Electronic Supplementary Material (ESI) for Analytical Methods.

Supporting data for

Strategy for evaluation of isotopic enrichment and structural integrity of deuterium labelled compounds by using HR-MS and NMR

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S1. Experimental

General Information. All starting materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were performed under a nitrogen atmosphere unless otherwise specified. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} pre-coated plates and visualized by a UV lamp for reaction monitoring. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 or 500 MHz spectrometer, chemical shifts are reported in ppm using TMS or the residual solvent peak as the reference. High-resolution mass spectra (HRMS) were recorded on Thermo Vanquish UHPLC connected to Orbitrap Exploris 240 MS (Thermo Scientific, USA). LC-MS analyses were conducted using an Agilent 6140 quadrupole LCMS instrument using C18 column.

S1.1. Synthesis of deuterated benzofuranone derivative (BEN-d_2)

Synthesis of 5-((3*R*,4*R*)-4-hydroxypiperidin-3-yl)-4-methylisobenzofuran-1(3*H*)-one-3,3-d_2, HCl from methyl 3-bromo-2-methylbenzoic acid as follows;

(i) Methyl 3-bromo-2-methylbenzoate (2):[1] To a solution of 3-bromo-2-methylbenzoic acid **(1)** (200 g, 930 mmol) in methanol (2 L) was added sulfuric acid (54.5 mL, 1023 mmol) dropwise over 30 min at 0 °C. After completion of addition, reaction mixture was heated to reflux at 80 °C for 12 h. Upon completion of the reaction as monitored by TLC/LCMS, volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (2 L) and slowly quenched using a 10% sodium bicarbonate solution. Aqueous layer was extracted with ethyl acetate (2 x 500 mL). Combined organic layer was washed with water (2 x 500 mL), brine solution (500 mL), dried over anhydrous sodium sulfate and concentrated. Crude product purified by column chromatography using 5-30 % ethyl acetate in petroleum ether as eluent to obtain methyl 3-bromo-2-methylbenzoate **(2)** (200 g, 94% yield) as colorless liquid. **^{1}H NMR** (400 MHz, DMSO-d_6): 2.52 (s, 2H) 2.52 - 2.54 (m, 1H) 3.85 (s, 3H) 7.25 (t, *J*=7.91 Hz, 1H) 7.72 (d, *J*=7.78 Hz, 1H) 7.82 (d, *J*=8.03 Hz, 1H).

(ii) (3-Bromo-2-methylphenyl) methan-d_2-ol (3): To a solution of methyl 3-bromo-2-methylbenzoate **(2)** (30 g, 131 mmol) in THF (600 mL), was added sodium borodeuteride (16.44 g, 393 mmol) at 0 °C. Methanol-d_4 (53.2 mL, 1310 mmol) was added dropwise at 0 °C for 30 min. Then, the reaction mixture was slowly warmed to RT and stirred for 16 h. Upon completion of reaction as monitored by LCMS, reaction mass was cooled to 0 °C and D_2O (100 mL) was added

dropwise over 15 min. Reaction mixture was further stirred for 0.5 h at 0 °C and 10% ammonium chloride solution (400 mL) was added slowly under stirring. Then, the reaction mixture was extracted with ethyl acetate (3 x 200 mL), washed with brine (100 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain (3-bromo-2-methylphenyl) methan-d_2-ol **(3)** (24 g, 90% yield) as white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3H) 5.19 (s, 1H) 7.07 - 7.17 (m, 1H) 7.38 (dd, *J*=7.78, 1.25 Hz, 1H) 7.49 (dd, *J*=8.03, 1.00 Hz, 1H)

