Supporting Information

Interaction of A_3 Adenosine Receptor Ligands with the Human Multidrug Transporter ABCG2

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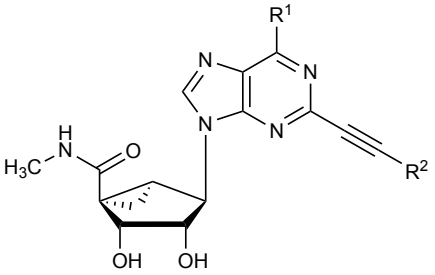
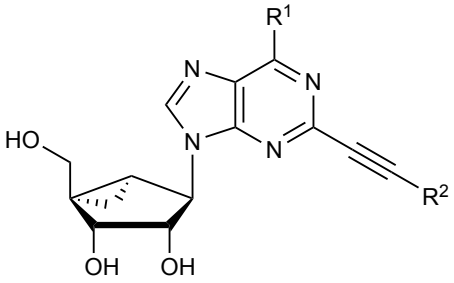
TABLE S1

A_3AR, KOR (κ-opioid) and translocator protein (TSPO) affinity of N^6 and C2-phenylethynyl modifications of (N)-methanocarba 2-arylethynyl-purine derivatives (5'-amides and 5'-alcohols).[a] References are listed on p. S14.



5 – 11, 13 – 15



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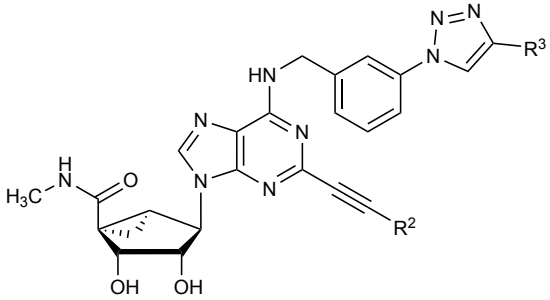

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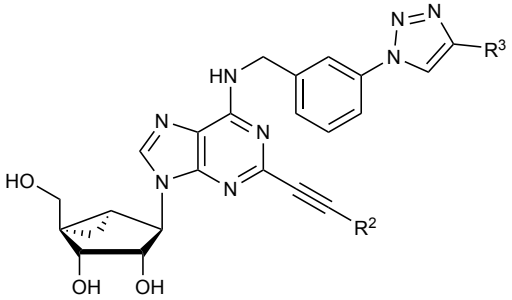

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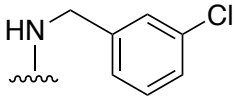
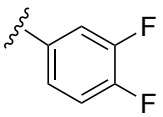
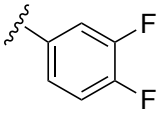
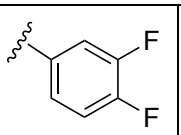
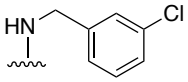
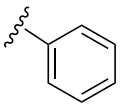
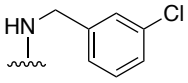
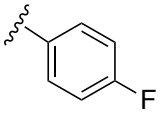
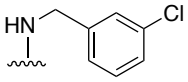
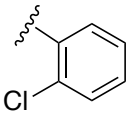
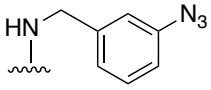
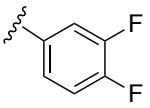
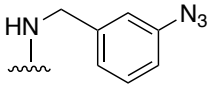
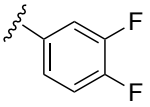
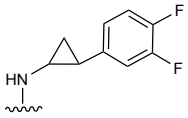
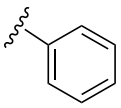
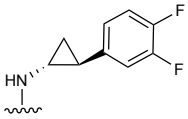
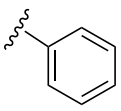
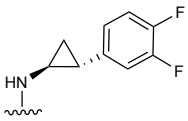
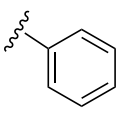
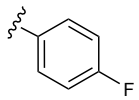
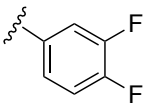
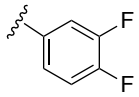
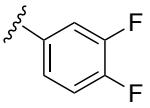
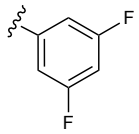
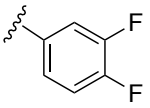
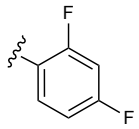
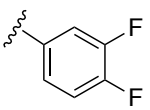
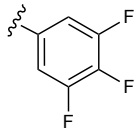
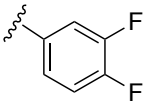
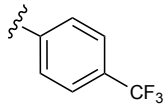
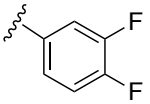
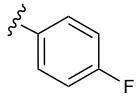
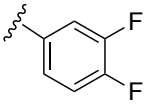
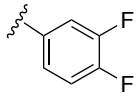
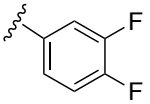
No.	R^1 or R^3	R^2	(K_i, nM), h, unless noted			
			A_3AR	KOR (TSPO)	Compound In reference	Reference
6-Benzylamino and 6-Alkyl derivatives						
5 MRS 5698			3.49 (h), 3.08 (m)	>10,000 (340)	31	1
6 MRS 7202	H		124 (h)	ND	20	4

7 **MRS 7196**	CH_3		98.5 (h)	ND	16	4
8 **MRS 5655**			1.34 (h), 1.23 (m)	>10,000 (2650±210)	27	1
9 **MRS 5678**			2.16 (h), 2.38 (m)	>10,000 (2530)	28	1
10 **MRS 5697**			1.92 (h), 2.64 (m)	>10,000 (344)	29	1
11 **MRS 7328**			2.60±0.83	ND	7	7
12 **MRS 7779**			129	ND	-	New here
6-Phenylcyclopropylamino derivatives						
13 **MRS 5627**			20.2	ND	15	2
14 **MRS 7030**			16.9	ND	16	2
15 **MRS 7034**			4.55	ND	17	2

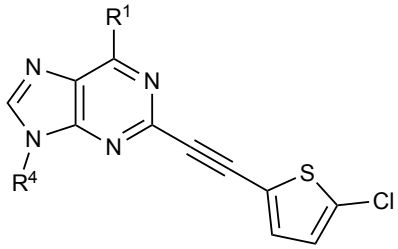
Triazole-extended 6-Benzylamino derivatives						
16[b] **MRS 7769**			45.7	>10,000 (3450±800)	-	New here
17 **MRS 7323**			5.23±0.45	ND	8	7
18[b] **MRS 7767**			16.8	>10,000 (3450±800)	-	New here
19[b] **MRS 7768**			23.5	>10,000 (2220±200)	-	New here
20[b] **MRS 7778**			126	>10,000 (1560±320)	-	New here
21[b] **MRS 7770**			106	>10,000 (>10,000)	-	New here
22 **MRS 7780**			596	ND	-	New here
23 **MRS 7781**			1100	ND	-	New here

[a] The binding affinity for human (h) or mouse (m) A_3AR (expressed in CHO cells) as a K_i values using agonist [^{125}I]*N*^{6}-(4-amino-3-iodobenzyl)adenosine-5′-N-methyluronamide. A percent refers to inhibition of binding at 10 μM. See reference provided for more detail. ND, not determined.

[b] The binding affinity (μM) at s_2 receptor: **16**, 6.1; **18**, 4.3; **19**, 4.4; **20**, 4.1; **21**, >10. The binding affinity (μM) at b_3 receptor: **18**, 3.9.

TABLE S2

A_3AR, KOR (κ-opioid) and translocator protein (TSPO) affinity of N^6, C2 and riboside modifications of adenosine derivatives (both (N)-methanocarba and ribose-containing).[a] References are listed on p. S14.



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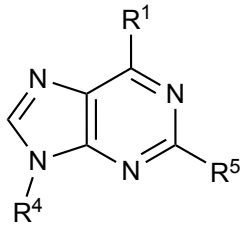

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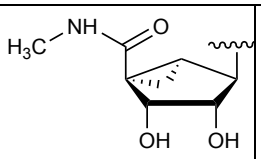
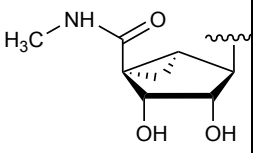
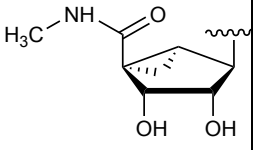
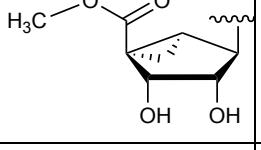
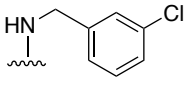
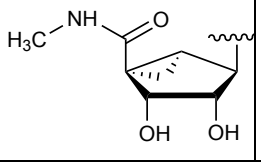
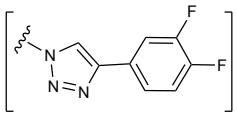
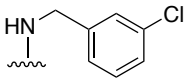
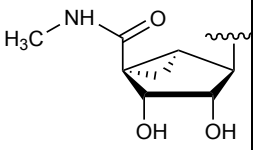
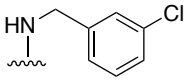
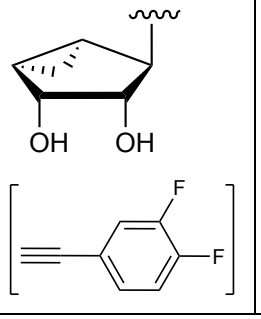
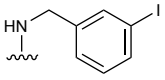
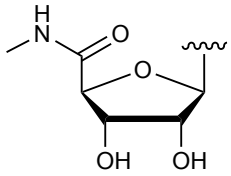
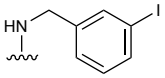
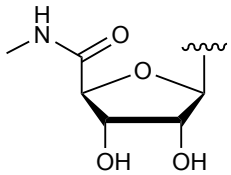
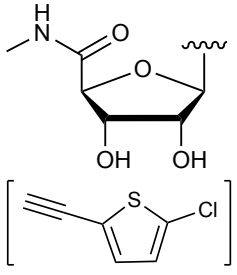
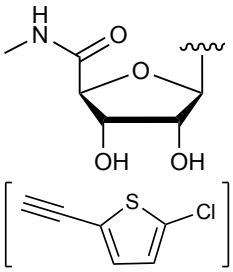
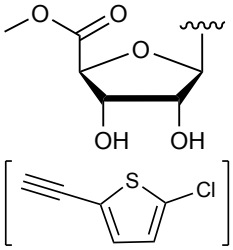
No.	R^1	R^4 [R^5]	(K_i, nM), h, unless noted			
			A_3AR	KOR (TSPO)	Compound in reference	Reference
(N)-Methanocarba derivatives						
24 MRS7220	H		60 (h), 396 (m)	>10,000 (>10,000)	21	4
25 MRS 5980	$NHCH_3$		0.70 (h), 36 (m)	>10,000 (>10,000)	4	8
26 MRS 7154	$NH(CH_2)_2CH_3$		1.1 (h), 6.8 (m)	>10,000 (1310)	12	8
27 MRS 7292	$NHCH_3$		5.38 (h), >10,000 (m)	3130 (>10,000)	21	8
28 MRS 7117			1.06	ND	7	3

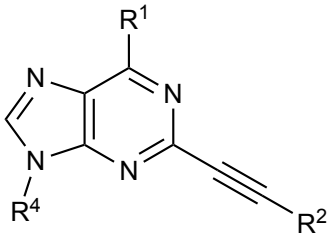
						
29 **MRS 7131**		 [N_3]	1.08	ND	33	3
30 **MRS 5755**			100	>10,000 (1750)	11	11
Ribose derivatives						
31 **IB-MECA**		 [H]	1.8 (h), 0.087 (m)	>10,000 (>10,000)	IB-MECA	9
4 **Cl-IB-MECA**		 [Cl]	1.4 (h), 0.18 (m)	>10,000 (>10,000)	Cl-IB-MECA	9
32 **MRS 7294**	$NHCH_3$		1.55 (h), 1170 (m)	>10,000 (>10,000)	6	8

33 **MRS 7295**	$NH(CH_2)_2CH_3$		6.25 (h), 597 (m)	>10,000 (>10,000)	7	8
34 **MRS 7296**	$NHCH_3$		11.5 (h), 34 (m)	>10,000 (>10,000)	20	8

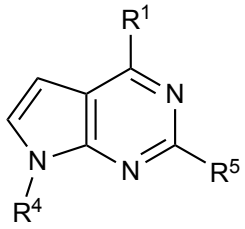
[a] The binding affinity for human (h) or mouse (m) A_3AR (expressed in CHO cells) as a K_i values using agonist [^{125}I]*N*^{6}-(4-amino-3-iodobenzyl)adenosine-5′-N-methyluronamide. See reference provided for more detail. ND, not determined.

TABLE S3

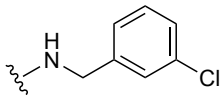
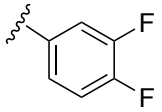
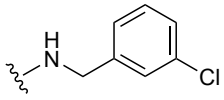
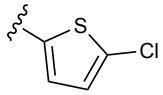
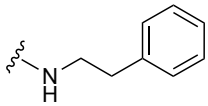
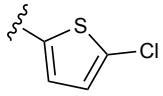
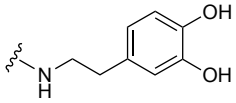
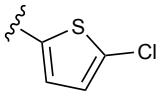
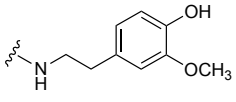
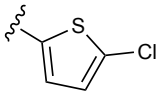
A_3AR, KOR (κ-opioid) and translocator protein (TSPO) affinity of N^6 and C2 modifications of adenine and 7-deazaadenine derivatives. R^4 is either H or CH_3. References are listed on p. S14.

