid. ES-MS analysis showed the presence of a single peak with *m/z* = 339 (MH^+).

Step 2. Preparation of *tert*-butyl 3-{[6-bromo-2-[2-fluoro-4-(2-hydroxyethoxy) phenyl]-4-oxoquinazolin-3(4H)-yl]methyl}piperidine-1-carboxylate. A solution of 6-bromo-2-(2,4-difluorophenyl)-4H-3,1-benzoxazin-4-one (7.00 g, 20.7 mmol) (step 1) and tert-butyl 3-(aminomethyl)piperidine-1-carboxylate (6.21 g, 29 mmol) in toluene (250 mL) was heated to reflux for 4 h. The solvent was removed under reduced pressure to afford the crude intermediate. The intermediate (7.30 g, 13.2 mmol) and K_2CO_3 (100 mL) were combined and heated in ethylene glycol at 140 ^{0}C for 10 h. TLC analysis (EtOAc/hexanes 1:1) indicated an R_f value of the product of 0.15. The solution was partitioned between EtOAc and water. The organic phase was separated, concentrated, and the crude product purified via flash silica gel column chromatography using a gradient elution from 10% to 90% EtOAc in hexanes to afford 1.4 g (18%) of the product as a white solid. ES-MS *m/z* 576.5 (MH^+); HPLC RT (min) 3.54.

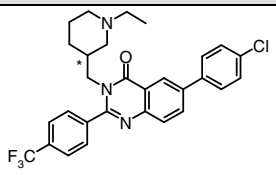
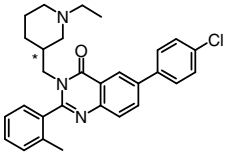
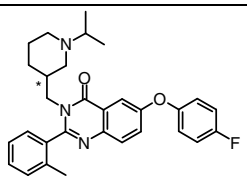
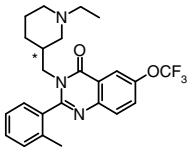
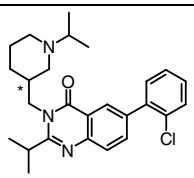
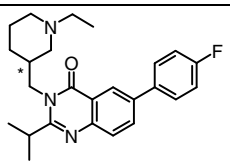
Step 3. Preparation of *tert*-butyl 3-{[2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-4-oxoquinazolin-3(4H)-yl]methyl}piperidine-1-carboxylate. A solution of *tert*-butyl 3-{[6-bromo-2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-4-oxoquinazolin-3(4H)-yl]methyl}piperidine-1-carboxylate (1.8 g, 3.1 mmol), 4-fluorophenol (525 mg, 4.68 mmol), cesium carbonate (2.0 g, 6.25 mmol), copper(I) chloride (156 mg, 1.56 mmol), and TMHD (260 mg, 0.87 mmol) in 1-methyl-2-pyrrolidinone (30 mL) was degassed and then heated at 115 ^{0}C for 10 h. The mixture was diluted with ether and passed through a celite bed. The organic solution was washed with water (2x). After removal of the solvent under reduced pressure, the residue was purified using a Gilson reversed-phase HPLC system with a gradient elution from 10 % to 90% acetonitrile in water to give 900 mg (47%) of the product. ES-MS *m/z* 630.3 [$(M+Na)^+$]; HPLC RT (min) 3.91.

Step 4. Preparation of 2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-3-(piperidin-3-ylmethyl)quinazolin-4(3H)-one. A solution of *tert*-butyl 3-{[2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-4-oxoquinazolin-3(4H)-yl]methyl}piperidine-1-carboxylate (0.9 g, 1.48 mmol) and TFA (1 mL) in CH_2Cl_2 (15 mL) was stirred at rt for 2 h. The solvent was removed under reduced pressure, and the residue was purified via silica gel column chromatography using a gradient elution from 0% to 6% NH_3 (2N in MeOH) in CH_2Cl_2 to afford 165 mg (22%) of a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.67 (m, 2H), 7.44 (m, 2H), 7.09 (m, 4H), 6.91 (d, 1H), 6.76 (d, 1H), 4.20-3.57 (m, 4H), 3.00-2.19 (m, 4H), 1.89-0.87 (m, 7H); ES-MS *m/z* 508.4 (MH^+); HPLC RT (min) 2.53.