(iii) 5-Bromo-4-methylisobenzofuran-1(3*H*)-one-3,3-d_2 (4): To a solution of (3-bromo-2-methylphenyl) methan-d_2-ol **(3)** (24 g, 118 mmol) in trifluoroacetic acid (500 mL) was added thallium (III) trifluoroacetate (67.4 g, 124 mmol) at 0 °C. Reaction mixture was warmed to room temperature and stirred for 16 h. Reaction progress was monitored by TLC/LCMS. After completion of the reaction, trifluoroacetic acid was evaporated completely using rotary evaporator under reduced pressure. The obtained residue was dissolved in methanol (800 mL), followed by the addition of lithium chloride (10.02 g, 236 mmol), magnesium oxide (9.76 g, 236 mmol) and palladium (II) chloride (2.096 g, 11.82 mmol). Reaction mixture was stirred at RT under CO atmosphere (using a balloon) for 16 h. After reaction completion (as monitored by TLC), reaction mixture was diluted with methanol and filtered through celite bed. The obtained filtrate was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (400 mL) and washed with water (400 mL), brine (100 mL), dried over anhydrous sodium sulfate. The solution was filtered and concentrated to the minimum of 10% volume. Ethyl acetate (25 mL) was added to the crude reaction mixture and warmed to 45 °C (for 15 min) until complete dissolution. Further, the reaction mixture was cooled to RT followed by the addition of petroleum ether (240 mL) at RT and stirred for 1 h. The obtained solid was filtered and dried overnight to afford 5-bromo-4-methylisobenzofuran-1(3*H*)-one-3,3-d_2 **(4)** (17.6 g, 63.7% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3H) 5.42 (s, 0.05H) 7.57 - 7.65 (m, 1H) 7.83 (d, *J*=8.03 Hz, 1H). **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_9H_5D_2BrO_2$ in 228.9828; found: 228.9824

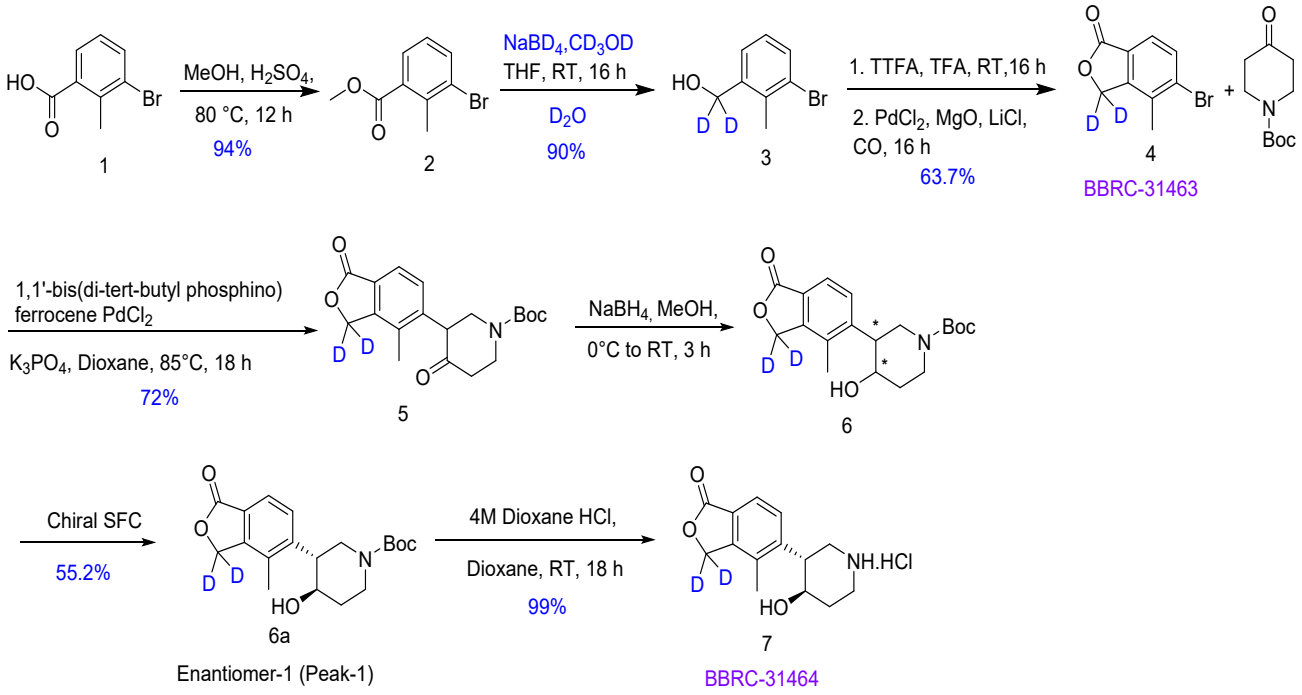
(iv) *tert*-Butyl 3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2)-4-oxopiperidine-1-carboxylate (5): To a solution of 5-bromo-4-methylisobenzofuran-1(3H)-one-3,3-d_2 **(4)** (7.5 g, 32.74 mmol) in 1,4-dioxane (80mL) was added *tert*-butyl 4-oxopiperidine-1-carboxylate (26.1 g, 131 mmol) followed by potassium phosphate (tri basic) (27.8 g, 131 mmol) and the mixture was