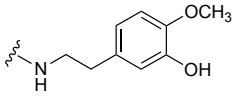
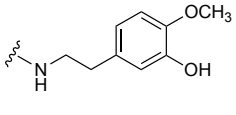
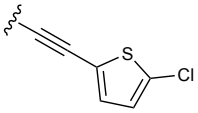
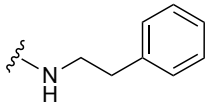
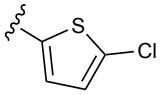


35 – 37, **40**



38, **39**

No.	**R^1**	**R^2**	**(K_i, nM, or *% inhibition at 10 μM*), h, unless noted**			
			A_3AR	**KOR (TSPO)**	**Compound in reference**	**Reference**
R^4 = H						
35 MRS 5923			120	>10,000 (>10,000)	14	6
36 MRS 7327			128	>10,000 (>10,000)	23	6
37a MRS 7350			13 (h), >10,000 (m)	>10,000 (>10,000)	24	6
37b MRS 7610			*20%*	ND	25	6
37c MRS 7608			6820	ND	26	6

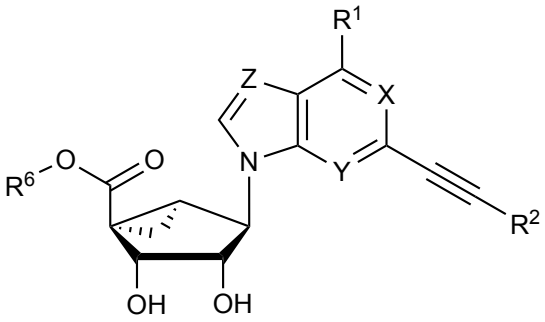
38[b] **MRS 7883**		I	826±51	*9%* (*27%*)	-	New here
39[b] **MRS 7884**			260±9	4080 (960)	-	New here
R^4 = CH_3						
40 **MRS 7320**			116 (h), >10,000 (m)	>10,000 (>10,000)	27	6

[a] The binding affinity for human (h) or mouse (m) A_3AR (expressed in CHO cells) as a K_i values using agonist [^{125}I]*N*^{6}-(4-amino-3-iodobenzyl)adenosine-5'-N-methyluronamide. A percent refers to inhibition of binding at 10 μM. See reference provided for more detail. ND, not determined.

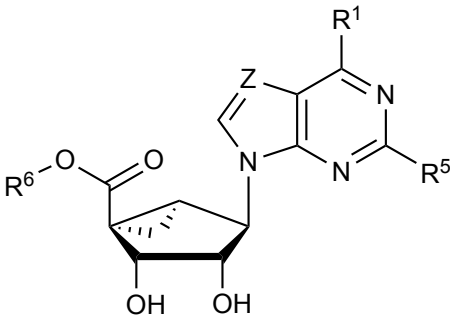
[b] The binding affinity (μM) at s_2 receptor: **38**, 4.0; **39**, 2.7.

TABLE S4

A_3AR affinity of N^6 and C2 modifications of (N)-methanocarba 5'-ester derivatives. R^2 is 2-chloro-thien-5-yl, unless noted. X, Y, Z = N, unless noted.[a] References are listed on p. S14.

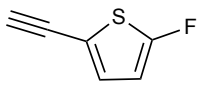


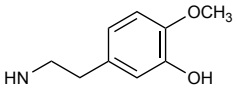
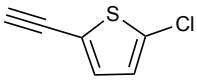
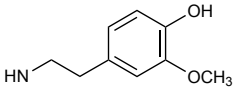
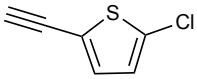
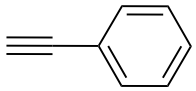
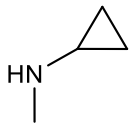
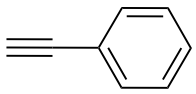
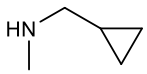
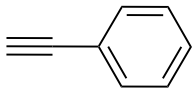
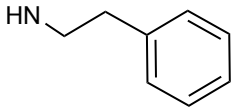
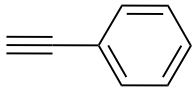
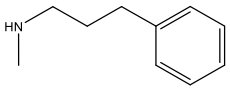
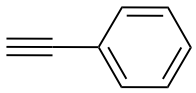
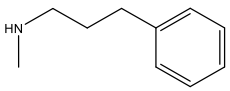
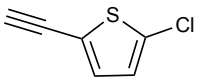
41 – 51

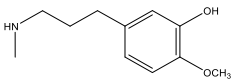
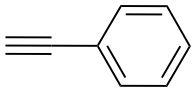
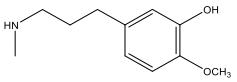
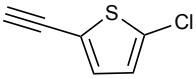


52 – 64

No.	**R^1**	**R^6 (and other)**	**(K_i, nM, or *% inhibition at 10 μM*), h, unless noted**		**Source**	
			A_3AR	**KOR (TSPO)**	**Compound in reference**	**Reference**
X, Y, Z as indicated						
41 MRS 7232	$NHCH_3$	CH_2CH_3	14.5 (h), >10,000 (m)	396 (1290)	24	5
42 MRS 7332	$NHCH_3$	CH_2CH_3 (X = CH)	29.4 (h), 828 (m)	806 (3810)	26	5
43 MRS 7315	$NHCH_3$	CH_2CH_3 (Y = CH)	47.3 (h), >10,000 (m)	>10,000 (3390)	27	5
44 MRS 7299	$NHCH_3$	CH_2CH_3 (Z = CH)	448 (h), >10,000 (m)	42 (869)	28	5

R^6 as indicated, X, Y, Z = N						
45 **MRS 7251**	$NHCH_3$	$(CH_2)_2CH_3$	5.78 (h), 2810 (m)	437 (1060)	30	5
46 **MRS 7252**	$NHCH_3$	$CH(CH_3)_2$	42.9 (h), >10,000 (m)	>10,000 (>10,000)	31	5
47 **MRS 7304**	$NHCH_3$	$(CH_2)_3CH_3$	17.5 (h), ~10,000 (m)	1210 (>10,000)	32	5
48 **MRS 7305**	$NHCH_3$	$(CH_2)_2$-$CH(CH_3)_2$	24.4 (h), >10,000 (m)	1090 (>10,000)	33	5
49 **MRS 7316**	$NHCH_3$	$(CH_2)_2$-c-Hex	334 (h), >10,000 (m)	>10,000 (>10,000)	34	5
50 **MRS 7317**	$NHCH_3$	CH_2Ph	7.81 (h), 891 (m)	629 (4050)	35	5
51 **MRS 7318**	$NHCH_3$	$(CH_2)_2Ph$	114 (h), >10,000 (m)	3670 (>10,000)	36	5
52 **MRS 7319**	$NHCH_3$	$(CH_2)_3Ph$	132 (h), >10,000 (m)	8920 (1090)	37	5
$R^6 = CH_2CH_3$, X, Y, Z = N						
53 **MRS 7333**	$NHCH_3$	R^5 = 	10.4 (h), 625 (m)	2650±880 (>10,000)	23	8

54 **MRS 7636**		R^5 = 	32.8 (h) 104 (m)	*23%* (1880)	29	10
55 **MRS 7626**		R^5 = 	37.4	*32%* (890)	28	10
R^6 = CH_2CH_3, Z = CH						
56 **MRS 7331**	$NHCH_3$	R^5 = I	390	104 (>10,000)	39	5
57 **MRS 7335**	$NHCH_3$	R^5 = 	344 (h), >10,000 (m)	91.5 (>10,000)	40	5
58 **MRS 7347**		R^5 = 	228 (h), >10,000 (m)	852 (>10,000)	41	5
59 **MRS 7348**		R^5 = 	791 (h), >10,000 (m)	1400 (4470)	42	5
60 **MRS 7343**		R^5 = 	483 (h), ~10,000 (m)	207 (480)	43	5
61[b] **MRS 7820**		R^5 = 	4330	146 (3000)	-	New here
62[b] **MRS 7819**		R^5 = 	3760	167 (345)	-	New here

63[b] **MRS 7801**		R^5 = 	2300	764 (1610)	-	New here
64[b] **MRS 7800**		R^5 = 	1620	341 (1270)	-	New here

[a] The binding affinity for human (h) or mouse (m) A_3AR (expressed in CHO cells) as a K_i values using agonist [^{125}I]*N*^{6}-(4-amino-3-iodobenzyl)adenosine-5′-N-methyluronamide. See reference provided for more detail.

[b] The binding affinity (μM) at s_2 receptor: **61**, 0.87; **62**, 0.92; **63**, 2.8; **64**, 1.1. The binding affinity (μM) at d opioid receptor: **61**, 0.52; **62**, 0.63; **64**, 3.9; m opioid receptor: **61**, 0.93; **62**, 0.78; **63**, 1.9; **64**, 1.95; $GABA_A$ receptor: **62**, 4.1; DAT, 4.3; b_3 receptor **61**, 5.7.

Off-target binding activity determined by the Psychoactive Drug Screening Program (PDSP) at the University of North Carolina. We thank Dr. Bryan L. Roth (Univ. North Carolina at Chapel Hill) and National Institute of Mental Health's Psychoactive Drug Screening Program (Contract # HHSN-271-2008-00025-C) for screening data. Initially, the compounds are tested at 10 μM in a primary screen at 45 different receptors, transporters and channels. If the percent of binding inhibition exceeds 50% at any of the targets listed below, a secondary screen of that compound is performed with a full concentration-response curve (concentrations of 0.1 nM to 10 μM, in increments of half-integral log values).
Unless noted in the text, no significant interactions (<50% inhibition at 10 μM) for any of the nucleosides were found at the following sites (human unless noted): $5HT_{1A}$ (serotonin), $5HT_{1B}$, $5HT_{1D}$, $5HT_{1E}$, $5HT_{2A}$, $5HT_{2B}$, $5HT_{2C}$, $5HT_3$, $5HT_{5A}$, $5HT_6$, $5HT_7$, α_{1A} (adrenergic), α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, β_3, BZP (benzodiazepine) rat brain site, D_1 (dopamine), D_2, D_3, D_4, D_5, delta opioid receptor (DOR), kappa opioid receptor (KOR), $GABA_A$, H_1 (histamine), H_2, H_3, H_4, M_1 (muscarinic acetylcholine), M_2, M_3, M_4, M_5, mu opioid receptor (MOR), σ_1, σ_2 (sigma), DAT (dopamine transporter), NET (norepinephrine transporter), SERT (serotonin transporter), TSPO (translocator protein).

Reference: Besnard, J.; Ruda, G. F.; Setola, V.; Abecassis, K.; Rodriguiz, R. M.; Huang, X. P.; Norval, S.; Sassano, M. F.; Shin, A. I.; Webster, L. A.; Simeons, F. R.; Stojanovski, L.; Prat, A.; Seidah, N. G.; Constam, D. B.; Bickerton, G. R.; Read, K. D.; Wetsel, W. C.; Gilbert, I. H.; Roth, B. L.; Hopkins, A. L. Automated design of ligands to polypharmacological profiles. *Nature* **2012**, *492*, 215–220.

Procedures: https://pdsp.unc.edu/pdspweb/content/UNC-CH%20Protocol%20Book.pdf

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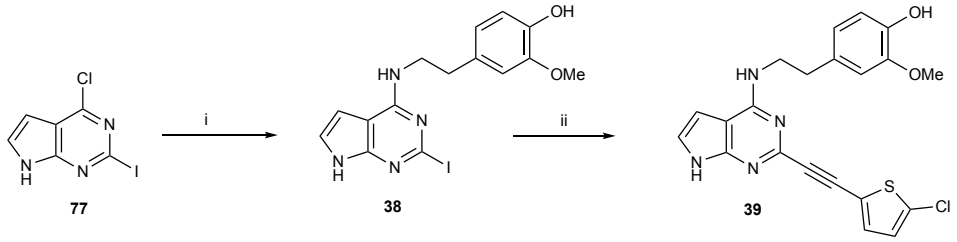
Chemical synthesis

Scheme S1. Synthesis of 7-deaza-adenine (7*H*-pyrrolo[2,3-*d*]pyrimidin-4-amine) derivatives. Reagents and conditions: (i) 3-OH-4-OMe-Ph$(CH_2)_2NH_2$, DIPEA, 2-propanol, 70 ^{O}C, 68%; (ii) 5-Cl-thienyl, $PdCl_2(Ph_3)_2$, CuI, Et_3N, DMF, rt, 76%.



Materials and instrumentation

All reagents and solvents were purchased from Sigma-Aldrich (St. Louis, MO, USA). ^{1}H NMR spectra were obtained with a Bruker 400 spectrometer using $CDCl_3$, CD_3OD and DMSO as solvents. Chemical shifts are expressed in δ values (ppm) with tetramethylsilane (δ 0.00) for $CDCl_3$ and water (δ 3.30) for CD_3OD. NMR spectra were collected with a Bruker AV spectrometer equipped with a z-gradient [^{1}H, ^{13}C, ^{15}N]-cryoprobe. TLC analysis was carried out on glass sheets precoated with silica gel F254 (0.2 mm) from Aldrich. The purity of final nucleoside derivatives was checked using a Hewlett−Packard 1100 HPLC equipped with a Zorbax SB-Aq 5 µm analytical column (50 × 4.6 mm; Agilent Technologies Inc., Palo Alto, CA, USA). Mobile phase: linear gradient solvent system, 5 mM TBAP (tetrabutylammoniumdihydrogenphosphate):CH_3CN from 80:20 to 0:100 in 13 min; the flow rate was 0.5 mL/min. Peaks were detected by UV absorption with a diode array detector at 230, 254, and 280 nm. All derivatives tested for biological activity showed >95% purity by HPLC analysis (detection at 254 nm). Low-resolution mass spectrometry was performed with a JEOL SX102 spectrometer with 6-kV Xe atoms following desorption from a glycerol matrix or on an Agilent LC/MS 1100 MSD, with a Waters (Milford, MA, USA) Atlantis C18 column. High resolution mass spectroscopic (HRMS) measurements were performed on a proteomics optimized Q-TOF-2 (Micromass-Waters) using external calibration with polyalanine, unless noted. Observed mass accuracies are those expected based on known performance of the instrument as well as trends in masses of standard compounds observed at intervals during the series of measurements. Reported masses are observed masses uncorrected for this time-dependent drift in mass accuracy. All of the monosubsituted alkyne intermediates were purchased from Sigma-Aldrich (St. Louis, MO), Small Molecules, Inc. (Hoboken, NJ, USA), Anichem (North Brunswick, NJ, USA), PharmaBlock, Inc. (Sunnyvale, CA, USA), Frontier Scientific (Logan, UT, USA) and Tractus (Perrineville, NJ, USA).

(1R,2R,3S,4R,5S)-4-(6-((3-Azidobenzyl)amino)-2-((3,4-difluorophenyl)ethynyl)-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (12)

A solution of compound **69** (27 mg, 0.04 mmol) in methanol (2.0 mL) and 10% trifluoroacetic acid (2.0 mL) was heated at 70 °C for 1.5 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 15:1) to give the compound **12** (22 mg, 89%) as colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 8.52 (s, 1H), 7.58-7.53 (m, 1H), 7.47-7.44 (m, 1H), 7.36-7.29 (m, 2H), 7.23-7.21 (m, 1H), 7.15 (s, 1H), 6.96-6.94 (m, 1H), 4.87 (br s, 2H), 4.84-4.79 (m, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 3.91 (d, *J* = 6.4 Hz, 1H), 1.68-1.65 (m, 1H), 1.56 (t, *J* = 4.8 Hz, 1H), 0.78-0.75 (m, 1H). HRMS calculated for $C_{27}H_{23}N_8O_3F_2$ (M + H) $^+$: 545.1861; found 545.1865.

