Supplemental Information

Selectivity and Physicochemical Optimization of Repurposed Pyrazolo[1,5-*b*]pyridazines for the Treatment of Human African Trypanosomiasis

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Table of Contents

Table S1. Measured pEC_{50} values from original hits at different time points against *T. b. brucei*. Compounds with a $pEC_{50} \geq 6$ at 18 h were deemed fast acting. The pEC_{99} values were determined by incubating compound with the parasite for 18 h, then washing out the compound and incubating for 72 h, to determine the minimal trypanocidal concentration (EC_{99}) which abolishes 99 % of growth recovery. Compounds with a $pEC_{99} \geq 6$ were deemed cidal.[1] 3

Table S2. Expanded table of R^1 and R^3 substituents activity against *T. b. brucei* and ADME properties. ...3

Figure S1. Comparison of *T. b. brucei* pEC_{50} inhibition data to literature values for **a.** GSK-3β pIC_{50}; **b.** CDK-2 pIC_{50}; **c.** CDK-4 pIC_{50}. Colored on whether there was no substitution at R^1 and R^2 (blue), substitution at R^1 (orange), or substitution at R^2 (grey). 12

Table S3. Mouse plasma stability in CD-1 mouse cells. Compounds were dosed at 5μM and incubated for 2 h, with CD-1 cells and K2-EDTA as an anticoagulant. 13

Table S4. Measured % Stability of the compounds and fold induction of hydroxylation of testosterone to hydroxytestosterone in cytochrome P450 (CYP450) isozymes 3A4 after 2 h. Both compounds were deemed to not induce or be substrates of CYP450 3A4. 13

Table S5. Measured permeability between Apical (A) and Basal (B) plasma membrane domains of Caco-2 cells. Compounds were dosed either in the A or B receiver compartment, then measured after 2 h. The apparent permeability (P_{app}) is equal to $dQ/(dt*X*C_0)$ where dQ/dt = amount of product present in basal (A-B) or apical (B-A) in function of time (nmol/s), X = area of transwell (cm^2) and C_0 = initial concentration of product (nmol/ml) applied in apical or basal compartment. Compounds with a $P_{app} > 1*10^{-6}$ (cm/s) are deemed highly permeable. Compounds with an efflux ratio > 2 are deemed to be effluxed. 13

Table S6. Measured pEC_{50} values at different time points against *T. b. brucei*. Compounds with a $pEC_{50} \geq 6$ at 18 h were deemed fast acting. The washout value was obtained after incubating *T. b. brucei* with the compound for 18 h, then washing out the compound, and incubating the parasite for 72 h; compounds with a $pEC_{99} \geq 6$ were deemed cidal. 14

Figure S2. Peripheral blood levels of **20r** after IP administration to female NMRI mice (n=3) at a target dose 10 mg/kg in 1% DMSO, 20% Captisol® in water. Individual values for each time point are represented in the plot. 14

Table S7. Blood and brain levels of **20r**, after IP administration of 10 mg/kg single dose (target dose) to female NMRI mice (n=3). LLOQ=10 ng/mL(blood); 50 ng/g (brain). 14

Table S8. Blood and brain levels of **20g**, after IP administration of 10 mg/kg single dose (target dose) to female NMRI mice (n=3). 15

Table S9. Percentage inhibition of **20g** against human kinase panel (Eurofins) at 1 μM. 15

Table S10. Parasitemia levels (measured as parasites per milliliter) of *T. b. brucei* STIB795 from efficacy study of **20g** dosed at 10 mg/kg/day during 5-day treatment of mice. 16

Table S11. Measured activity of compounds against *Trypanosoma cruzi*, and *Leishmania donovani* as well as L6 and THP-1. 17

Table S.12. Measured severity score of compounds (10 μM) against adult *Schistosoma mansoni* at the indicated time points. Compounds were scored based on the non-mutually exclusive phenotypic responses of the parasite that involved changes in translucency, motility and ability to adhere to the substratum. Each response was awarded a score of 1 and added up to the maximum score of 4. Degeneracy or damage to the outer surface of the worm was scored as 4. The anthelmintic, niclosamide, was used as a positive control and causes degeneracy, tegumental damage and eventually death. 19