degassed with nitrogen for 15 min. Finally added 1,1'-bis (di-*tert*-butyl phosphino) ferrocene palladium dichloride (0.640 g, 0.982 mmol) and degassed for 5 min. The reaction mixture was heated at 85 °C for 18 h. Upon completion, reaction mixture was filtered through celite and volatiles were concentrated under reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel using the mixture of petroleum ether and ethyl acetate 1:1 (v/v) which resulted tert-butyl 3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2)-4-oxopiperidine-1-carboxylate **(5)** (8.25 g, 72.5 % yield) as a yellow solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 1.36 - 1.52 (m, 9H) 2.16 - 2.23 (m, 1H) 2.21 (s, 2H) 2.43 - 2.48 (m, 1H) 2.65 - 2.76 (m, 1H) 3.40 - 3.58 (m, 2H) 4.17 (br dd, *J*=11.49, 5.62 Hz, 3H) 5.41 (s, 0.05H) 7.40 (d, *J*=8.07 Hz, 1H) 7.66 (d, *J*=8.07 Hz, 1H). **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{21}D_2NO_5$ in 348.1775; found: 348.1773

(v) *tert*-Butyl(3*R*,4*R*)-4-hydroxy-3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2) piperidine-1-carboxylate (6a): To a solution of *tert*-butyl 3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2)-4-oxopiperidine-1-carboxylate **(5)** (7.2 g, 20.72 mmol) in MeOH (105mL) at 0 °C was added sodium borohydride (1.568 g, 41.44 mmol) slowly in 4 lots over 10 min. Reaction mixture was warmed to room temperature and stirred for 3h. After completion, reaction mixture was quenched with water slowly at 0 °C and further concentrated, obtained crude as white solid which further stirred with (v/v = 1/1) petroleum ether and ethyl acetate (150 mL) at RT for 30 min. Filtered the slurry mass, washed with petroleum ether (20 mL), suck dried overnight, resulted with 2% other diastereomer. After chiral purification, desired fraction was concentrated to generate tert-butyl(*3R,4R*)-4-hydroxy-3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2) piperidine-1-carboxylate **(6a)** (2 g, 55.2% yield) as a white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm: 1.42 (s, 9H) 1.89 - 2.01 (m, 1H) 2.30 (s, 3H) 2.58 - 2.90 (m, 3H) 3.70 - 4.08 (m, 3H) 4.71 (d, *J*=6.02 Hz, 1H) 5.40 - 5.41 (m, 1H) 5.76 (s, 1H) 7.56 (d, *J*=8.03 Hz, 1H) 7.67 (d, *J*=8.03 Hz, 1H). **HRMS** (ESI) m/z: $[M+H]^+$ calcd for $C_{19}H_{23}D_2NO_5$ in 350.1931; found: 350.1931

(vi) 5-((*3R,4R*)-4-Hydroxypiperidin-3-yl)-4-methylisobenzofuran-1(3*H*)-one-3,3-d_2, HCl (7): To a solution of *tert*-butyl (*3R,4R*)-4-hydroxy-3-(4-methyl-1-oxo-1,3-dihydroisobenzofuran-5-yl-3,3-d_2) piperidine-1-carboxylate (**6a**) (2 g, 5.72 mmol) in 1,4-dioxane (20 mL) was added 1,4-dioxane. HCl (4M solution) (20 mL, 658 mmol) slowly at RT and stirred for 18 h. Upon completion, reaction mixture was evaporated under reduced pressure. Crude was stirred with