(1S,2R,3S,4R,5S)-4-(2-((3,4-Difluorophenyl)ethynyl)-6-((3-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (16)

p-Fluoro-phenyl acetylene (5 mg, 0.014 mmol) was added to a solution of compound **65** (16 mg, 0.028 mmol) in a mixture of ^{t}BuOH (0.7 mL) and water (0.7 mL). Subsequently freshly prepared 1M sodium ascorbate solution (28 µL, 0.028 mmol) followed by 7.5% solution of copper sulphate (47 µL, 0.014 mmol) was added into the reaction mixture and the mixture stirred at room temperature overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 20:1) to give the compound **16** (17.5 mg, 90%) as an colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 8.80 (s, 1H), 8.12 (s, 1H), 8.03 (s, 1H), 7.87-7.84 (m, 2H), 7.78-7.73 (m, 2H), 7.55-7.53 (m, 2H), 7.51-7.46 (m, 1H), 7.40-7.37 (m, 1H), 7.31-7.17 (m, 1H), 7.15-7.13 (m, 2H), 5.04 (d, *J* = 6.4 Hz, 1H), 4.96 (br s, 2H), 4.02 (d, *J* = 6.4 Hz, 1H), 2.84 (d, *J* = 4.4 Hz, 3H), 2.12-2.09 (m, 1H), 1.87 (t, *J* = 5.2 Hz, 1H), 1.40-1.37 (m, 1H). HRMS calculated for $C_{36}H_{29}N_9O_3F_3$ (M + H) $^+$: 692.2345; found 692.2355.

(1S,2R,3S,4R,5S)-4-(6-((3-(4-(3,5-Difluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-2-((3,4-difluorophenyl)ethynyl)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (18)

Compound **18** (88%) was prepared from compound **65** following the same method as for compound **16**. ^{1}H NMR (CD_3OD, 400 MHz) 8.91 (s, 1H), 8.12 (s, 1H), 8.02 (s, 1H), 7.76-7.73 (m, 1H), 7.55-7.50 (m, 2H), 7.49-7.44 (m, 3H), 7.43-7.36 (m, 1H), 7.30-7.23 (m, 1H), 6.94-6.90 (m, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.96 (br s, 2H), 4.85 (s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 2.83 (s, 3H), 2.12-2.09 (m, 1H), 1.87 (t, *J* = 4.8 Hz, 1H), 1.40-1.37 (m, 1H). HRMS calculated for $C_{36}H_{28}N_9O_3F_4$ (M + H) $^+$: 710.2251; found 710.2258.

(1S,2R,3S,4R,5S)-4-(6-((3-(4-(2,4-Difluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-2-((3,4-difluorophenyl)ethynyl)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (19)

Compound **19** (89%) was prepared from compound **65** following the same method as for compound **16**. ^{1}H NMR (CD_3OD, 400 MHz) 8.68 (d, *J* = 3.2 Hz, 1H), 8.18-8.11 (m, 2H), 8.04 (s, 1H), 7.78-7.75 (m, 1H), 7.54-7.46 (m, 3H), 7.40-7.37 (m, 1H), 7.31-7.24 (m, 1H), 7.11-7.03 (m, 2H), 5.04 (d, *J* = 6.4 Hz, 1H), 4.94 (br s, 2H), 4.85 (s, 1H), 2.83 (s, 3H), 2.12-2.09 (m, 1H), 1.87 (t, *J* = 4.8 Hz, 1H), 1.40-1.36 (m, 1H). HRMS calculated for $C_{36}H_{28}N_9O_3F_4$ (M + H) $^+$: 710.2251; found 710.2252.

(1S,2R,3S,4R,5S)-4-(2-((3,4-Difluorophenyl)ethynyl)-6-((3-(4-(3,4,5-trifluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (20)

Compound **20** (90%) was prepared from compound **65** following the same method as for compound **16**. ^{1}H NMR (CD_3OD, 400 MHz) 8.86 (s, 1H), 8.12 (s, 1H), 7.99 (s, 1H), 7.75-7.71 (m, 1H), 7.59-7.50 (m, 4H), 7.48-7.43 (m, 1H), 7.33-7.30 (m, 1H), 7.28-7.24 (m, 1H), 5.02 (d, *J* = 6.4 Hz, 1H), 4.94 (br s, 2H), 4.84 (s, 1H), 4.00 (d, *J* = 6.4 Hz, 1H), 2.83 (s, 3H), 2.11-2.08 (m, 1H), 1.87 (t, *J* = 4.8 Hz, 1H), 1.40-1.36 (m, 1H). HRMS calculated for $C_{36}H_{27}N_9O_3F_5$ (M + H) $^+$: 728.2157; found 728.2150.

(1S,2R,3S,4R,5S)-4-(2-((3,4-Difluorophenyl)ethynyl)-6-((3-(4-(4-(trifluoromethyl)phenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-9H-purin-9-yl)-2,3-dihydroxy-N-methylbicyclo[3.1.0]hexane-1-carboxamide (21)

Compound **21** (87%) was prepared from compound **65** following the same method as for compound **16**. ^{1}H NMR (CD_3OD, 400 MHz) 8.96 (s, 1H), 8.16 (s, 1H), 8.12-7.99 (m, 3H), 7.78-7.73 (m, 1H), 7.71-7.69 (m, 2H), 7.55-7.54 (m, 2H), 7.50-7.45 (m, 1H), 7.37 (br s, 1H), 7.29-7.23 (m, 1H), 5.03 (d, *J* = 6.4 Hz, 1H), 4.96 (br s, 2H), 4.85 (s, 1H), 4.01 (d, *J* = 6.4 Hz, 1H), 2.83 (s, 3H), 2.11-2.08 (m, 1H), 1.87 (d, *J* = 4.8 Hz, 1H), 1.39-1.36 (m, 1H). HRMS calculated for $C_{37}H_{29}N_9O_3F_5$ (M + H) $^+$: 742.2314; found 742.2305.

(1R,2R,3S,4R,5S)-4-(2-((3,4-difluorophenyl)ethynyl)-6-((3-(4-(4-fluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (22)

Compound **22** (88%) was prepared from compound **65** following the same method as for compound **12**. ^{1}H NMR (CD_3OD, 400 MHz) 8.82 (s, 1H), 8.54 (s, 1H), 8.04 (s, 1H), 7.88-7.85 (m, 2H), 7.79-7.76 (m, 1H), 7.56-7.47 (m, 3H), 7.41-7.38 (m, 1H), 7.30-7.24 (m, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 4.97 (br s, 2H), 4.86 (s, 1H), 4.80 (d, *J* = 6.4 Hz, 1H), 4.31 (d, *J* = 7.6 Hz, 1H), 3.89 (d, *J* = 7.6 Hz, 1H), 1.67-1.64 (m, 1H), 1.56 (t, *J* = 4.4 Hz, 1H), 0.78-0.75 (m, 1H). HRMS calculated for $C_{35}H_{28}N_8O_3F_3$ (M + H) $^+$: 665.2236; found 665.2235.

(1R,2R,3S,4R,5S)-4-(6-((3-(4-(3,4-Difluorophenyl)-1H-1,2,3-triazol-1-yl)benzyl)amino)-2-((3,4-difluorophenyl)ethynyl)-9H-purin-9-yl)-1-(hydroxymethyl)bicyclo[3.1.0]hexane-2,3-diol (23)

Compound **23** (87%) was prepared from compound **65** following the same method as for compound **12**. ^{1}H NMR (CD_3OD, 400 MHz) 8.86 (s, 1H), 8.54 (s, 1H), 8.03 (s, 1H), 7.78-7.72 (m, 2H), 7.67-7.64 (m, 1H), 7.56-7.54 (m, 2H), 7.52-7.47 (m, 1H), 7.41-7.38 (m, 1H), 7.35-7.24 (m, 2H), 4.97 (br s, 2H), 4.85 (s, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 3.89 (d, *J* = 6.4 Hz, 1H), 1.67-1.64 (m, 1H), 1.56 (d, *J* = 4.4 Hz, 1H), 0.78-0.75 (m, 1H). HRMS calculated for $C_{35}H_{27}N_8O_3F_4$ $(M + H)^+$: 683.2142; found 683.2138.

4-(2-((2-Iodo-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-2-methoxyphenol (38)

4-Hydroxy-3-methoxy-phenylethyl amine (172.2 mg, 0.1.61 mmol) and DIPEA (0.35 mL, 3.2 mmol) was added to a solution of compound **77** (90 mg, 0.32 mmol) in 2-propanol (2.0 mL) and heated at 70 ^{o}C for 3 h. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 2:1) to give the compound **38** (89 mg, 68%) as a colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 6.93 (d, *J* = 3.6 Hz, 1H), 6.83 (s, 1H), 6.73-6.68 (m, 2H), 6.46 (d, *J* = 3.2 Hz, 1H), 3.81 (s, 3H), 3.70 (t *J* = 7.6 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H). HRMS calculated for $C_{15}H_{16}N_4O_2I$ $(M + H)^+$: 411.0318; found 411.0323.

4-(2-((2-((5-Chlorothiophen-2-yl)ethynyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)ethyl)-2-methoxyphenol (39)

$PdCl_2(PPh_3)_2$ (8.5 mg, 0.017 mmol), 2-chloro-5-ethynylthiophene (52 mg, 0.26 mmol), CuI (1mg, 0.006 mmol) and triethylamine (80 µL, 0.60 mmol) were added to a solution of compound **38** (25 mg, 0.08 mmol) in anhydrous DMF (1.0 mL) and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give the alkyne derivative **39** (28 mg, 76%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) 7.29 (d, *J* = 4.0 Hz, 1H), 7.14 (d, *J* = 3.2 Hz, 1H), 7.00 (d, *J* = 4.0 Hz, 1H), 6.85 (s, 1H), 6.74-6.69 (m, 2H), 6.56 (d, *J* = 3.2 Hz, 1H), 3.79-3.76 (m, 5H), 2.91 (t, *J* = 7.2 Hz, 2H). HRMS calculated for $C_{21}H_{18}N_4O_2SCl$ $(M + H)^+$: 623.1731; found 623.1736.

Ethyl (1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(2-(phenylethynyl)-4-((3-phenylpropyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)bicyclo[3.1.0]hexane-1-carboxylate (61)

A solution of compound **73** (22 mg, 0.03 mmol) in methanol (2.0 mL) and 10% trifluoroacetic acid (2.0 mL) was heated at 70 ^{o}C for 2 h. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (CH_2Cl_2:MeOH = 25:1) to give the compound **61** (18 mg, 90%) as colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 7.70-7.68 (m, 2H), 7.49-7.46 (m, 3H), 7.28-7.23 (m, 4H), 7.16-7.14 (m, 2H), 6.70 (d, *J* = 2.4 Hz, 1H), 5.16 (d, *J* = 6.4 Hz, 1H), 5.04 (s, 1H), 4.28-4.20 (m, 2H), 3.98 (d, *J* = 6.8 Hz, 1H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 2.12-2.02 (m, 3H), 1.95 (t, *J* = 5.2 Hz, 1H), 1.67-1.63 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{32}H_{33}N_4O_4$ $(M + H)^+$: 537.2502; found 537.2496.

Ethyl (1S,2R,3S,4R,5S)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-4-((3-phenylpropyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate (62)

Compound **62** (91%) was prepared from compound **74** following the same method as for compound **61**. ^{1}H NMR (CD_3OD, 400 MHz) 7.25 (d, *J* = 4.0 Hz, 1H), 7.18-7.14 (m, 5H), 7.04-7.02 (m, 2H), 6.65 (d, *J* = 3.2 Hz, 1H), 5.12 (d, *J* = 6.8 Hz, 1H), 5.02 (s, 1H), 4.31-4.21 (m, 2H), 3.92 (d, *J* = 6.4 Hz, 1H), 3.60 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.11-2.06 (m, 1H), 2.00 (t, *J* = 7.6 Hz, 2H), 1.97 (t, *J* = 4.8 Hz, 1H), 1.66-1.62 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{30}H_{30}N_4O_4SCl$ $(M + H)^+$: 577.1676; found 577.1683.

Ethyl (1S,2R,3S,4R,5S)-2,3-dihydroxy-4-(4-((3-(3-hydroxy-4-methoxyphenyl)propyl)amino) -2-(phenylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)bicyclo[3.1.0]hexane-1-carboxylate (63)

Compound **63** (88%) was prepared from compound **74** following the same method as for compound **61**. ^{1}H NMR (CD_3OD, 400 MHz) 7.68-7.66 (m, 2H), 7.44-7.43 (m, 3H), 7.01 (d, *J* = 3.6 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.70-6.67 (m, 2H), 6.63 (d, *J* = 3.6 Hz, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 5.05 (s, 1H), 4.29-4.21 (m, 2H), 3.92 (d, *J* = 6.4 Hz, 1H), 3.80 (s, 3H), 3.61 (d, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.11-2.08 (m, 1H), 2.02-1.94 (m, 3H), 1.66-1.63 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{33}H_{35}N_4O_6$ $(M + H)^+$: 583.2557; found 583.2567.

Ethyl (1S,2R,3S,4R,5S)-4-(2-((5-chlorothiophen-2-yl)ethynyl)-4-((3-(3-hydroxy-4-methoxyphenyl)propyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,3-dihydroxybicyclo[3.1.0]hexane-1-carboxylate (64)

Compound **64** (89%) was prepared from compound **74** following the same method as for compound **61**. ^{1}H NMR (CD_3OD, 400 MHz) 7.31 (d, *J* = 4.0 Hz, 1H), 7.2 (d, *J* = 4.0 Hz, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.70-6.66 (m, 2H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.12 (d, *J* = 6.4 Hz, 1H), 5.02 (s, 1H), 4.31-4.21 (m, 2H), 3.91 (d, *J* = 6.4 Hz, 1H), 3.81 (s, 3H), 3.57 (t, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.10-2.07 (m, 1H), 1.98-1.95 (m, 3H), 1.65-1.62 (m, 1H), 1.30 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{31}H_{32}N_4O_6SCl$ $(M + H)^+$: 623.1731; found 623.1736.