Table S.13. SEM measurements for *T. b. brucei* and MRC5 activity. 19

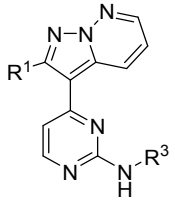
Table S14. HPLC trace of key compounds. 21

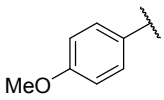
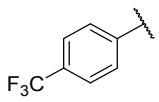
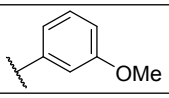
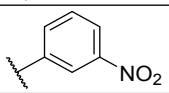
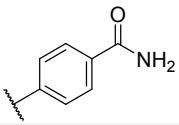
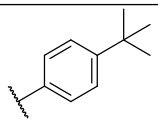
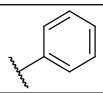
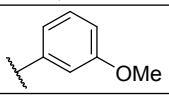
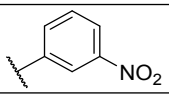
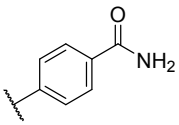
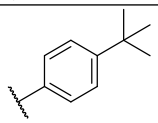
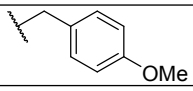
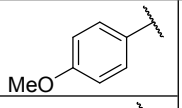
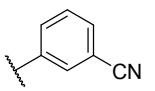
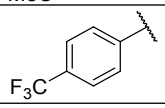
Table S1. Measured pEC_{50} values from original hits at different time points against *T. b. brucei*. Compounds with a $pEC_{50} \geq 6$ at 18 h were deemed fast acting. The pEC_{99} values were determined by incubating compound with the parasite for 18 h, then washing out the compound and incubating for 72 h, to determine the minimal trypanocidal concentration (EC_{99}) which abolishes 99 % of growth recovery. Compounds with a $pEC_{99} \geq 6$ were deemed cidal.[1]

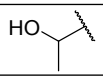
Cpd	6 h	12 h	18h	24 h	pEC_{99}
10c	5.3	5.5	5.6	5.8	5.5
1	6.3	7.2	7.3	7.5	7.1
10o	5.7	6.5	6.6	6.8	6.2
10e	5.2	6.4	6.6	6.8	6.3
10k	6.2	6.3	6.3	6.7	6.3
10r	6.3	6.8	7.2	7.5	6.7
10m	4.4	6.0	6.1	6.2	5.6
10i	4.4	4.7	4.8	5.3	*nt*
10l	4.5	4.4	4.5	4.8	4.2
9	5.1	5.5	5.8	6.2	*nt*

nt = not tested

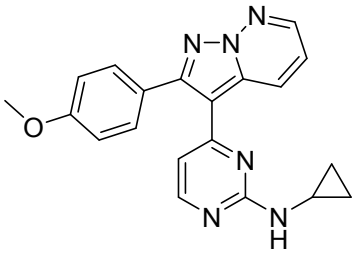
Table S2. Expanded table of R^1 and R^3 substituents activity against *T. b. brucei* and ADME properties.



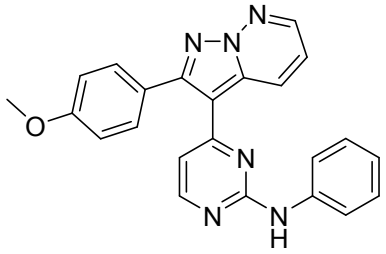
Cpd	R^1	R^3	*T. b. brucei* pEC_{50}	Aq. Sol. (µM)	LogD 7.4	RH Cl_{int}*	HLM Cl_{int}**	PPB (%)	MRC 5 pTC_{50}
S1a			5.6 ± 0.13	1	3.6	74	40	98	< 4.3 ± 0.00
S1b			5.7 ± 0.21	1	4.8	59	49	> 99	< 4.3 ± 0.00
10f			5.3 ± 0.07	< 0.3	> 4.3	10	16	> 99	< 4.3 ± 0.00
S1c			5.3 ± 0.01	0.03	> 4.3	19	28	> 99	< 4.3 ± 0.00
S1d			5.5 ± 0.08	< 2	> 3.9	nt	< 3	> 99	< 4.3 ± 0.00
S1e			5.3 ± 0.03	< 0.09	4.3	56	< 3	100	< 4.3 ± 0.00
S1f			4.4 ± 0.00	< 0.1	4	15	< 3	> 99	< 4.3 ± 0.00
S1g			< 4.4 ± 0.00	560	2.8	21	43	90	< 4.3 ± 0.00
S1h			4.3	10	2.9	23	49	93	< 4.3 ± 0.00
S1i			5.6 ± 0.11	< 6	*nt*	25	87	96	< 4.3 ± 0.00
S1j			5.3 ± 0.04	7	1.6	< 1	< 3	66	< 4.3 ± 0.00
S1k			4.6 ± 0.22	10	4.4	> 300	52	99	< 4.3 ± 0.00
S2a			< 4.4 ± 0.00	11	2.9	78	32	94	< 4.3 ± 0.00
21a			5.9 ± 0.01	*nt*	*nt*	*nt*	*nt*	*nt*	< 4.9 ± 0.00
21b			6.2 ± 0.08	0.2	4.8	37	16	97	< 4.3 ± 0.00
21c			4.9 ± 0.04	12	2.8	25	46	95	< 4.3 ± 0.00
21d			6.5 ± 0.05	20	2.5	63	240	93	< 4.3 ± 0.00