Step 5. Preparation of 2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-3-[(1-isopropylpiperidin-3-yl)methyl]quinazolin-4(3H)-one. A solution of 2-[2-fluoro-4-(2-hydroxyethoxy)phenyl]-6-(4-fluorophenoxy)-3-(piperidin-3-ylmethyl)quinazolin-4(3H)-one (180 mg, 0.36 mmol), 2-iodopropane (0.042 mL, 0.43 mmol) and K_2CO_3 (147 mg, 1.1 mmol) in acetonitrile (30 mL) with few drops water was stirred at 80 ^oC for 10 h. The precipitate was filtered off and the solvent was removed under reduced pressure. The residue was purified via silica gel column chromatography using a gradient elution from 0% to 7% MeOH in CH_2Cl_2 to afford 56 mg (25%) of the product as white foam. ^1H NMR (300 MHz, *METHANOL-d_4*) δ ppm 7.69 (t, *J*=8.07 Hz, 1 H) 7.49 - 7.61 (m, 3 H) 7.10 - 7.22 (m, 4 H) 6.90 - 7.04 (m, 2 H) 4.07 - 4.21 (m, 3 H) 3.86 - 3.97 (m, 2 H) 3.73 (m, 1 H) 2.64 (m, 3 H) 1.96 - 2.10 (m, 1 H) 1.91 (m, 2 H) 1.57 (m, 2 H) 1.39 (m, 2 H) 0.96 (m, 6 H). LC-MS method 1: *m/z* 550.3 (MH^+); RT (min) 4.16; LC-MS method 2: *m/z* 550.3 (MH^+); RT (min) 2.71.

Comparison of the ghrelin binding affinities of multiple enantiomeric pair members

(*S*)-enantiomers were consistently found to be more potent than corresponding (*R*)-enantiomers. The degree of enantiomer discrimination is varying and depends on the substituents at the quinzolinone core.

Structure	GHS-R Ki [nM] (*S*)-enantiomer	GHS-R Ki [nM] (*R*)-enantiomer	Factor of enantiomer discrimination
	16	240	15
	18	71	4
	0.9	47	52
	16	95	6
	127	1800	14
	40	5700	143

Analytical data and purity assessment of key compounds

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
7	444.0	*(METHANOL-d_4)* δ ppm 8.47 (d, *J*=2.14 Hz, 1 H) 8.12 (dd, *J*=8.48, 1.66 Hz, 1 H) 7.71 - 7.76 (m, 3 H) 7.50 (t, *J*=7.99 Hz, 4 H) 7.39 - 7.41 (m, 2 H) 4.08-4.23 (dd, *J*=13.74, 7.89 Hz, 1 H) 3.46-3.66 (dd, *J*=13.64, 7.99 Hz, 1 H) 2.94 (s, 1 H) 2.90 (d, *J*=7.21 Hz, 1 H) 2.44 - 2.55 (m, 1 H) 2.17 - 2.28 (m, 3 H) 1.88 (s, 1 H) 1.85 (d, *J*=3.51 Hz, 1 H) 1.56 - 1.67 (m, 2 H) 1.33 - 1.43 (m, 2 H) 1.00 - 1.11 (m, *J*=11.50, 11.50, 11.21, 8.48 Hz, 1 H).	444.3	4.25	444.2	2.84	>98%