N-(3-Azidobenzyl)-9-((3aR,3bR,4aS,5R,5aS)-3b-(((tert-butyldiphenylsilyl)oxy)methyl)-2,2-dimethylhexahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-5-yl)-2-iodo-9H-purin-6-amine (67)

3-Azido-benzylamine (440 mg, 5.70 mmol) and DIPEA (2.5 mL, 14.2 mmol) was added to a solution of compound **66** (1 g, 0.08 mmol) in 2-propanol (12 mL) and the mixture stirred at room temperature overnight. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the compound **67** (1.02 mg, 87%) as a colorless foamy solid. ^{1}H NMR (CD_3OD, 400 MHz) 8.13 (s, 1H), 7.63-7.59 (m, 4H), 7.40-7.22 (m, 8H), 7.18 (s, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 5.28 (d, *J* = 6.8 Hz, 1H), 4.72-4.70 (m, 3H), 4.21 (d, *J* = 10.4 Hz, 1H), 3.91 (d, *J* = 10.4 Hz, 1H), 1.52-1.49 (m, 4H), 1.30 (t, *J* = 6.4 Hz, 1H), 1.25 (s, 3H), 1.05 (s, 9H), 1.02-0.99 (m, 1H). HRMS calculated for $C_{38}H_{42}N_8O_3ISi$ $(M + H)^+$: 813.2194; found 813.2206.

((3aR,3bR,4aS,5R,5aS)-5-(6-((3-azidobenzyl)amino)-2-iodo-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (68)

TBAF (1.84 mL, 1M solution in THF) was added to a solution of compound **67** (1 gm, 1.23 mmol) in anhydrous THF (8 mL) and the mixture stirred for 1 h at room temperature. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give the alcohol derivative **68** (0.643 mg, 91%) as a syrup. ^{1}H NMR (CD_3OD, 400 MHz) 8.13 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.14 (s, 1H), 6.97-6.95 (m, 1H), 5.35 (d, *J* = 7.2 Hz, 1H), 4.93 (s, 1H), 4.71 (m, 3H), 3.94 (d, *J* = 11.6 Hz, 1H), 3.76 (d, *J* = 11.6 Hz, 1H), 1.65-1.62 (m, 1H), 1.52 (s, 3H), 1.26 (s, 3H), 1.12 (t, *J* = 5.2 Hz, 1H), 0.99-0.96 (m, 1H). HRMS calculated for $C_{22}H_{24}N_8O_3I$ $(M + H)^+$: 575.1016; found 575.1019.

((3aR,3bR,4aS,5R,5aS)-5-(6-((3-Azidobenzyl)amino)-2-((3,4-difluorophenyl)ethynyl)-9H-purin-9-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxol-3b(3aH)-yl)methanol (69)

$PdCl_2(PPh_3)_2$ (12.4 mg, 0.017 mmol), 3,4-difluoro-phenylethynyl (32 µL, 0.26 mmol) and triethylamine (120 µL, 0.88 mmol) were added to a solution of compound **68** (51 mg, 0.08 mmol) in anhydrous DMF (1.2 mL) and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give the alkyne derivative **69** (35 mg, 68%) as a brown syrup. ^{1}H NMR (CD_3OD, 400 MHz) 8.30 (s, 1H), 7.64-7.59 (m, 1H), 7.53-7.49 (m, 1H), 7.37-7.33 (m, 2H), 7.24-7.16 (m, 2H), 6.98 (m, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 5.02 (s, 1H), 4.84 (br s, 2H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.09 (d, *J* = 7.6 Hz, 1H), 3.56 (d, *J* = 7.6 Hz, 1H), 1.78-1.75 (m, 1H), 1.53 (s, 3H), 1.26 (s, 3H), 1.17 (t, *J* = 5.2 Hz, 1H), 1.00-0.97 (m, 1H). HRMS calculated for $C_{30}H_{27}N_8O_3F_2$ $(M + H)^+$: 585.2174; found 585.2170.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-iodo-4-((3-phenylpropyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (71)

3-phenyl-propyl amine (0.16 mL, 1.12 mmol) and DIPEA (0.4 mL, 2.24 mmol) was added to a solution of compound **70** (113 mg, 0.22 mmol) in 2-propanol (1.5 mL) and heated 70 ^oC under microwave condition for 1.5 h. Solvent was evaporated and the residue was purified on flash silica gel column chromatography (hexane: ethyl acetate = 1:1) to give the compound **71** (97 mg, 72%) as a colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 7.28-7.13 (m, 5H), 6.89 (d, *J* = 3.6 Hz, 1H), 6.50 (d, *J* = 2.8 Hz, 1H), 5.80 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 4.74 (d, *J* = 6.8 Hz, 1H), 4.30-4.22 (m, 2H), 3.52 (t, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.18-2.15 (m, 1H), 2.02-1.93 (m, 2H), 1.63-1.60 (m, 1H), 1.52-1.47 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.27 (s, 3H). HRMS calculated for $C_{27}H_{32}N_4O_4I$ $(M + H)^+$: 603.1468; found 603.1458.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(4-((3-(3-hydroxy-4-methoxyphenyl)propyl)amino)-2-iodo-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (72)

Compound **72** (69%) was prepared from compound **65** following the same method as for compound **70**. ^{1}H NMR (CD_3OD, 400 MHz) 6.88 (d, *J* = 3.6 Hz, 1H), 6.82-6.80 (m, 2H), 6.68-6.64 (m, 2H), 5.80 (d, *J* = 7.2 Hz, 1H), 4.86 (s, 1H), 4.74 (d, *J* = 7.2 Hz, 1H), 4.29-4.22 (m, 2H), 3.81 (s. 3H), 3.49 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.18-2.15 (m, 1H), 1.63-1.59 (m, 1H), 1.51-1.47 (m, 4H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 3H). HRMS calculated for $C_{28}H_{34}N_4O_4I$ $(M + H)^+$: 649.1523; found 649.1513.

Ethyl (3aR,3bS,4aS,5R,5aS)-2,2-dimethyl-5-(2-(phenylethynyl)-4-((3-phenylpropyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)tetrahydrocyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (73)

$PdCl_2(PPh_3)_2$ (10.5 mg, 0.014 mmol), CuI (1.4 mg, 0.007 mmol), phenylethynyl (0.05 mL, 0.44 mmol) and triethylamine (0.1 mL, 0.63 mmol) were added to a solution of compound **71** (45 mg, 0.074 mmol) in anhydrous DMF (1.2 mL) and the mixture stirred at room temperature overnight. Solvent was evaporated under vacuum and the residue was purified on flash silica gel column chromatography (hexane:ethyl acetate = 1:2) to give the phenyl alkyne derivative **73** (30 mg, 72%) as a colorless syrup. ^{1}H NMR (CD_3OD, 400 MHz) 7.72-7.70 (m, 2H), 7.44-7.43 (m, 3H), 7.23-7.24 (m, 4H), 7.17-7.13 (m, 1H), 7.07 (d, *J* = 3.6 Hz, 1H), 6.63 (d, *J* = 3.2 Hz, 1H), 5.85 (d, *J* = 7.2 Hz, 1H), 5.07 (s, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.26-4.12 (m, 1H), 3.61 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.25-2.21 (m, 1H), 2.05-1.98 (m, 2H), 1.76-1.67 (m, 1H), 1.57-1.53 (m, 4H), 1.23 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{35}H_{37}N_4O_4$ $(M + H)^+$: 577.2815; found 577.2805.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-4-((3-phenylpropyl) amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydrocyclopropa[3,4] cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate ((74)

Compound **74** (69%) was prepared from compound **71** following the same method as for compound **73**. ^{1}H NMR (CD_3OD, 400 MHz) 7.35 (d, *J* = 4.4 Hz, 1H), 7.26-7.24 (m, 4H), 7.16-7.13 (m, 1H), 7.08 (d, *J* = 3.6 Hz, 1H), 7.01 (d, *J* = 4.4 Hz, 1H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.83 (d, *J* = 6.8 Hz, 1H), 5.04 (s, 1H), 4.72 (d, *J* = 7.2 Hz, 1H), 4.25-4.15 (m, 2H), 3.59 (d, *J* = 7.2 Hz, 2H), 2.74 (t, *J* = 7.2 Hz, 2H), 2.24-2.21 (m, 1H), 2.04-1.97 (m, 2H), 1.71-1.67 (m, 1H), 1.56-1.53 (m, 4H), 1.29 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{33}H_{34}N_4O_4SCl$ $(M + H)^+$: 617.1989; found 617.1986.

Ethyl (3aR,3bS,4aS,5R,5aS)-5-(4-((3-(3-hydroxy-4-methoxyphenyl)propyl)amino)-2-(phenylethynyl)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydrocyclopropa [3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (75)

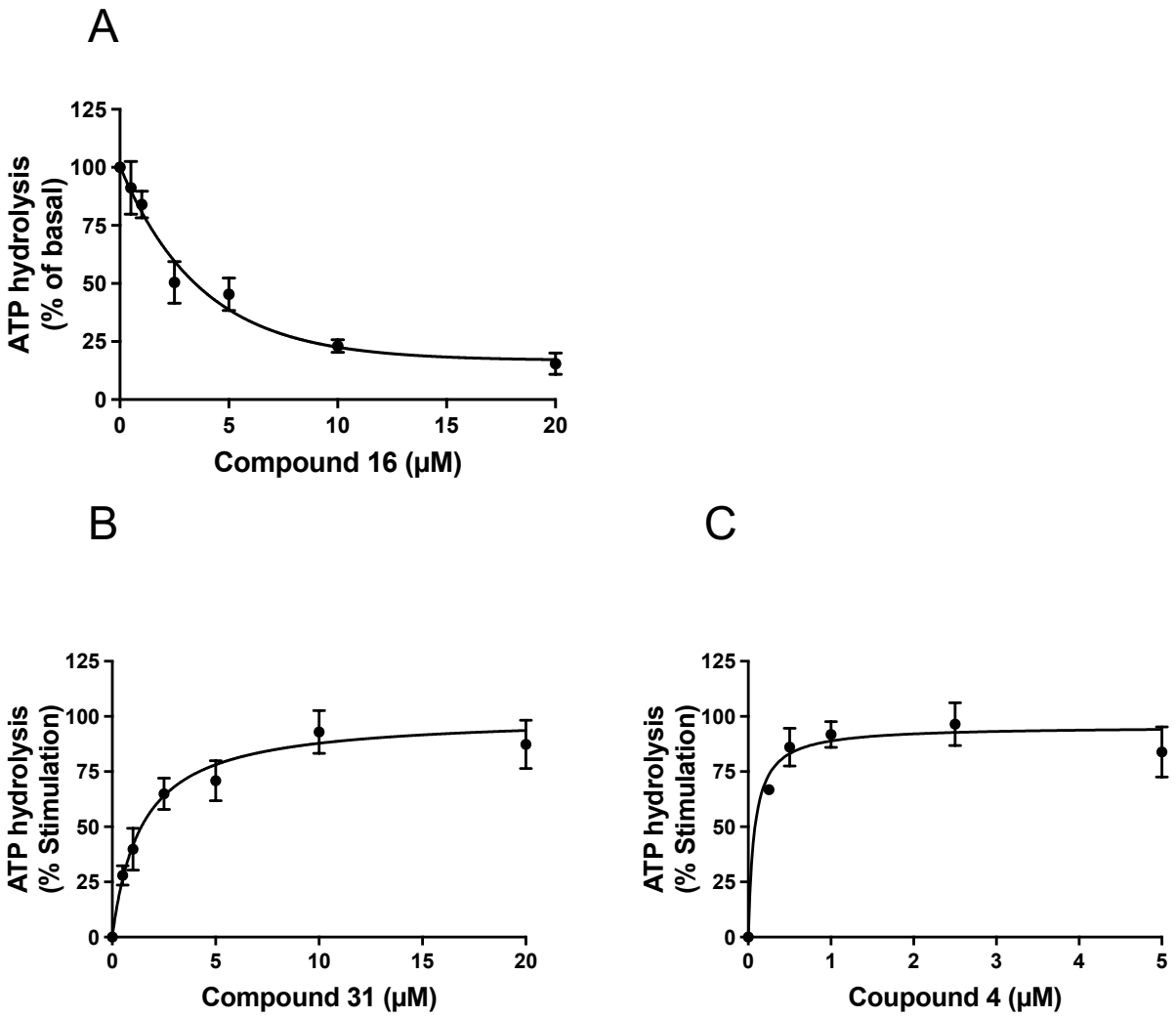
Compound **75** (67%) was prepared from compound **72** following the same method as for compound **73**. ^{1}H NMR (CD_3OD, 400 MHz) 7.72-7.70 (m, 2H), 7.44-7.42 (m, 2H), 7.07 (d, *J* = 3.6 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.70-6.66 (m, 2H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.84 (d, *J* = 6.8 Hz, 1H),

5.07 (s, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.23-4.08 (m, 2H), 3.80 (s, 3H), 3.58 (t, *J* = 7.2 Hz, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.25-2.21 (m, 1H), 2.00-1.93 (m, 2H), 1.70-1.67 (m, 1H), 1.57-1.53 (m, 4H), 1.28 (s, 3H), 1.21 (t, *J* = 7.2 Hz, 3H). HRMS calculated for $C_{36}H_{39}N_4O_6$ $(M + H)^+$: 623.2870; found 623.2875.