21e			6.2 ± 0.07	0.9	3.3	53	> 300	99	< 4.3 ± 0.00
21f			6.1 ± 0.07	2	2.9	27	150	*nt*	< 4.3 ± 0.00
21g			6.2 ± 0.04	28	4.4	83	100	*nt*	4.5 ± 0.03
21h			6.7 ± 0.05	11	> 4.2	18	80	> 99	< 4.3 ± 0.00

* = (µL/min/10^6 cells)
** = (µL/min/mg)
nt = not tested

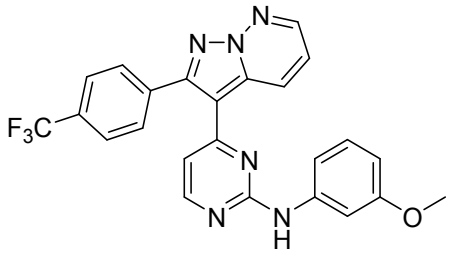


***N*-Cyclopropyl-4-(2-(4-methoxyphenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-amine (S1a)**. In a vial 3-(2-chloropyrimidin-4-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-*b*]pyridazine **7f** (15 mg, 44 µmol), cyclopropylamine (6 µL, 87 µmol), and DIPEA (16 µL, 87 µmol) were stirred in *n*-BuOH and the reaction mixture was subjected to microwave irradiation at 150 °C for 1 h. Reaction mixture was then concentrated and column purification was performed using EtOAC: hex, 40-100%, 10 CV to provide the title compound as a buff solid (11 mg, 69%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.91 - 8.99 (m, 1 H) 8.36 (dd, *J*=4.40, 1.95 Hz, 1 H) 8.14 (d, *J*=5.37 Hz, 1 H) 7.62 - 7.69 (m, 2 H) 7.13 (dd, *J*=9.28, 4.39 Hz, 1 H) 6.96 - 7.03 (m, 2 H) 6.55 (d, *J*=5.37 Hz, 1 H) 3.89 (s, 3 H) 2.81 - 2.90 (m, 1 H) 0.83 - 0.92 (m, 2 H) 0.62 - 0.69 (m, 2 H). LC-MS (m/z): 359.0 [M+1].

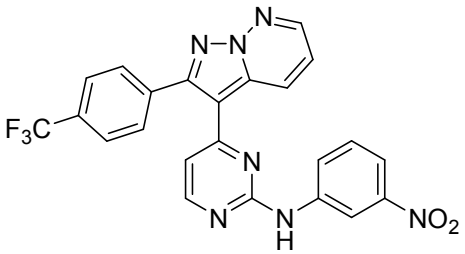


4-(2-(4-Methoxyphenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)-*N*-phenylpyrimidin-2-amine (S1b). In a vial 3-(2-chloropyrimidin-4-yl)-2-(4-methoxyphenyl)pyrazolo[1,5-*b*]pyridazine **7f** (11 mg, 33 µmol), and aniline (6 µL, 65 µmol) were stirred in *n*-BuOH at 110 °C for 16 h. Reaction mixture was then concentrated and