8	472.0	*(METHANOL-d_4)* δ ppm 8.49 (d, *J*=1.57 Hz, 1 H) 8.13 (dd, *J*=8.41, 2.15 Hz, 1 H) 7.75 (dd, *J*=8.31, 2.05 Hz, 3 H) 7.47 - 7.53 (m, 4 H) 7.38 - 7.44 (m, 2 H) 4.15 - 4.21 (m, 1 H) 3.52 - 3.62 (m, 1 H) 2.84 (t, *J*=9.49 Hz, 1 H) 2.76 (d, *J*=10.96 Hz, 1 H) 2.32 - 2.41 (m, 2 H) 2.28 (d, *J*=4.89 Hz, 3 H) 1.89 - 1.99 (m, 1 H) 1.80 - 1.89 (m, 1 H) 1.53 - 1.64 (m, 2 H) 1.41 - 1.47 (m, 1 H) 1.32 - 1.39 (m, 1 H) 1.02 (dt, *J*=9.78, 7.24 Hz, 3 H) 0.89 - 0.96 (m, 1 H)	472.5	4.24	472.3	2.85	>98%
9	486.1	*(METHANOL-d_4)* δ ppm 8.49 (t, *J*=1.85 Hz, 1 H) 8.12 (dd, *J*=8.58, 2.14 Hz, 1 H) 7.75 (dd, *J*=8.38, 2.53 Hz, 3 H)	486.6	4.26	486.3	2.91	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		7.47 - 7.53 (m, 4 H) 7.42 (d, *J*=7.80 Hz, 2 H) 7.39 (s, 1 H) 4.17 (dd, *J*=13.74, 5.55 Hz, 1 H) 3.55 (dd, *J*=13.54, 6.72 Hz, 1 H) 2.70 - 2.80 (m, 1 H) 2.63 - 2.70 (m, 1 H) 2.55 (d, *J*=9.55 Hz, 1 H) 2.27 (d, *J*=2.34 Hz, 3 H) 1.99 - 2.09 (m, 1 H) 1.87 - 1.98 (m, 1 H) 1.55 - 1.66 (m, 1 H) 1.39 - 1.46 (m, 1 H) 1.31 - 1.37 (m, 1 H) 0.94 - 1.04 (m, 6 H) 0.90 (dd, *J*=12.38, 4.00 Hz, 1 H) 0.85 (dd, *J*=8.19, 3.70 Hz, 1 H)					
10	498.1	*(METHANOL-d_4)* δ ppm 8.42 (d, *J*=1.17 Hz, 1 H) 8.05 (dd, *J*=8.48, 2.05 Hz, 1 H) 7.64 - 7.70 (m, 3 H) 7.40 - 7.47 (m, 4 H) 7.32 - 7.37 (m, 2 H) 5.43 (s, 1 H) 4.05 - 4.16 (m, 1 H) 3.44 - 3.56 (m, 1 H) 2.64 - 2.75 (m, 1 H) 2.18 - 2.23 (m, 4 H) 2.13 - 2.16 (m, 1 H) 2.10 (dd, *J*=10.43, 6.92 Hz, 1 H) 1.80 - 1.91 (m, 2 H) 1.49 - 1.60 (m, 3 H) 1.40 (ddd, *J*=12.18, 8.38, 3.80 Hz, 1 H) 1.34 (s, 1 H) 0.82 - 0.87 (m, 1 H) 0.76 - 0.81 (m, 1 H) 0.34 - 0.45 (m, 1 H) 0.01 (t, *J*=4.09 Hz, 1 H)	498.5	4.32	498.3	2.96	>98%
11	502.1	*(METHANOL-d_4)* δ ppm 8.48 (s, 1 H) 8.11 (dd, *J*=8.48, 2.24 Hz, 1 H) 7.71 - 7.76 (m, 3 H) 7.47 - 7.53 (m, 4 H) 7.37 - 7.43 (m, 2 H) 4.11 - 4.20 (m, 1 H) 3.55 (td, *J*=13.20, 7.11 Hz, 1 H) 3.38 - 3.45 (m, 2 H)	502.5	4.28	502.3	2.87	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		3.29 - 3.35 (m, 3 H) 2.72 - 2.84 (m, 2 H) 2.42 - 2.51 (m, 2 H) 2.27 (d, *J*=2.53 Hz, 3 H) 1.88 - 1.99 (m, 2 H) 1.51 - 1.63 (m, 2 H) 1.43 - 1.49 (m, 1 H) 1.38 - 1.43 (m, 1 H) 0.87 (td, *J*=12.03, 3.80 Hz, 1 H)					