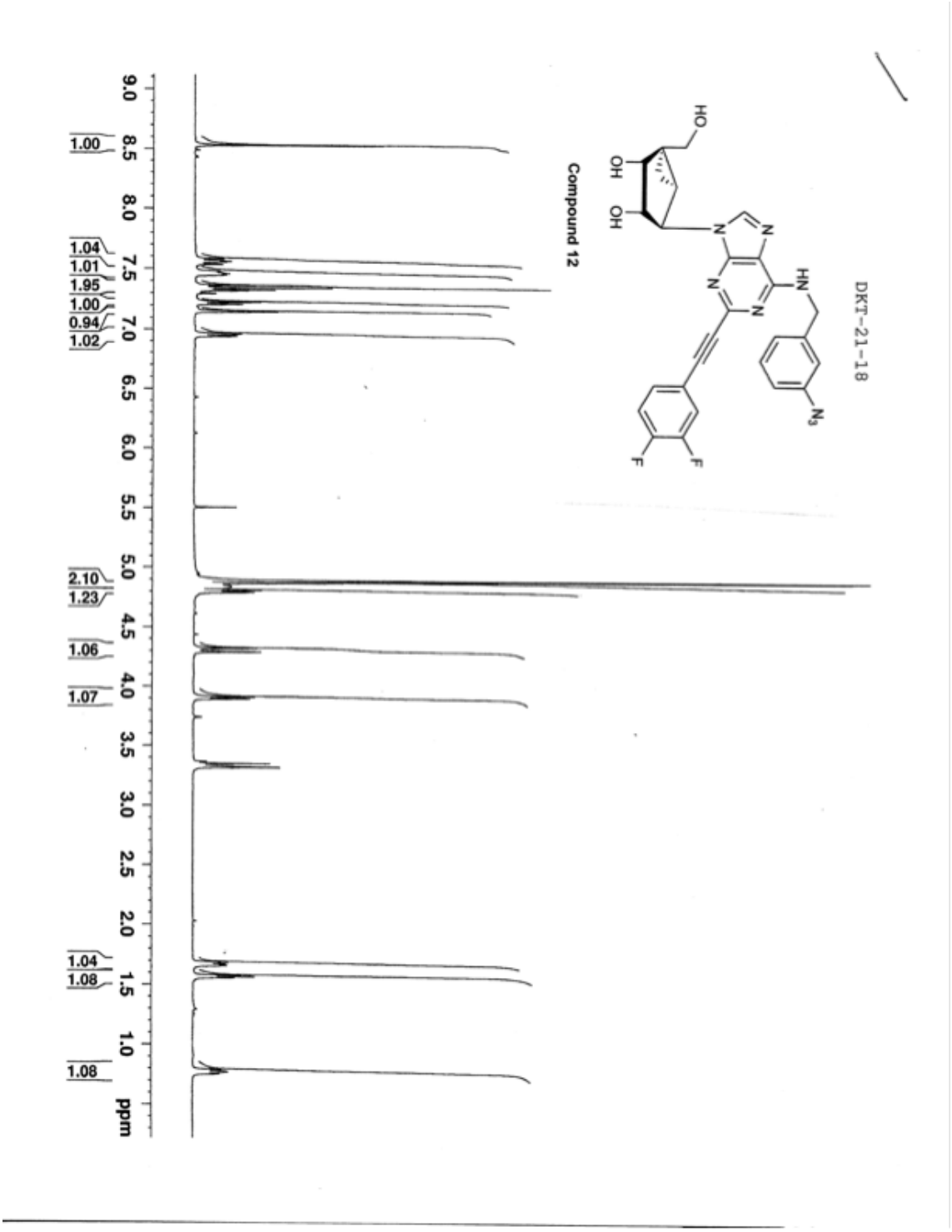
Ethyl (3aR,3bS,4aS,5R,5aS)-5-(2-((5-chlorothiophen-2-yl)ethynyl)-4-((3-(3-hydroxy-4-methoxyphenyl)propyl)amino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-2,2-dimethyltetrahydro cyclopropa[3,4]cyclopenta[1,2-d][1,3]dioxole-3b(3aH)-carboxylate (76)

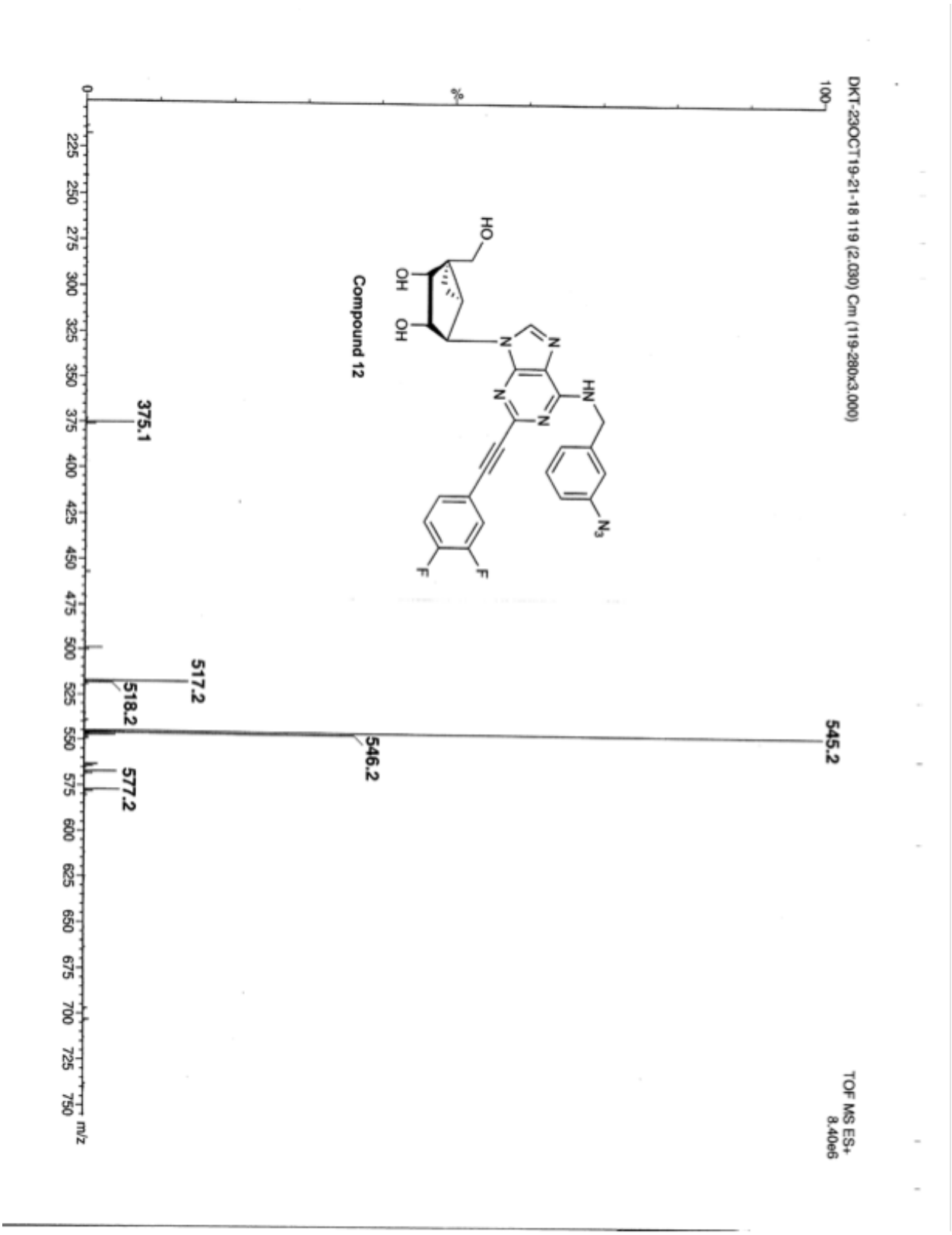
Compound **76** (68%) was prepared from compound **72** following the same method as for compound **73**. ^{1}H NMR (CD_3OD, 400 MHz) 7.35-7.27 (m, 2H), 7.08 (d, *J* = 4.0 Hz, 1H), 6.83 (d, *J* = 4.0 Hz, 1H), 6.70-6.66 (m, 2H), 5.83 (d, *J* = 7.2 Hz, 1H), 4.98 (s, 1H), 4.73 (d, *J* = 6.8 Hz, 1H), 4.24-4.17 (m, 2H), 3.81 (s, 3H), 3.69 (t, *J* = 6.0 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.28-2.22 (m, 1H), 1.96 (t, *J* = 7.6 H z, 2H), 1.73-1.67 (m, 1H), 1.53 (s, 3H), 1.30-1.25 (m, 4H). HRMS calculated for $C_{34}H_{36}N_4O_6SCl$ $(M + H)^+$: 663.2044; found 663.2035.

Figure S1. The modulation of A_3 adenosine ligands on the ABCG2 ATPase activity. The curves of the representative ligands, compounds **16** (A), **31** (B), and **4** (C), are shown. Each experiment was performed at least three times in duplicate.



NMR and HPLC results for representative newly prepared compounds

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TOF MS ES+
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100
%
0
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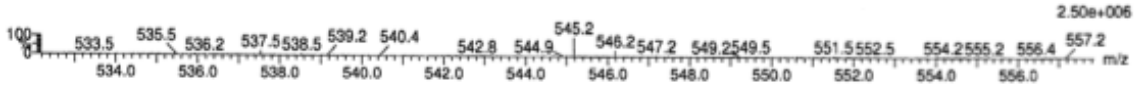
375.1
517.2
518.2
545.2
546.2
577.2
HO
OH
OH
HN
N3
F
F
Compound 12

Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
100 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 8-8 O: 0-60 F: 2-2
DKT-23OCT19-21-18 277 (4.702) AM2 (Ar,25000.0,0.00,0.00); ABS
TOF MS ES+



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Maximum:		5.0	5.0	100.0				
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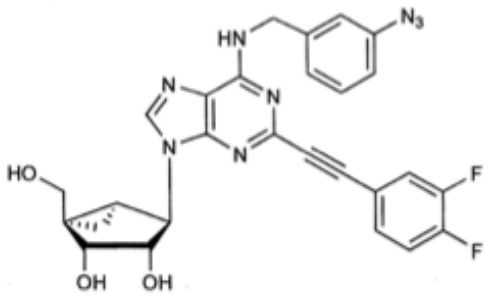
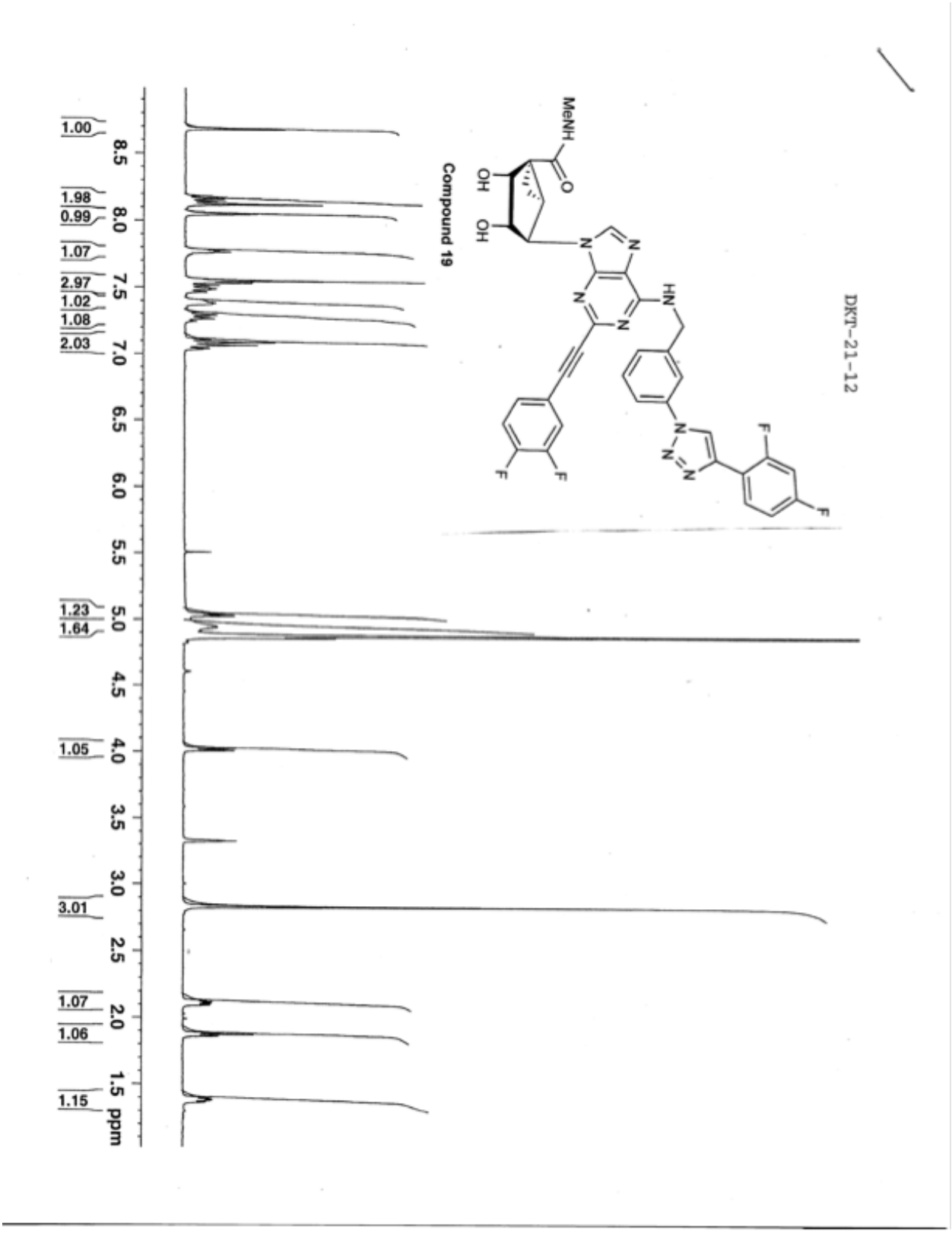