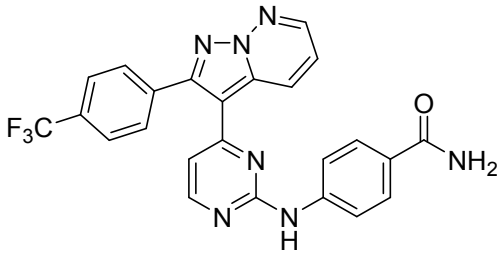
column purification done on using EtOAC: hex, 40-100%, 8 CV followed by EtOAc: MeOH, 0-20%, 10 CV to afford the title compound as a beige solid (12 mg, 93%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.72 (dd, *J*=9.28, 1.95 Hz, 1 H) 8.37 (dd, *J*=4.40, 1.95 Hz, 1 H) 8.24 (d, *J*=5.37 Hz, 1 H) 7.60 - 7.69 (m, 4 H) 7.31 - 7.39 (m, 3 H) 7.06 - 7.12 (m, 2 H) 6.98 - 7.03 (m, 2 H) 6.67 (d, *J*=5.37 Hz, 1 H) 3.89 (s, 3 H). LC-MS (m/z): 395.0 [M+1].



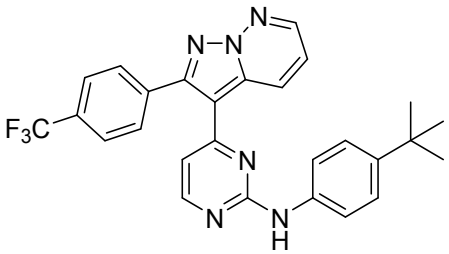
***N*-(3-Methoxyphenyl)-4-(2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-amine (S1c)**. To an oven-dried flask containing a solution of 3-(2-chloropyrimidin-4-yl)-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazine **7d** (20 mg, 53 µmol) in 1 mL *n*-BuOH was added m-anisidine (12 µL, 106 µmol) and the reaction was heated to 110 °C for 16 h. Solid ppt seen in the vial. After completion, the reaction was concentrated to dryness and purified by column chromatography using EtOAc: hex, 20-100% 12 CV to afford the title compound as a yellow solid (20 mg, 81%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.75 (dd, *J*=8.79, 1.95 Hz, 1 H) 8.45 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.22 (d, *J*=5.37 Hz, 1 H) 7.91 (br. s., 1 H) 7.86 (d, *J*=8.30 Hz, 2 H) 7.75 (d, *J*=8.30 Hz, 2 H) 7.37 (t, *J*=2.44 Hz, 1 H) 7.25 - 7.28 (m, 1 H) 7.17 (dd, *J*=8.79, 4.39 Hz, 1 H) 7.13 (dd, *J*=7.81, 2.44 Hz, 1 H) 6.69 (dd, *J*=7.81, 2.44 Hz, 1 H) 6.59 (d, *J*=5.37 Hz, 1 H) 3.80 (s, 3 H). LC-MS (m/z): 463.1 [M+1].



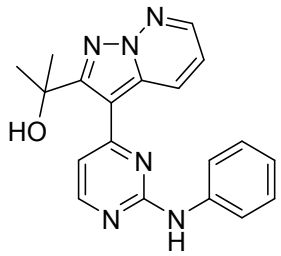
***N*-(3-Nitrophenyl)-4-(2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-amine (S1d)**. To an oven-dried flask containing a solution of 3-(2-chloropyrimidin-4-yl)-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazine **7d** (20 mg, 53 µmol) in *n*-BuOH, 3-nitroaniline (15 mg, 106 µmol) was added and the reaction was heated to 110 °C for 16 h. A precipitate was filtered out and washed with methanol followed by diethyl ether and dried under high vacuum to provide the title compound as a solid (16 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.22 (s, 1 H) 8.83 - 8.91 (m, 1 H) 8.79 (t, *J*=2.44 Hz, 1 H) 8.69 (dd, *J*=4.40, 1.95 Hz, 1 H) 8.50 (d, *J*=5.37 Hz, 1 H) 7.96 - 8.01 (m, 1 H) 7.90 (d, *J*=8.30 Hz, 2 H) 7.84 (d, *J*=8.30 Hz, 2 H) 7.76 (dd, *J*=8.30, 2.44 Hz, 1 H) 7.44 - 7.54 (m, 2 H) 6.77 (d, *J*=5.37 Hz, 1 H). LC-MS (m/z): 478.0 [M+1].