methyl tertiary butyl ether (20 mL) at RT for 30 min. Slurry mass was filtered, dried under reduced pressure at 50 °C for 3 h resulted 5-((*3R,4R*)-4-hydroxypiperidin-3-yl)-4-methylisobenzofuran-1(3*H*)-one-3,3-d_2, HCl **(7)** (1.63 g, 99% yield) as an off-white solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ ppm 1.59 - 1.94 (m, 1 H) 1.96 - 2.15 (m, 1 H) 2.29 (s, 3 H) 2.91 - 3.19 (m, 3 H) 3.31 - 3.46 (m, 2 H) 3.91-4.0 (m, 1 H) 4.96 (br d, *J*=5.63 Hz, 1 H) 7.60 (d, *J*=8.13 Hz, 1 H) 7.68 (t, *J*=7.63 Hz, 1 H) 9.31 (br s, 2 H), **^{13}C NMR** (126 MHz,) δ = 171.36, 147.30, 145.30, 132.71, 127.95, 123.47, 122.74, 69.17, 46.98, 42.98, 42.80, 32.44, 14.88, **HRMS** (ESI) m/z: $[M+H]^+$ calcd. for $C_{14}H_{15}D_2NO_3$•HCl in 250.1407; found: 250.1405. Melting Point: 342.1 °C.



Scheme S1. Synthetic scheme for the BEN-d_2 compound.

Table S1. ^{1}H NMR chemical shift values (δ in ppm) of BEN.HCl and BEN-d_2.HCl

	^{1}H NMR δ in ppm	
Atom #	**BEN.HCl**	**BEN-d_2. HCl**
1	2.99-3.20,m,1H	2.91-3.19,m,1H
2	3.95-4.01,m,1H	3.91-4.00, m ,1H
3	2.00-2.18 & 1.68-1.93,m,2H	1.96-2.15 & 1.59-1.94,m,2H
4	2.99-3.44,m,2H	2.91-3.46,m,2H
5	9.20,br s,2H (NH.HCl)	9.31,br s,2H (NH.HCl)
6	2.99-3.44,m,2H	2.91-3.46,m,2H
7	4.99,br s,1H	4.96,br d *J*= 5.63 Hz,1H
8	-	-
9	7.62,d J= 8.13 Hz,1H	7.60,d J= 8.13 Hz,1H
10	7.63,d J= 7.63 Hz,1H	7.68,d J= 7.63 Hz,1H
11	-	-
12	-	-
13	-	-
14	2.31,s,3H	2.29,s,3H
15	-	-
16	-	-
17	-	-
18	-	-
19 & 20	5.36-5.45,m, 2H	-

Table S2. ^{1}H NMR chemical shift values (δ in ppm) of TAM. HCl and TAM-d_4

	^{1}H NMR δ in ppm	
Atom #	**TAM.HCl**	**TAM-d_4**
1	-	-
2	7.19,d *J*= 8.5 Hz,1H	7.1,d *J*= 8.51 Hz,1H
3	7.46,dd,*J*= 8.25,2 Hz, 1H	7.38,dd,*J*= 8.44,2.19 Hz,1H
4	-	-
5	7.64,d,*J* = 2.5 Hz,1H	7.56,d,*J* = 2.19 Hz,1H
6	-	-
7	-	-
8	3.90,s,3H	3.86,s,3H
9	-	-
10	br s,7.09,2H	6.99,br s,2H
11	-	-
12	-	-
13	-	-
14	-	-
15	9.15,br s,(NH.HCl),2H	-
16	3.56,br s,1H	3.01,br s, 1H
17	3.27-3.31 & 2.67-2.72,m,2H	2.84-2.87 & 2.67-2.72,m,2H
18	-	-
19	-	-
20 & 21	3.43,br s,2H	-
22 & 23	4.3,t, *J* = 5.25 Hz,2H	-
24	1.16,d,*J* = 6.5,3H	0.96,d,*J* = 6.13 Hz,3H
25	-	-
26	6.98-7.03,m,1H	6.93-6.97,m,1H
27	6.98-7.03,m,1H	6.83-6.91,m,1H
28	6.89-6.93,m,1H	6.83-6.91,m,1H
29	7.03-7.09,m,1H	6.93-6.97,m,1H
30	-	-
31	4.03,q,*J* = 7 Hz,2H	3.98,d,*J* = 6.98,2H
32	1.27,t, *J* = 7 Hz,3H	1.27,t, *J* = 6.94 Hz,3H