Compound 12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N
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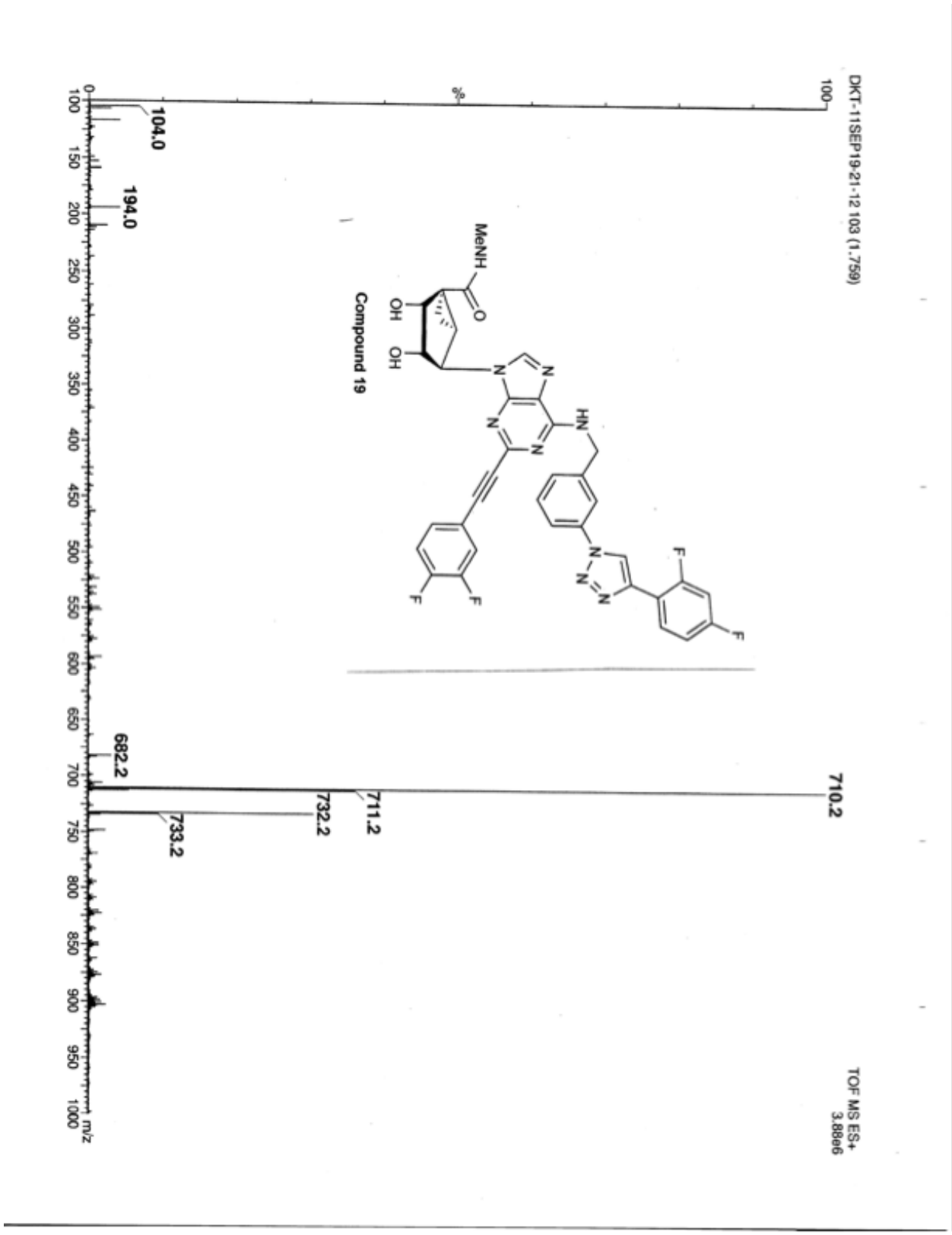
1.08
2.03
1.23
1.64
1.05
3.01
1.07
1.06
1.15
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

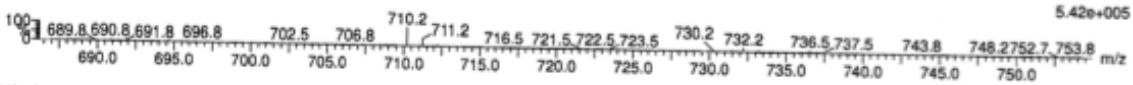

DKT-11SEP19-21-12 103 (1.759)
TOF MS ES+
3.88e6
Compound 19
MeNH
O
OH
OH
HN
N
F
104.0
194.0
682.2
710.2
711.2
732.2
733.2
m/z

Elemental Composition Report

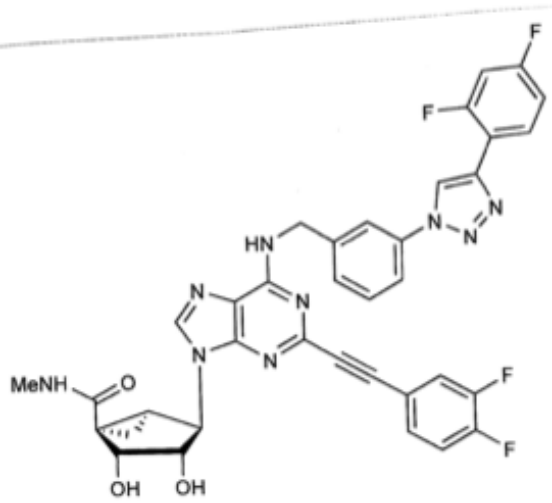
Page 1

Single Mass Analysis
Tolerance = 10.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

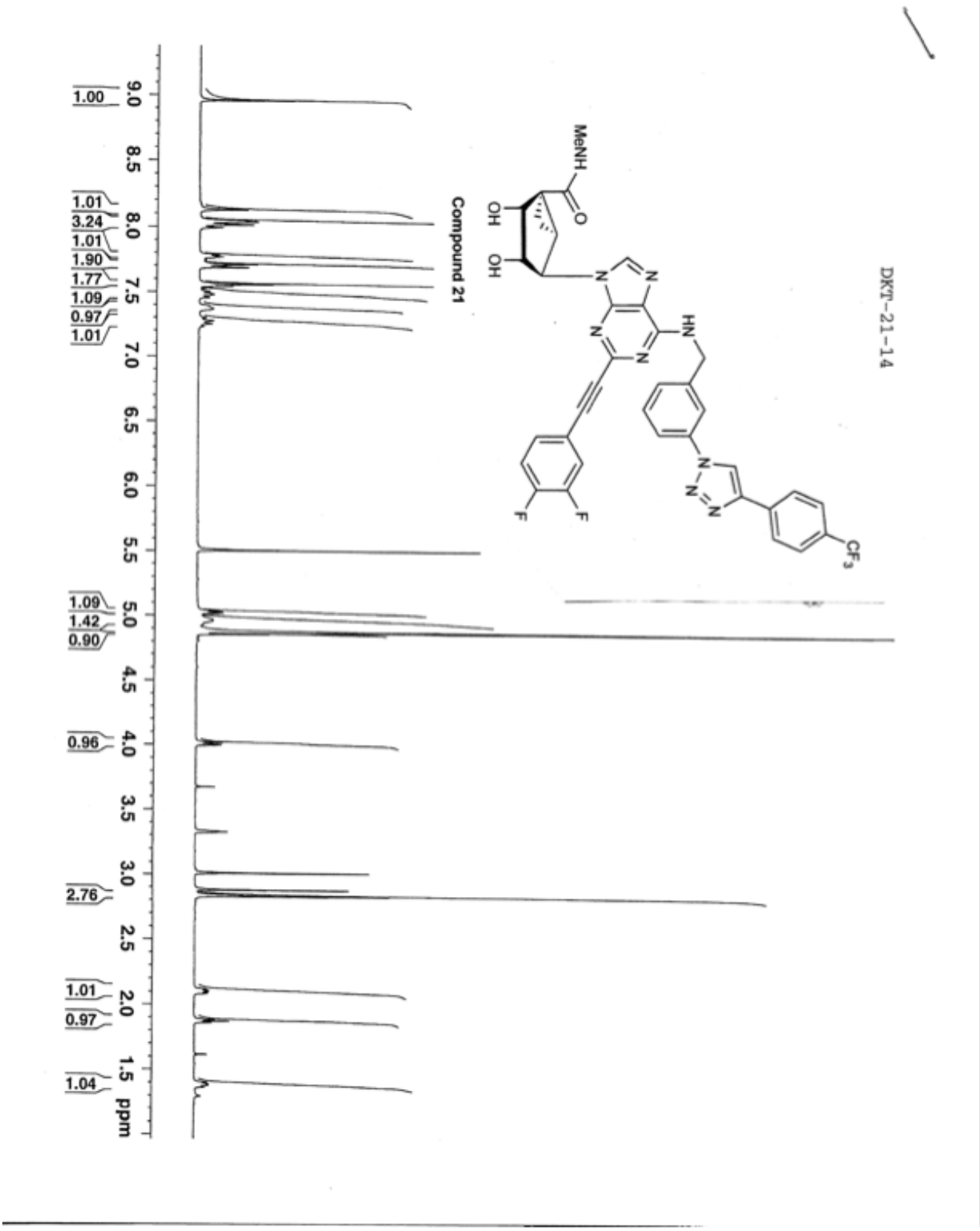
Monoisotopic Mass, Even Electron Ions
144 formula(e) evaluated with 4 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 9-9 O: 0-60 F: 4-4
DKT-11SEP19-21-12 108 (1.844) AM2 (Ar,25000.0,0.00,0.00); ABS
TOF MS ES+

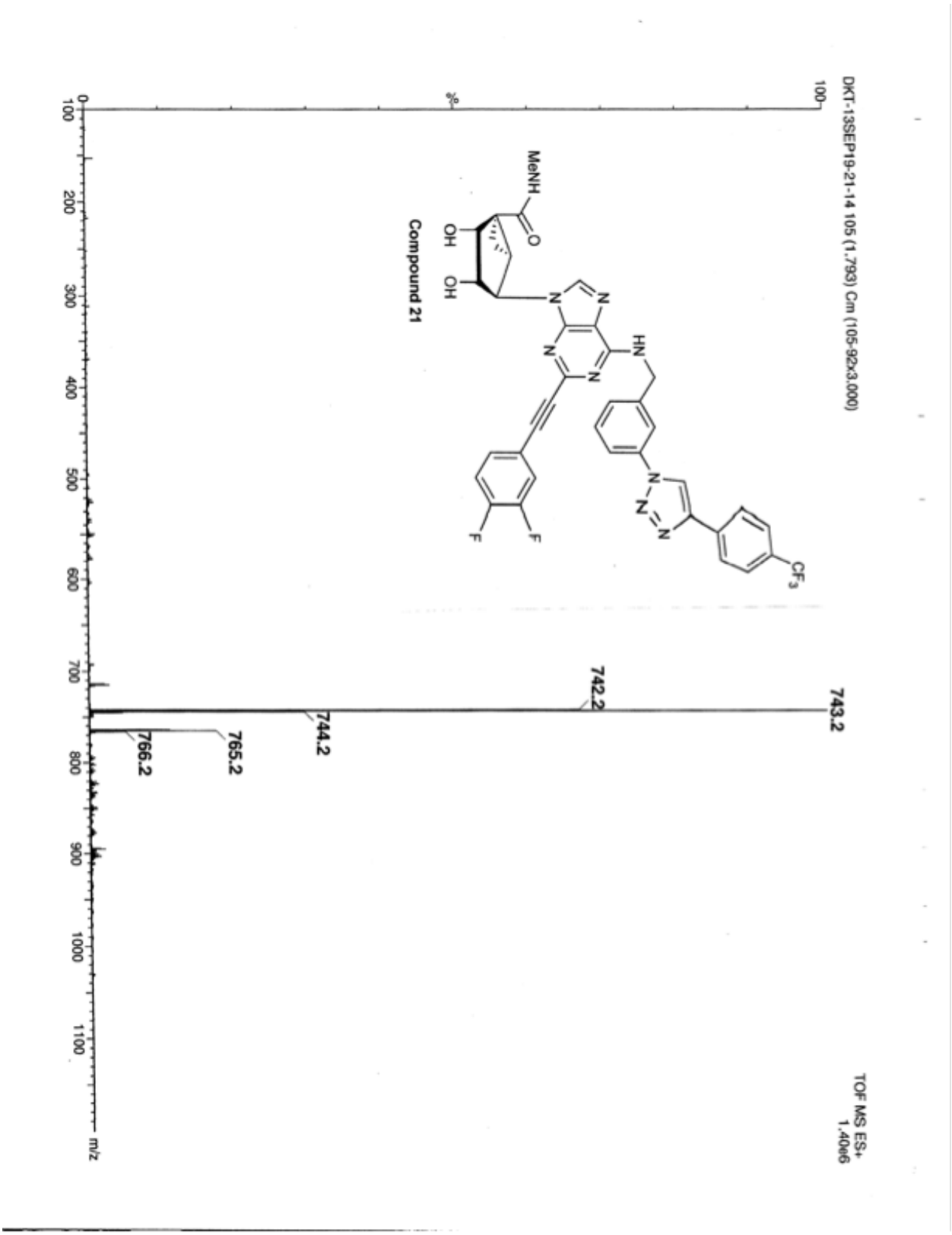


Minimum:				-1.5				
Maximum:		10.0	5.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
710.2252	710.2251	0.1	0.1	25.5	350.8	0.001	99.87	C36 H28 N9 O3 F4
	710.2216	3.6	5.1	3.5	361.8	10.973	0.00	C18 H36 N9 O16 F4
	710.2310	-5.8	-8.2	16.5	357.6	6.715	0.12	C29 H32 N9 O8 F4
	710.2157	9.5	13.4	12.5	361.6	10.770	0.00	C25 H32 N9 O11 F4



pound 19

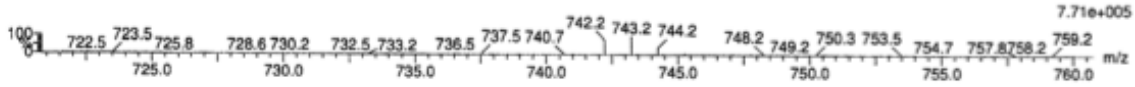

DKT-21-14
Compound 21
MeNH
O
OH
OH
N
HN
F
F
CF3
1.00
1.01
3.24
1.01
1.90
1.77
1.09
0.97
1.01
1.09
1.42
0.90
0.96
2.76
1.01
0.97
1.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm


DKT-13SEP19-21-14 105 (1.793) Cm (105-92x3.000)
TOF MS ES+
1.40e6
Compound 21
MeNH
O
OH
OH
HN
N
F
F
CF3
743.2
742.2
744.2
765.2
766.2
m/z
%
100
0
100
200
300
400
500
600
700
800
900
1000
1100

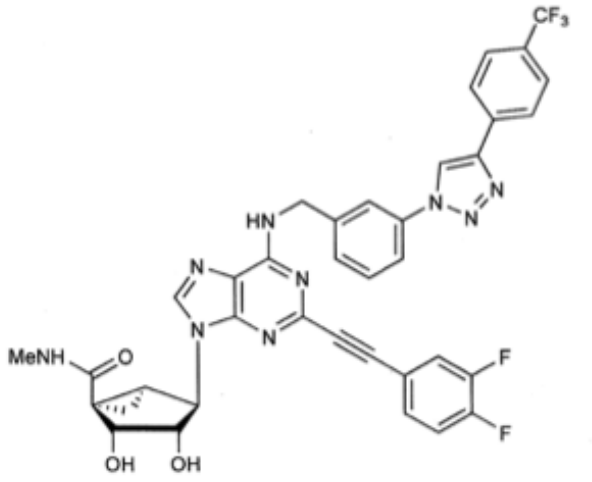
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