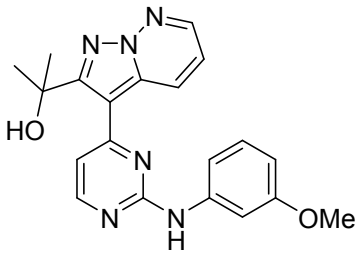
4-((4-(2-(4-(Trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-yl)amino)benzamide (S1e). To an oven-dried flask containing a solution of 3-(2-chloropyrimidin-4-yl)-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazine **7d** (20 mg, 53 µmol) in *n*-BuOH, 4-aminobenzamide (15 mg, 110 µmol) was added and the reaction was heated to 110 °C for 16 h. After 16 h additional 4-aminobenzamide (30 mg, 220 µmol) was add the reaction mixture was heated to 110 °C for another 16 h. A precipitate was filtered and washed with methanol followed by diethyl ether and dried under high vacuum to provide the title compound as an off-white solid (12 mg, 47%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.95 (s, 1 H) 8.83 - 8.91 (m, 1 H) 8.68 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.46 (d, *J*=5.37 Hz, 1 H) 7.86 - 7.93 (m, 4 H) 7.68 - 7.79 (m, 5 H) 7.50 (dd, *J*=8.79, 4.39 Hz, 1 H) 7.15 (br. s, 1 H) 6.72 (d, *J*=5.37 Hz, 1 H). LC-MS (m/z): 476.1 [M+1].



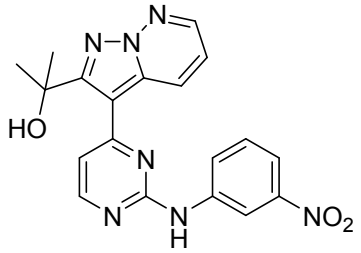
***N*-(4-(*tert*-Butyl)phenyl)-4-(2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-amine (S1f)**. To an oven-dried flask containing a solution of 3-(2-chloropyrimidin-4-yl)-2-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-b]pyridazine **7d** (20 mg, 53 µmol) in *n*-BuOH, 4-(tert-butyl)aniline (17 µL, 110 µmol) was added and the reaction was heated to 110 °C for 16 h. Solid precipitation seen in the reaction vial, which was filtered and washed with methanol followed by diethyl ether and the product isolated was dried over high vacuum to afford the title compound as a yellow solid (17 mg, 65%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.55 (s, 1 H) 8.78 - 8.85 (m, 1 H) 8.66 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.39 (d, *J*=5.37 Hz, 1 H) 7.85 - 7.93 (m, 4 H) 7.41 - 7.48 (m, 3 H) 7.18 (d, *J*=8.79 Hz, 2 H) 6.64 - 6.69 (m, 1 H) 1.25 (s, 9 H). LC-MS (m/z): 489.1 [M+1].



2-(3-(2-(Phenylamino)pyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol (S1g). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (20 mg, 69 µmol) in 1 mL *n*-BuOH, aniline (13 µL, 140 µmol) was added and the reaction was heated to 110 °C for 16 h. On completion the reaction was concentrated to dryness and purified by column chromatography using EtOAc: hex, 50-100% 12 CV to afford the title compound as a yellow solid (14 mg, 58%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.47 (d, *J*=5.37 Hz, 1 H) 8.37 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.22 (dd, *J*=8.79, 1.95 Hz, 1 H) 7.65 (br. s, 1 H) 7.59 (d, *J*=7.81 Hz, 2 H) 7.37 (t, *J*=7.81 Hz, 2 H) 7.11 - 7.18 (m, 3 H) 1.72 (s, 6 H). LC-MS (m/z): 347.7 [M+1].