Table S3. ^{1}H NMR chemical shift values (δ in ppm) of OXY and OXY-d_5.HCL

	^{1}H NMR δ in ppm	
Atom #	**OXY**	**OXY-d_5.HCl**
1 & 5	7.31-7.35,m,2H	7.31-7.35,m,2H
2 & 4	7.55-7.57,m,2H	7.53-7.55,m,2H
3	-	-
6	7.24-7.27,m,1H	7.23-7.27,m,1H
7	-	-
8	5.66,s,1H	5.71,s,1H
9	2.14-2.20,m,1H	2.14-2.16,m,1H
10	-	-
11	-	-
12	4.72-4.83,m,2H	4.87,br s ,2H
13	-	
14 &18	1.53-1.74,m,4H	1.46-1.73,m,4H
15,16 & 17	1.00-1.43,m,6H	0.96-1.45,m,6H
19	-	-
20	-	-
21	3.35,t,2H	4.14,br s,2H
22	-	10.46,br s,(N.HCl)
23,30 & 31	2.35, q *J* = 7.17 Hz,4H	2.97-3.07,m,2H
24	-	-
25	-	-
26,27,28,29	0.92,t J = 7 Hz,6H	1.12-1.15,m,3H

Table S4. ^{1}H NMR chemical shift values (δ in ppm) of EPL and EPL-d_3

	^{1}H NMR δ in ppm	
Atom #	**EPL**	**EPL-d_3**
1	2.14-2.21,m,2H	2.12-2.19,m,2H
2	2.42-2.49,m,2H	2.42-2.47,m,2H
3	-	-
4	5.72,s,1H	5.69,s,1H
5	-	-
6	-	-
7	2.56-2.66,m,1H	2.54-2.61,m,1H
8	3.16,d, *J* = 5 Hz,1H	3.14,d, *J* = 5.25 Hz,1H
9	2.81-2.87,m,1H	2.79-2.84,m,1H
10	-	-
11	2.56-2.66,m,2H	2.54-2.61,m,2H
12	-	-
13	1.96-2.05 & 1.69-1.94,m,2H	1.94-2.03 & 1.67-1.91,m,2H
14	-	-
15	1.69-1.94 & 1.50-1.61,m,2H	1.67-1.91 & 1.47-1.58,m,2H
16	1.50-1.61 & 1.40-1.44,m,2H	1.47-1.58 & 1.38-1.42,m,2H
17	-	-
18	-	-
19	-	-
20	-	-
21,22 & 23	3.52,s,3H	-
24	-	-
25	-	-
26	1.46,s,3H	1.44,s,3H
27	2.81-2.87,m,1H	2.79-2.84,m,1H
28	-	-
29	1.69-1.94,m,2H	1.67-1.91,m,2H
30	1.69-1.94,m,2H	1.67-1.91,m,2H
31	-	-
32	-	-
33	-	-

Table S5. ^{1}H NMR chemical shift values (δ in ppm) of PRO.HCl and PRO-d_7.HCl

	^{1}H NMR δ in ppm	
Atom #	**PRO.HCl**	**PRO-d_7.HCl**
1	-	-
2 &13	7.15-7.19,m,2H	7.14-7.17,m,2H
3 & 5	7.51-7.57,m,2H	7.50-7.55,m,2H
4	7.05,t, *J* = 7.5Hz,1H	7.03,t, *J* = 8.13Hz,1H
6	-	-
7	-	-
8 & 9	2.91-3.14,m,4H	2.88-3.11,m,4H
10	-	-
11,12,14 & 15	7.24-7.30,m,4H	7.21-7.27,m,4H
16	-	-
17	-	-
18	4.13, d, *J* = 5Hz,2H	4.10, d , *J* = 4.88 Hz, 2H
19	4.22-4.29,m,1H	4.15-4.21, m , 1H
20	3.32-3.35,m,2H	3.31-3.33,m,2H
21	5.91,d, *J* = 5 Hz,1H	5.85, d , *J* = 4.88Hz, 2H
22	8.85,br s,2H (NH.HCl)	8.54,br s, 1H 2H (NH. HCl)
23	-	-
24	-	-
25	-	-
26,27 &28	0.9,t, *J* = 7.25 Hz,3H	-
29 & 30	1.59-1.69,m,2H	-
31& 32	2.77, t, *J* = 7.75 Hz,2H	-