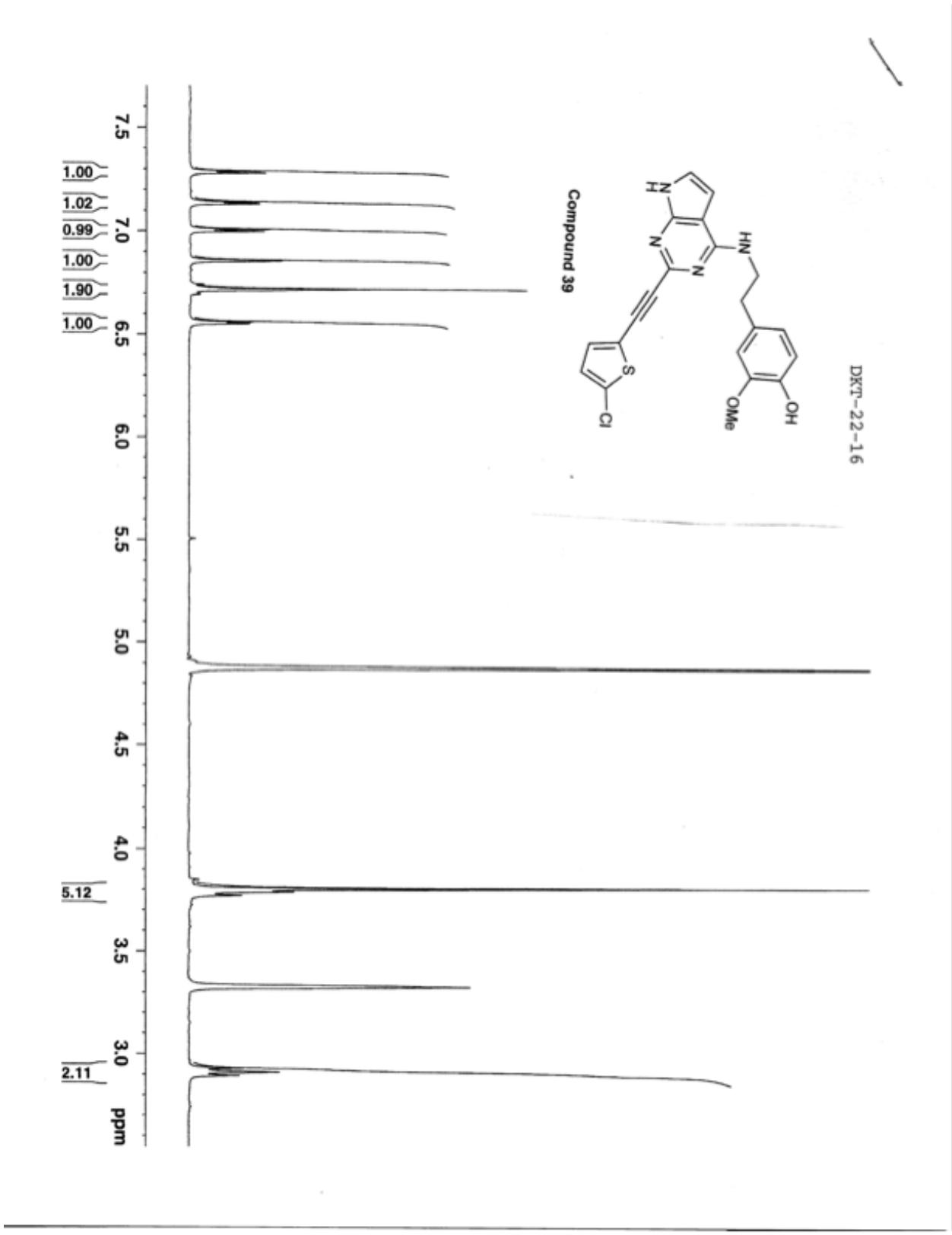
Monoisotopic Mass, Even Electron Ions
145 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 9-9 O: 0-60 F: 5-5
DKT-13SEP19-21-14 106 (1.810) AM2 (Ar,25000.0,0.00,0.00); ABS
TOF MS ES+

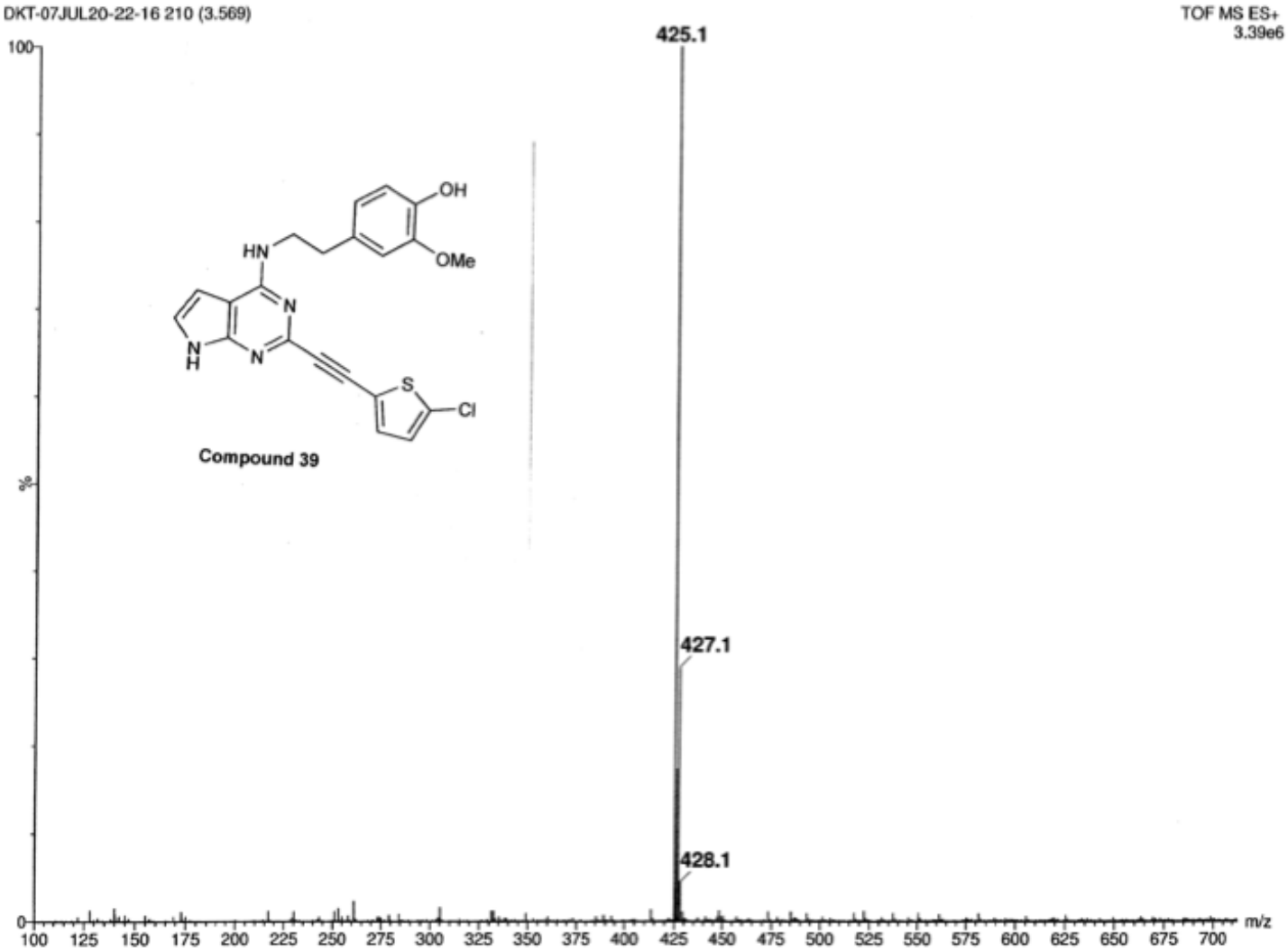


Minimum:				-1.5				
Maximum:		5.0	5.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
742.2305	742.2314	-0.9	-1.2	25.5	357.1	0.062	94.01	C37 H29 N9 O3 F5
	742.2278	2.7	3.6	3.5	359.9	2.815	5.99	C19 H37 N9 O16 F5



Compound 21

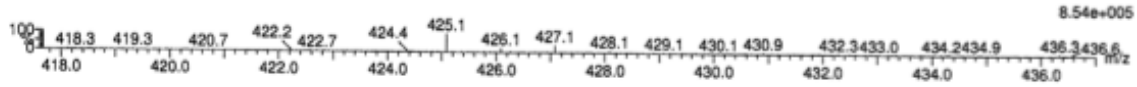

DKT-22-16
Compound 39
HN
OMe
OH
S
Cl
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm
1.00
1.02
0.99
1.00
1.90
1.00
5.12
2.11


DKT-07JUL20-22-16 210 (3.569)
TOF MS ES+
3.39e6
425.1
427.1
428.1
100
%
0
m/z
100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600 625 650 675 700
OH
OMe
HN
N
N
H
N
S
Cl
Compound 39

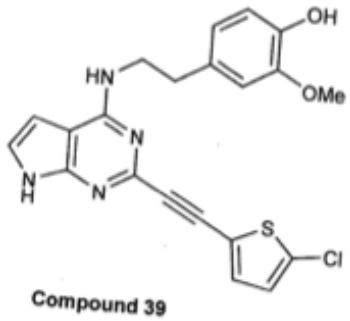
Elemental Composition Report **Page 1**

Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

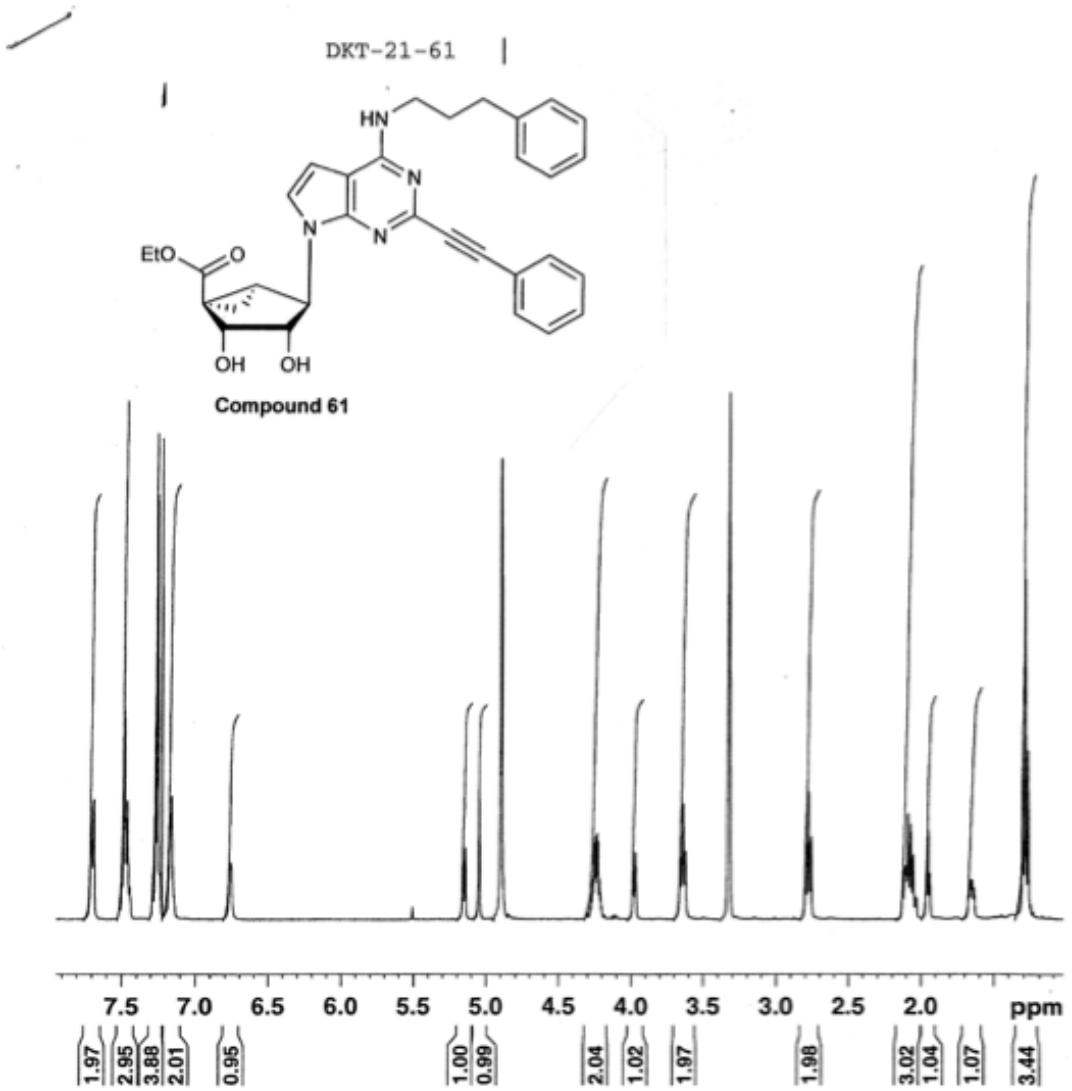
Monoisotopic Mass, Even Electron Ions
56 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 4-4 O: 0-60 32S: 1-1 35Cl: 1-1
DKT-07JUL20-22-16 219 (3.721) AM2 (Ar,25000.0,0.00,0.00); ABS
TOF MS ES+