12	490.0	*(METHANOL-d_4)* δ ppm 8.52 (d, *J*=1.56 Hz, 1 H) 8.17 (d, *J*=8.57 Hz, 1 H) 7.76 (m, 3 H) 7.52 (m, 4 H) 7.40 - 7.48 (m, 2 H) 4.80 - 4.88 (m, 1 H) 4.72 (d, *J*=3.90 Hz, 1 H) 4.34 (dd, *J*=13.84, 7.60 Hz, 1 H) 4.20 (dd, *J*=14.03, 5.46 Hz, 1 H) 3.73 (dd, *J*=13.74, 7.50 Hz, 1 H) 3.47 - 3.59 (m, 3 H) 3.39 - 3.47 (m, 2 H) 2.90 (d, *J*=12.28 Hz, 1 H) 2.65 - 2.75 (m, 1 H) 2.22 - 2.32 (m, 3 H) 1.89 - 1.99 (m, 1 H) 1.62 - 1.73 (m, 1 H) 1.13 - 1.24 (m, 1 H)	490.4	4.28	490.2	2.89	>98%
13	526.0	*(METHANOL-d_4)* δ ppm 8.51 (d, *J*=1.96 Hz, 1 H) 8.15 (dd, *J*=8.51, 1.27 Hz, 1 H) 7.72 - 7.79 (m, 3 H) 7.52 (d, *J*=8.41 Hz, 3 H) 7.49 (d, *J*=2.74 Hz, 1 H) 7.39 - 7.49 (m, 2 H) 4.20 (dd, *J*=13.79, 6.94 Hz, 1 H) 4.12 (d, *J*=6.26 Hz, 1 H) 3.81 - 3.83 (m, 1 H) 3.75 - 3.79 (m, 1 H) 3.64 - 3.73 (m, 2 H) 3.18 - 3.22 (m, 1 H) 3.12 (q, *J*=9.72 Hz, 1 H) 3.00 (s, 1 H) 2.87 - 2.96 (m, 1 H) 2.35 - 2.47 (m, 1 H) 2.26 - 2.32 (m, 3 H) 2.10 - 2.14 (m, 1 H) 1.98 - 2.09 (m, 1 H) 1.95 (s, 1 H)	526.3	5.70	526.2	3.93	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		1.58 - 1.68 (m, 1 H) 1.43 - 1.54 (m, 1 H) 1.36 (d, *J*=12.72 Hz, 1 H) 0.91 - 1.01 (m, 1 H).					
14	540.0	*(METHANOL-d_4)* δ ppm 8.53 (t, *J*=2.25 Hz, 1 H) 8.14 - 8.21 (m, 1 H) 7.76 (d, *J*=8.41 Hz, 3 H) 7.50 - 7.54 (m, 4 H) 7.40 - 7.47 (m, 2 H) 4.29 - 4.39 (m, 1 H) 4.16 (s, 1 H) 3.78 (s, 1 H) 3.58 - 3.65 (m, 2 H) 3.55 (d, *J*=4.11 Hz, 1 H) 3.49 (dd, *J*=3.42, 1.66 Hz, 1 H) 2.82 - 2.90 (m, 1 H) 2.75 (m, 2 H) 2.19 - 2.28 (m, 3 H) 1.90 - 2.00 (m, 1 H) 1.58 - 1.69 (m, 1 H) 1.36 - 1.46 (m, 1 H) 1.29 - 1.32 (m, 1 H) 1.12 - 1.23 (m, 1 H)	540.5	4.39	540.3	3.04	>98%
15	502.1	*(METHANOL-d_4)* δ ppm 8.50 (d, *J*=1.47 Hz, 1 H) 8.14 (dd, *J*=8.59, 2.28 Hz, 1 H) 7.72 - 7.79 (m, 3 H) 7.60 - 7.66 (m, 1 H) 7.49 - 7.55 (m, 3 H) 7.26 (d, *J*=8.37 Hz, 1 H) 7.20 (td, *J*=7.49, 0.88 Hz, 1 H) 4.20 - 4.35 (m, 1 H) 3.89 (s, 3 H) 3.80 (s, 1 H) 3.76 (ddd, *J*=13.62, 3.08, 2.97 Hz, 1 H) 3.35 - 3.50 (m, 2 H) 3.05 - 3.14 (m, 2 H) 2.69 - 2.81 (m, 1 H) 2.45 (d, *J*=11.45 Hz, 1 H) 1.89 (d, *J*=14.53 Hz, 1 H) 1.71 (s, 1 H) 1.63 (d, *J*=14.68 Hz, 4 H) 1.30 (td, *J*=7.34, 0.88 Hz, 3 H)	502.4	4.27	502.3	2.88	>98%