Table S6. Calculations of % isotopic purity of deuterated compound 1-5

Compound	Formula	*m/z*	Number of carbon atoms [NC]	^{13}C contribution factor [F]	No of deuterium atoms [DN]	Uncorrected Peak area of ^{12}C [A]	Corrected peak area of ^{12}C [B]	Calculated peak area of 13C [C]	Total area [TA]	Percent deuterium isotopic purity [P], uncorrected (%)	Percent deuterium isotopic purity [PC], corrected (%)	[P] and [PC] percent difference (%)
(1) Ben-d_2	$C_{14}H_{18}NO_3^+$	248.1281	14	0.154	0	427233	427233	65793	653986827	0.1	0.1	0.0
	$C_{14}H_{17}DNO_3^+$	249.1345			1	29624757	29558964	4562212		5.2	5.2	0.2
	$C_{14}H_{16}D_2NO_3^+$	250.1408			2	536661033	532098821	82645799		94.7	94.0	0.7
(2) Tam-d_4	$C_{20}H_{29}N_2O_5S^+$	409.1792	20	0.22	0	0	0	0	1391760624			
	$C_{20}H_{28}DN_2O_5S^+$	410.1854			1	0	0	0				
	$C_{20}H_{27}D_2N_2O_5S^+$	411.1917			2	0	0	0				
	$C_{20}H_{26}D_3N_2O_5S^+$	412.198			3	6066979	6066979	1334735		0.5	0.5	0.0
	$C_{20}H_{25}D_4N_2O_5S^+$	413.2042			4	1134720418	1133385683	249638492		99.5	99.4	0.1
(3) Oxy-d_5	$C_{22}H_{32}NO_3^+$	358.2377	22	0.242	0	455001	344890	110110	3403898139	0.0	0.0	
	$C_{22}H_{31}DNO_3^+$	359.2439			1	0	0	0				
	$C_{22}H_{30}D_2NO_3^+$	360.2502			2	0	0	0				
	$C_{22}H_{29}D_3NO_3^+$	361.2565			3	0	0	0				
	$C_{22}H_{28}D_4NO_3^+$	362.2628			4	32667529	32667529	7905542		1.2	1.2	0.0
	$C_{22}H_{27}D_5NO_3^+$	363.2689			5	2707536198	2699630656	655223759		98.8	98.6	0.2
(4) Epl-d_3	$C_{24}H_{31}O_6^+$	415.2115	24	0.264	0	0	0	0	819234485			
	$C_{24}H_{30}DO_6^+$	416.2178			1	0	0	0				
	$C_{24}H_{29}D_2O_6^+$	417.2241			2	764341	764341	201786		0.1	0.1	0.0
	$C_{24}H_{28}D_3O_6^+$	418.2304			3	647364207	647162421	170904151		99.9	99.9	0.0
(5) Pro-d_7	$C_{21}H_{28}NO_3^+$	342.2064	21	0.231	0	0	0	0	2418359858			
	$C_{21}H_{27}DNO_3^+$	343.2126			1	0	0	0				
	$C_{21}H_{26}D_2NO_3^+$	344.2189			2	0	0	0				
	$C_{21}H_{25}D_3NO_3^+$	345.2252			3	0	0	0				
	$C_{21}H_{24}D_4NO_3^+$	346.2315			4	3440	3440	795		0.0	0.0	0.0
	$C_{21}H_{23}D_5NO_3^+$	347.2378			5	912157	911362	210708		0.0	0.0	0.1
	$C_{21}H_{22}D_6NO_3^+$	348.244			6	68677984	68467276	15864614		3.5	3.5	0.2
	$C_{21}H_{21}D_7NO_3^+$	349.2501			7	1894955451	1879090837	437734709		96.5	95.8	0.7

Formulae: F = NC * 0.011, B = [DN]A – [DN – 1]C, C = A * F, TA = [A+C], [P] = ((A + C) * 100) / TA, [PC] = ((B + C) * 100) / TA, percent difference = 100 x | P – PC | / ((P + PC)/2)

Reference:

1) Zhang, Peng; Cyriac, George; Kopajtic, Theresa; Zhao, Yongfang; Javitch, Jonathan A.; Katz, Jonathan L.; Newman, Amy Hauck; *J. Med. Chem*, 2010, ***53***, 6112.