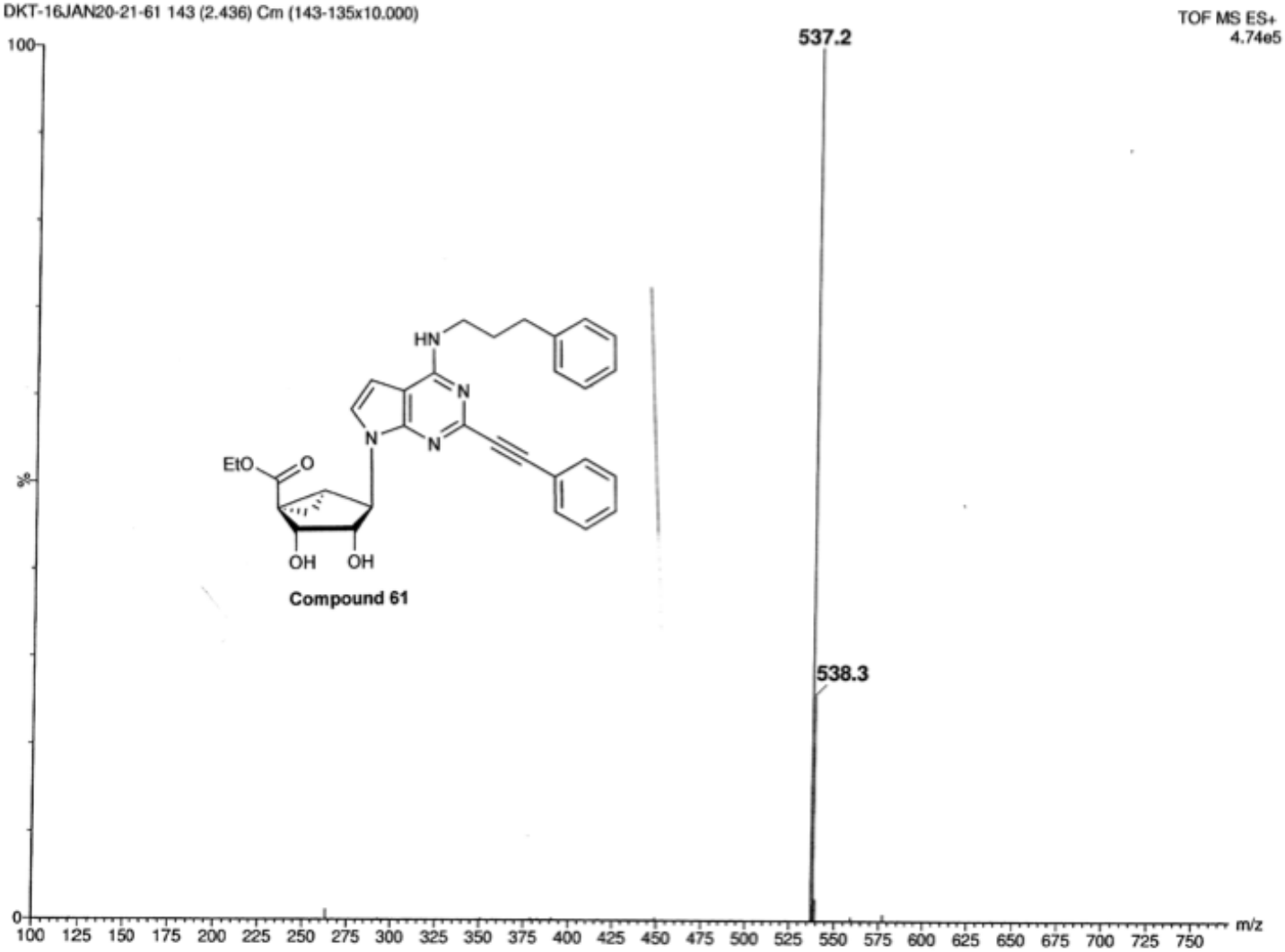
Minimum:				-1.5				
Maximum:		5.0	5.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
425.0844	425.0839	0.5	1.2	14.5	493.2	n/a	n/a	C21 H18 N4 O2 32S 35Cl



Compound 39



NAME	DKT-21-61
EXPNO	1
PROCNO	1
Date_	20200116
Time	16.33
INSTRUM	spect
PROBHD	5 mm PABBO BB-
PULPROG	zg30
TD	65536
SOLVENT	MeOD
NS	16
DS	0
SWH	8223.685 Hz
FIDRES	0.125483 Hz
AQ	3.9846387 se
RG	256
DW	60.800 us
DE	6.50 us
TE	296.2 K
D1	1.00000000 se
TD0	1
======== CHANNEL f1 ======	
NUC1	1H
P1	14.00 us
PL1	0.00 dB
PL1W	11.75562859 W
SFO1	400.1604711 MH
SI	32768
SF	400.1580000 MH
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00


DKT-16JAN20-21-61 143 (2.436) Cm (143-135x10.000)
TOF MS ES+
4.74e5
537.2
538.3
100
%
0
HN
N
N
N
EtO
O
OH
OH
Compound 61
100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600 625 650 675 700 725 750
m/z

Elemental Composition Report

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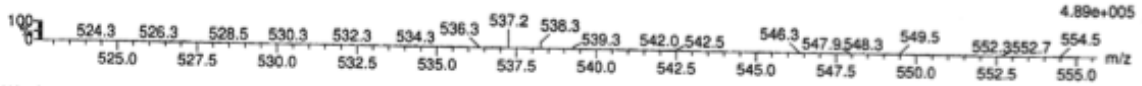
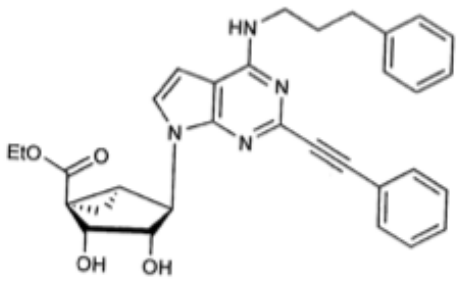
Single Mass Analysis
Tolerance = 8.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

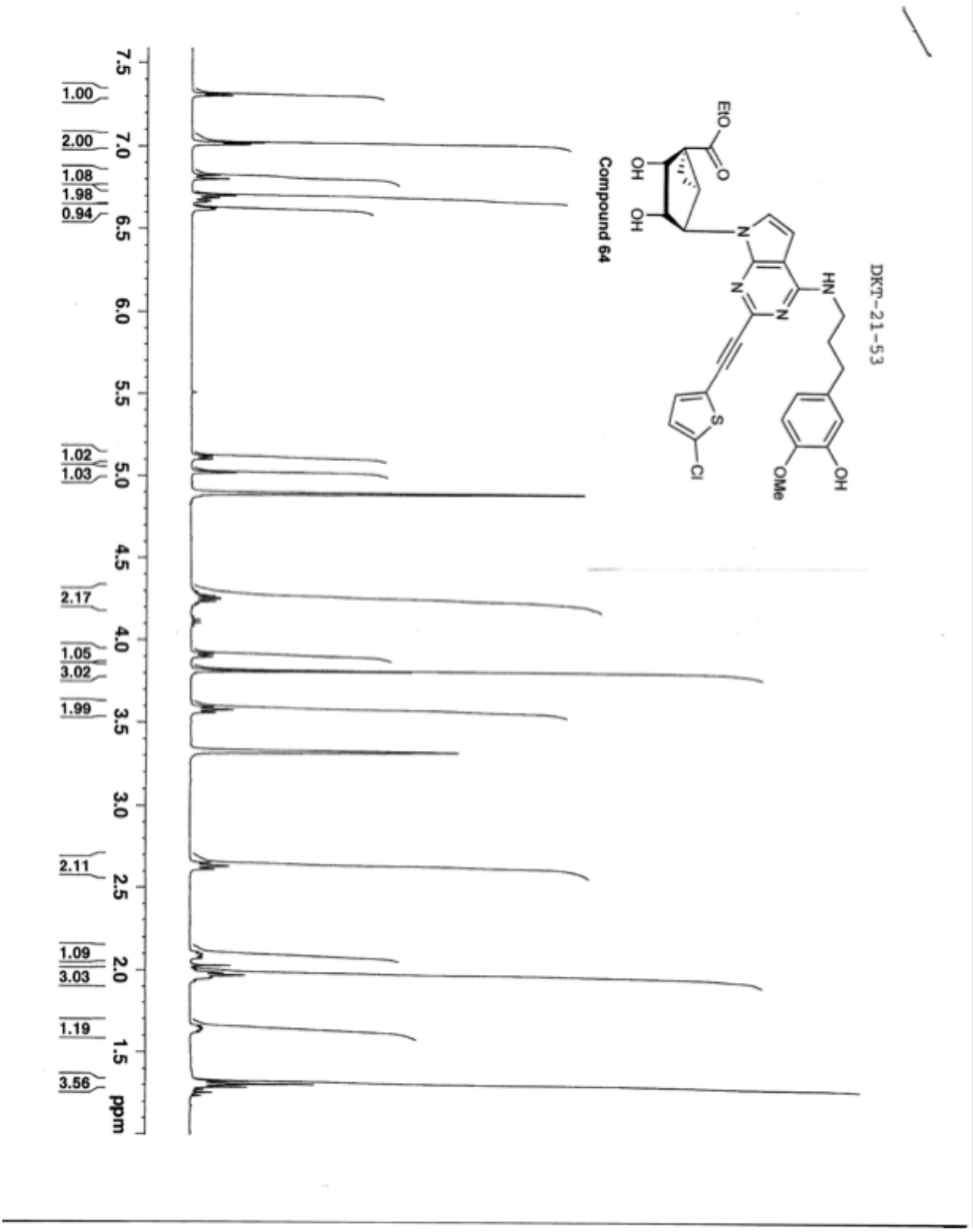
Monoisotopic Mass, Even Electron Ions
126 formula(e) evaluated with 2 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 4-4 O: 0-60
DKT-16JAN20-21-61 144 (2.453) AM2 (Ar,25000.0,0.00,0.00); ABS; Cm (144:145)
TOF MS ES+

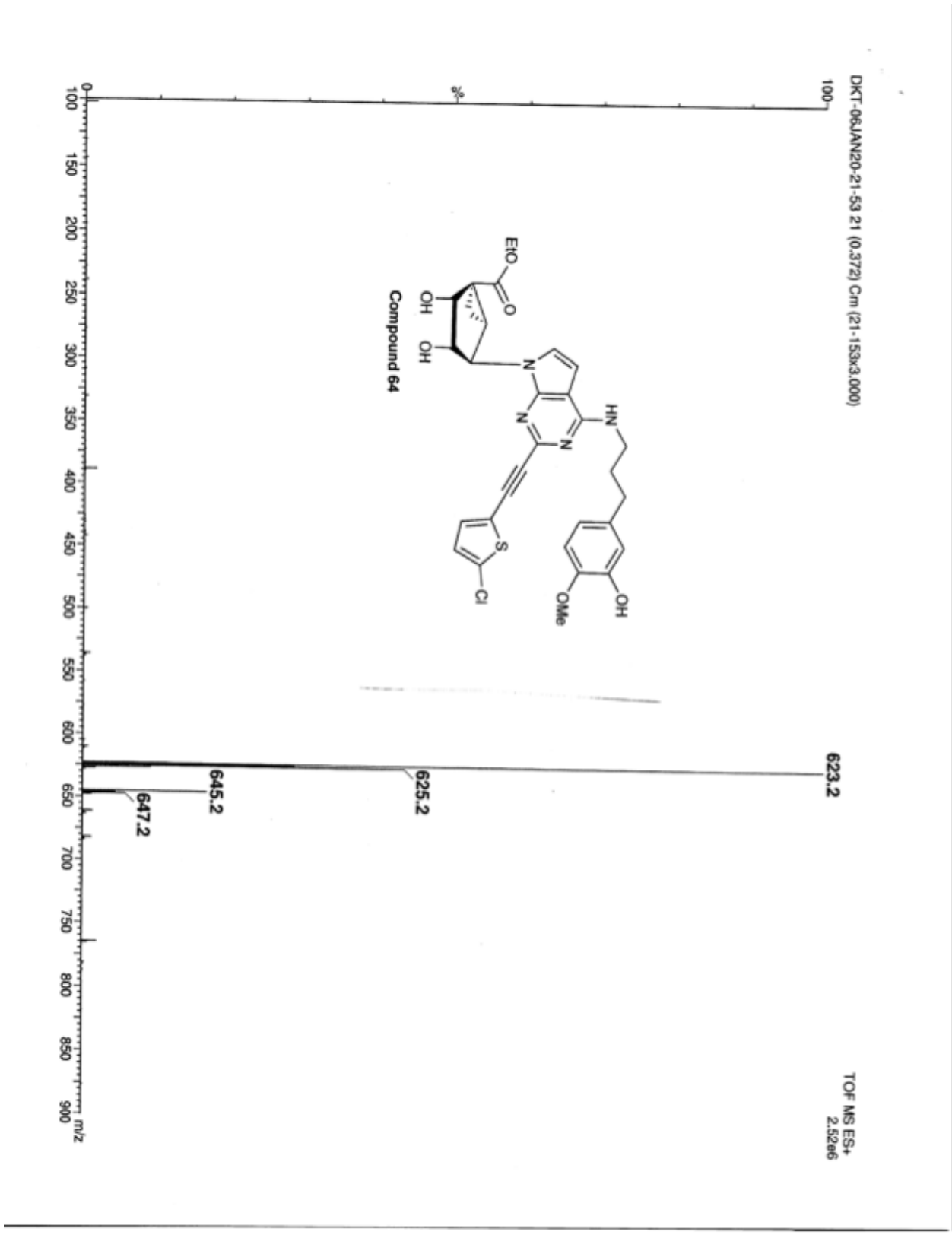


Minimum:				-1.5				
Maximum:		8.0	5.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
537.2496	537.2502	-0.6	-1.1	18.5	381.4	1.979	13.82	C32 H33 N4 O4
	537.2561	-6.5	-12.1	9.5	379.6	0.149	86.18	C25 H37 N4 O9



Compound 61


DKT-21-53
Compound 64
EtO
O
OH
OH
N
N
N
HN
S
Cl
OMe
OH
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
2.00
1.08
1.98
0.94
1.02
1.03
2.17
1.05
3.02
1.99
2.11
1.09
3.03
1.19
3.56

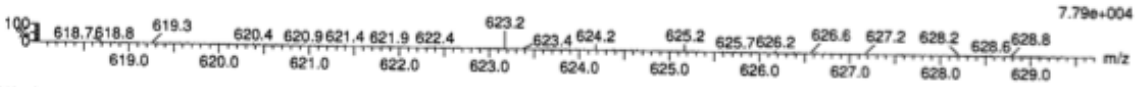

DKT-06JAN20-21-53 21 (0.372) Cm (21-153x3.000)
TOF MS ES+
2.52e6
623.2
625.2
645.2
647.2
m/z
Compound 64
EtO
O
OH
OH
HN
N
N
N
S
Cl
OMe
OH

Elemental Composition Report **Page 1**

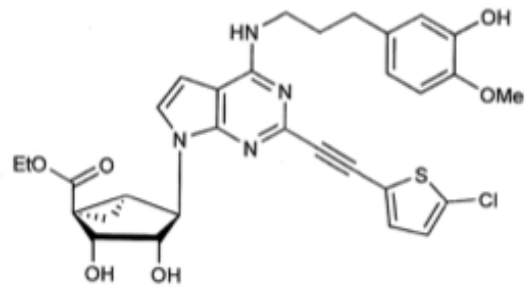
Single Mass Analysis
Tolerance = 5.0 mDa / DBE: min = -1.5, max = 100.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions
135 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:
C: 0-100 H: 0-250 N: 4-4 O: 0-60 32S: 1-1 35Cl: 1-1

DKT-06JAN20-21-53 26 (0.457) AM2 (Ar,25000.0,0.00,0.00); ABS
TOF MS ES+



Minimum:				-1.5				
Maximum:		5.0	5.0	100.0				
Mass	Calc. Mass	mDa	PPM	DBE	i-FIT	Norm	Conf(%)	Formula
623.1736	623.1731	0.5	0.8	17.5	348.2	n/a	n/a	C31 H32 N4 O6 32S 35Cl



Compound 64