18	470.0	*(METHANOL-d_4)* δ ppm 8.47 - 8.55 (m, 1 H) 8.13 (dd,	470.3	4.25	470.2	2.85	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		J=8.51, 2.25 Hz, 1 H) 7.73 - 7.80 (m, 3 H) 7.45 - 7.52 (m, 3 H) 7.39 (m, 3 H) 5.04 (s, 1 H) 4.73 (d, *J*=15.65 Hz, 1 H) 4.26 (d, *J*=15.65 Hz, 1 H) 2.71 - 2.80 (m, 1 H) 2.59 - 2.68 (m, 1 H) 2.40 - 2.51 (m, 4 H) 2.24 - 2.31 (m, 3 H) 2.09 (d, *J*=1.37 Hz, 2 H) 1.06 (t, *J*=7.14 Hz, 3 H)					
23	488.0	*(METHANOL-d_4)* δ ppm 8.49 (d, *J*=1.56 Hz, 1 H) 8.10 - 8.15 (m, 1 H) 7.71 - 7.77 (m, 3 H) 7.44 - 7.52 (m, 4 H) 7.33 - 7.41 (m, 2 H) 4.26 (dd, *J*=13.45, 3.51 Hz, 1 H) 3.99 - 4.11 (m, 1 H) 3.81 - 3.88 (m, 1 H) 3.70 - 3.79 (m, 2 H) 3.42 (tt, *J*=11.42, 2.41 Hz, 1 H) 2.71 - 2.80 (m, 1 H)) 2.57 (dt, *J*=13.11, 6.60 Hz, 1 H) 2.30 - 2.37 (m, 1 H) 2.12 - 2.23 (m, 3 H) 1.76 - 1.83 (m, 1 H) 1.03 (dd, *J*=6.43, 1.95 Hz, 6 H)	488.5	4.26	488.3	2.85	>98%
24	472.0	*(METHANOL-d_4)* δ ppm 8.49 (d, *J*=1.57 Hz, 1 H) 8.13 (dd, *J*=8.41, 2.15 Hz, 1 H) 7.75 (dd, *J*=8.31, 2.05 Hz, 3 H) 7.47 - 7.53 (m, 4 H) 7.38 - 7.44 (m, 2 H) 4.15 - 4.21 (m, 1 H) 3.52 - 3.62 (m, 1 H) 2.84 (t, *J*=9.49 Hz, 1 H) 2.76 (d, *J*=10.96 Hz, 1 H) 2.32 - 2.41 (m, 2 H) 2.28 (d, *J*=4.89 Hz, 3 H) 1.89 - 1.99 (m, 1 H) 1.80 - 1.89 (m, 1 H) 1.53 - 1.64 (m, 2 H) 1.41 - 1.47 (m, 1 H) 1.32 - 1.39 (m, 1 H) 1.02 (dt, *J*=9.78, 7.24 Hz, 3 H) 0.89 -	472.5	4.24	472.3	2.86	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		0.96 (m, 1 H)					
25	472.0	*(METHANOL-d_4)* δ ppm 8.50 (d, *J*=1.56 Hz, 1 H) 8.13 (dd, *J*=8.61, 2.15 Hz, 1 H) 7.75 (dd, *J*=8.51, 2.45 Hz, 3 H) 7.51 (ddd, *J*=11.30, 4.65, 2.25 Hz, 4 H) 7.38 - 7.44 (m, 2 H) 4.13 - 4.23 (m, 1 H) 3.52 - 3.62 (m, 1 H) 2.84 - 2.91 (m, 2 H) 2.41 (dq, *J*=13.60, 6.81 Hz, 2 H) 2.28 (d, *J*=5.48 Hz, 3 H) 1.90 - 2.00 (m, *J*=10.83, 7.15, 7.15, 3.42 Hz, 2 H) 1.57 - 1.68 (m, 2 H) 1.40 - 1.48 (m, 1 H) 1.33 - 1.38 (m, 1 H) 1.04 (dt, *J*=11.35, 7.24 Hz, 3 H) 0.88 - 0.97 (m, 1 H)	472.5	4.26	472.3	2.86	>98%
26	421.6	*(DICHLOROMETHANE-d_2)* δ ppm 8.40 (d, *J*=2.15 Hz, 1 H) 7.93 (dd, *J*=8.51, 2.25 Hz, 1 H) 7.65 - 7.72 (m, 3 H) 7.15 - 7.22 (m, 2 H) 4.07 - 4.18 (m, 2 H) 3.31 (dt, *J*=13.06, 6.48 Hz, 1 H) 2.72 (m, 3 H) 2.29 (m, 1 H) 2.18 (m, 1 H) 2.03 (m, 1 H) 1.66 - 1.77 (m, 2 H) 1.49 - 1.61 (m, 1 H) 1.39 (t, *J*=6.46 Hz, 6 H) 1.21 - 1.32 (m, 1 H) 0.97 - 1.07 (m, 6 H)	422.4	4.20	422.3	2.57	>98%
27	438.0	*(DICHLOROMETHANE-d_2)* δ ppm 8.42 (d, *J*=2.14 Hz, 1 H) 7.94 (dd, *J*=8.48, 2.24 Hz, 1 H) 7.65 - 7.73 (m, 3 H) 7.46 (ddd, *J*=8.92, 2.63, 2.29 Hz, 2 H) 4.12 (m, 2 H) 3.43 (d, *J*=4.09 Hz, 1 H) 2.68 (m, 2 H) 2.32 (m, 1 H) 2.20 - 2.30 (m, 1 H) 2.13 (m, 1 H) 1.90 - 1.98	438.5	4.27	438.3	2.90	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		(m, 1 H) 1.70 (m, 2 H) 1.39 (t, *J*=6.43 Hz, 6 H) 1.24 - 1.32 (m, 1 H) 1.22 (dd, *J*=8.96, 4.48 Hz, 1 H) 1.00 (m, 6 H)					
28	489.0	*(METHANOL-d_4)* δ ppm 8.31 - 8.39 (m, 1 H) 7.82 - 7.91 (m, 2 H) 7.74 (d, *J*=8.51 Hz, 2 H) 7.63 (td, *J*=6.46, 1.76 Hz, 1 H) 7.48 - 7.60 (m, 3 H) 7.16 - 7.28 (m, 2 H) 4.20 - 4.40 (m, 1 H) 3.90 (s, 3 H) 3.00 – 3.80 (m, 5 H) 2.40 – 2.80 (m, 3 H) 1.00 – 2.00 (m, 7 H)	488.4	4.24	488.3	2.88	>98%
29	375.5	*(METHANOL-d_4)* δ ppm 8.28 (d, *J*=7.99 Hz, 1 H) 7.82 - 7.87 (m, 1 H) 7.67 (d, *J*=8.19 Hz, 1 H) 7.59 (t, *J*=7.50 Hz, 1 H) 7.46 - 7.52 (m, 2 H) 7.37 - 7.43 (m, 2 H) 4.16 (dd, *J*=7.70, 5.94 Hz, 1 H) 4.13 (d, *J*=1.75 Hz, 1 H) 3.52 (dd, *J*=13.54, 6.92 Hz, 1 H) 2.75 (t, *J*=10.33 Hz, 1 H) 2.60 - 2.69 (m, 2 H) 2.26 (d, *J*=1.95 Hz, 3 H) 2.02 (t, *J*=11.50 Hz, 1 H) 1.87 - 1.92 (ddd, *J*=10.52, 7.21, 3.70 Hz, 1 H) 1.62 (tt, *J*=10.52, 3.80 Hz, 1 H) 1.38 - 1.46 (m, 1 H) 1.31 - 1.36 (m, 1 H) 0.95 - 1.02 (m, 6 H) 0.82 - 0.90 (m, *J*=12.11, 12.11, 4.04, 3.90 Hz, 1 H)	376.4	3.81	376.3	2.22	>98%
30	407.5	*(METHANOL-d_4)* δ ppm 7.59 - 7.72 (m, 3 H) 7.46 - 7.56 (m, 2 H) 7.21 - 7.28 (m, 1 H) 7.15 - 7.21 (m, 1 H) 4.20 - 4.50 (m, 1 H) 3.95 (s, 3 H) 3.90 (s, 3 H) 3.40- 3.89 (m, 3 H) 3.10	408.3	3.82	408.3	2.23	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		(m, 2 H) 2.40 - 2.80 (m, 2 H) 2.00 - 2.25 (brs, 1 H) 1.00 - 2.00 (m, 7 H)					
31	445.5	*(METHANOL-d_4)* δ ppm 8.11 (s, 1 H) 7.74 - 7.79 (m, 2 H) 7.49 (t, *J*=7.21 Hz, 2 H) 7.37 - 7.43 (m, 2 H) 4.14 (dd, *J*=13.64, 6.82 Hz, 1 H) 3.52 - 3.61 (m, 1 H) 2.79 - 2.87 (m, 1 H) 2.58 (m, 1 H) 2.32 - 2.41 (m, 2 H) 2.26 (d, *J*=4.48 Hz, 3 H) 1.85 - 1.96 (m, *J*=18.22, 11.01, 3.90, 3.70 Hz, 1 H) 1.84 (s, 1 H) 1.51 - 1.60 (m, 1 H) 1.31 - 1.38 (m, 1 H) 1.02 (dt, *J*=10.13, 7.21 Hz, 3 H) 0.89 (ddd, *J*=18.32, 12.08, 4.09 Hz, 1 H)	446.5	4.05	446.3	2.57	>98%
34	443.5	*(METHANOL-d_4)* δ ppm 7.68 (d, *J*=9.00 Hz, 1 H) 7.60 (d, *J*=2.74 Hz, 1 H) 7.53 (dd, *J*=8.80, 2.74 Hz, 1 H) 7.45 - 7.50 (m, 2 H) 7.35 - 7.43 (m, 2 H) 7.11 - 7.20 (m, 4 H) 4.02-4.15 (dd, *J*=13.60, 7.73 Hz, 1 H) 3.42-3.60 (dd, *J*=13.50, 8.02 Hz, 1 H) 2.85 (d, *J*=12.32 Hz, 1 H) 2.79 (dd, *J*=12.32, 2.74 Hz, 1 H) 2.42 (qd, *J*=11.80, 2.74 Hz, 1 H) 2.20 - 2.26 (m, 3 H) 2.11 (dd, *J*=12.03, 10.66 Hz, 1 H) 1.78 (ddd, *J*=10.32, 6.80, 3.23 Hz, 1 H) 1.51 - 1.61 (m, 2 H) 1.28 - 1.39 (m, 2 H) 0.93 - 1.04 (m, 1 H)	444.4	4.16	444.2	2.74	>98%
35	485.6	*(METHANOL-d_4)* δ ppm 7.68 (d, *J*=8.80 Hz, 1 H) 7.60 (d,	486.4	4.28	486.4	2.92	>98%*

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		J=2.74 Hz, 1 H) 7.45 - 7.54 (m, 3 H) 7.36 - 7.41 (m, 2 H) 7.10 - 7.19 (m, 4 H) 4.06 - 4.15 (m, 1 H) 3.45 - 3.55 (m, 1 H) 2.72 (t, *J*=9.68 Hz, 1 H) 2.59 - 2.67 (m, 2 H) 2.19 - 2.29 (m, 3 H) 1.96 - 2.03 (m, 1 H) 1.82 - 1.93 (m, 2 H) 1.58 - 1.63 (m, 1 H) 1.55 (dd, *J*=7.04, 4.11 Hz, 1 H) 1.27 - 1.34 (m, 1 H) 0.92 - 1.02 (m, 6 H) 0.78 - 0.84 (m, 1 H)					
36	485.6	*(METHANOL-d_4)* δ ppm 7.69 (d, *J*=8.77 Hz, 1 H) 7.62 (d, *J*=2.73 Hz, 1 H) 7.53 - 7.57 (m, 1 H) 7.45 - 7.50 (m, 2 H) 7.37 - 7.42 (m, 2 H) 7.13 - 7.22 (m, 4 H) 4.12 (dt, *J*=13.30, 5.63 Hz, 1 H) 3.50 (dd, *J*=13.54, 7.11 Hz, 1 H) 2.75 (t, *J*=10.62 Hz, 1 H) 2.65 (td, *J*=12.28, 6.63 Hz, 2 H) 2.24 (d, *J*=1.75 Hz, 3 H) 1.99 - 2.06 (m, 1 H) 1.83 - 1.94 (m, 2 H) 1.57 - 1.65 (m, 1 H) 1.36 - 1.45 (m, *J*=16.83, 8.40, 4.04, 4.04 Hz, 1 H) 1.34 - 1.36 (m, 1 H) 0.95 - 1.02 (m, 6 H) 0.80 - 0.91 (m, 1 H)	486.6	4.20	486.3	2.78	>98%
37	437.6	*(DICHLOROMETHANE-d_2)* δ ppm 7.76 - 7.85 (m, 1 H) 7.57 - 7.65 (m, 1 H) 7.48 - 7.56 (m, *J*=5.87, 2.98, 2.98, 2.98, 2.98 Hz, 1 H) 7.04 - 7.16 (m, 4 H) 4.26 (d, *J*=7.63 Hz, 1 H) 4.10 (dd, *J*=14.28, 5.87 Hz, 1 H) 3.41 - 3.51 (m, 3 H) 3.17 - 3.27 (m, *J*=6.75, 6.75, 6.75, 6.75, 6.75, 6.75	438.6	4.18	438.3	2.76	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		Hz, 1 H) 2.69 - 2.80 (m, 2 H) 2.50 - 2.61 (m, 1 H) 1.97 - 2.07 (m, 2 H) 1.87 - 1.95 (m, 1 H) 1.44 - 1.50 (m, 5 H) 1.38 - 1.42 (m, 1 H) 1.33 (dd, *J*=12.23, 6.75 Hz, 5 H)					
42	410.0	*(CHLOROFORM-d)* δ ppm 8.41 (d, *J*=1.96 Hz, 1 H) 7.92 (dd, *J*=8.51, 2.25 Hz, 1 H) 7.67 (d, *J*=8.41 Hz, 1 H) 7.61 (ddd, *J*=8.90, 2.54, 2.25 Hz, 2 H) 7.43 (ddd, *J*=8.85, 2.45, 2.20 Hz, 2 H) 4.03 - 4.14 (m, 2 H) 2.86 (d, *J*=8.41 Hz, 1 H) 2.67 - 2.79 (m, 5 H) 2.23 (d, *J*=4.89 Hz, 1 H) 2.17 (m, 1 H) 1.75 (m, 2 H) 1.54 (d, *J*=6.46 Hz, 1 H) 1.21 - 1.32 (m, 1 H) 1.15 (d, *J*=6.85 Hz, 1 H) 1.05 (s, 6 H).	410.3	4.10	410.2	2.60	>98%
43	409.5	*(DICHLOROMETHANE-d_2)* δ ppm 7.55-7.60 (m, 2H), 7.39 (dd, 1 H), 7.15-7.00 (m, 4H), 3.96 (d, 2H), 2.75-2.61 (m, 3H), 2.60 (s, 3H), 2.22 (t, 1 H), 2.11-2.02 (m, 2 H), 1.78-1.54 (m, 2H), 1.49-1.40 (m, 1H), 1.21-1.09 (m, 1H), 0.95 (d, 6H)	410.5	3.99	410.2	2.44	>98%
44	395.9	*(METHANOL-d_4)* δ ppm 8.47 (d, *J*=2.14 Hz, 1 H) 8.33 (s, 1 H) 8.13 (dd, *J*=8.57, 2.14 Hz, 1 H) 7.80 (d, *J*=8.38 Hz, 1 H) 7.69 - 7.75 (m, 2 H) 7.50 (d, *J*=8.38 Hz, 2 H) 4.11 - 4.18 (m, 1 H) 3.98 - 4.05 (m, 1 H) 3.49 - 3.58 (m, 1 H) 3.44 (d, *J*=11.89 Hz, 2 H) 2.93 - 3.01	396.4	4.07	396.3	2.56	>98%

No.	MW	^{1}H NMR (400 MHz)	LC-MS method 1		LC-MS method 2		Assessed purity from two HPLC methods
			m/z (MH^+)	RT (min)	m/z (MH^+)	RT (min)	
		(m, 2 H) 2.47 (m, 1 H) 2.08 (d, *J*=14.42 Hz, 1 H) 1.95 (m, 1 H) 1.79 (d, *J*=14.23 Hz, 1 H) 1.35 - 1.45 (m, 7 H)					
45	395.5	*(METHANOL-d_4)* δ ppm 8.19 - 8.23 (m, 1 H) 7.70 (d, *J*=8.77 Hz, 1 H) 7.49 - 7.57 (m, 2 H) 7.09 - 7.19 (m, 4 H) 3.88 - 3.99 (m, 2 H) 2.75 - 2.84 (m, 2 H) 2.70 - 2.73 (m, 1 H) 2.20 (td, *J*=11.55, 2.44 Hz, 1 H) 2.13 (td, *J*=6.97, 3.41 Hz, 1 H) 2.06 (d, *J*=10.52 Hz, 1 H) 1.68 - 1.79 (m, 2 H) 1.49 - 1.60 (m, 1 H) 1.11 (dd, *J*=11.60, 3.02 Hz, 1 H) 1.05 (dd, *J*=6.43, 5.07 Hz, 6 H)	396.5	3.96	396.2	2.43	>98%
46	549.6	*(METHANOL-d_4)* δ ppm 7.69 (t, *J*=8.07 Hz, 1 H) 7.49 - 7.61 (m, 3 H) 7.10 - 7.22 (m, 4 H) 6.90 - 7.04 (m, 2 H) 4.07 - 4.21 (m, 3 H) 3.86 - 3.97 (m, 2 H) 3.73 (m, 1 H) 2.64 (m, 3 H) 1.96 - 2.10 (m, 1 H) 1.91 (m, 2 H) 1.57 (m, 2 H) 1.39 (m, 2 H) 0.96 (m, 6 H)	550.3	4.16	550.3	2.71	>98%