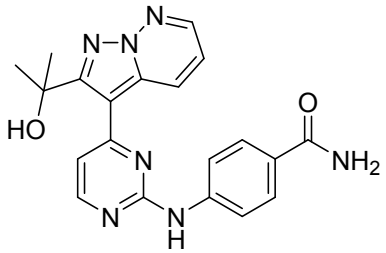


2-(3-(2-((3-Methoxyphenyl)amino)pyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol (S1h). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (30 mg, 104 µmol) in *n*-BuOH, 3-methoxyaniline (26 µL, 207 µmol) was added and the reaction was heated to 110 °C for 16 h. After completion of reaction the reaction mixture was concentrated to dryness and purified by column chromatography using EtOAc: hex, 50-100% 12 CV to afford the title compound as a brown solid (12 mg, 32%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.49 (d, *J*=5.37 Hz, 1 H) 8.36 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.23 (dd, *J*=9.28, 1.95 Hz, 1 H) 7.65 (br. s., 1 H) 7.29 - 7.31 (m, 1 H) 7.25 (t, *J*=8.30 Hz, 1 H) 7.12 - 7.18 (m, 2 H) 7.10 (d, *J*=5.37 Hz, 1 H) 6.66 (dd, *J*=8.30, 2.44 Hz, 1 H) 3.81 (s, 3 H) 1.72 (s, 6 H). LC-MS (m/z): 377.1 [M+1].

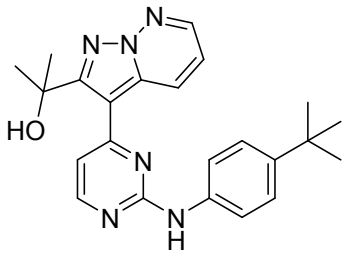


2-(3-(2-((3-Nitrophenyl)amino)pyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol (S1i). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (20 mg, 69 µmol) in *n*-BuOH, 3-nitroaniline (19 mg, 140 µmol) was added and the reaction was heated to 110 °C for 16 h. On completion of reaction the reaction mixture was concentrated to dryness and purified by column chromatography using EtOAc: hex, 50-100% 12 CV to afford the title compound as a solid (14 mg, 52%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.82 (t, *J*=1.95 Hz, 1 H) 8.54 (d, *J*=5.37 Hz, 1 H) 8.40 (dd, *J*=4.40, 1.95 Hz, 1 H) 8.29 (dd, *J*=9.28, 1.95 Hz, 1 H) 7.93 - 7.97 (m,

1 H) 7.81 - 7.84 (m, 1 H) 7.50 (t, *J*=8.30 Hz, 1 H) 7.37 (d, *J*=5.37 Hz, 1 H) 7.21 (dd, *J*=9.28, 4.39 Hz, 1 H) 1.75 - 1.77 (m, 6 H). LC-MS (m/z): 392.0 [M+1].

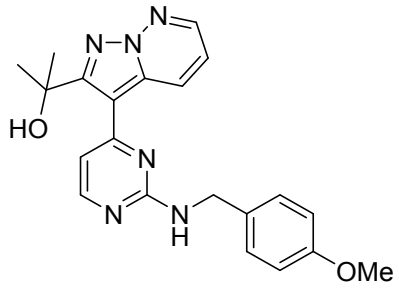


4-((4-(2-(2-Hydroxypropan-2-yl)pyrazolo[1,5-*b*]pyridazin-3-yl)pyrimidin-2-yl)amino)benzamide (S1j). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (20 mg, 69 µmol) in *n*-BuOH, 4-aminobenzamide (19 mg, 138 µmol) was added and the reaction was heated to 115 °C for 16 h. The reaction mixture was concentrated to dryness and purified by column chromatography using EtOAc: hex, 80-100% 5 CV, MeOH: EtOAc, 0-18% 12 CV) which yielded the title compound as a pale-yellow solid (10 mg, 37%). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 9.89 (s, 1 H) 8.76 (dd, *J*=9.16, 1.53 Hz, 1 H) 8.52 - 8.60 (m, 2 H) 7.77 - 7.88 (m, 6 H) 7.37 (dd, *J*=9.16, 4.27 Hz, 1 H) 7.17 (br. s., 1 H) 5.96 (s, 1 H) 1.63 (s, 6 H). LC-MS (m/z): 390.1 [M+1].



2-(3-(2-((4-(*tert*-Butyl)phenyl)amino)pyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol (S1k). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (20 mg, 69 µmol) in *n*-BuOH, 4-(tert-butyl)aniline (22 µL, 138 µmol) was added and the reaction was heated to 110 °C for 16 h. The reaction mixture was concentrated to dryness and purified by column chromatography using EtOAc: hex, 50-100% 12 CV to afford the title compound as a yellow solid (13 mg, 47%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.44 (d, *J*=5.37 Hz, 1 H)

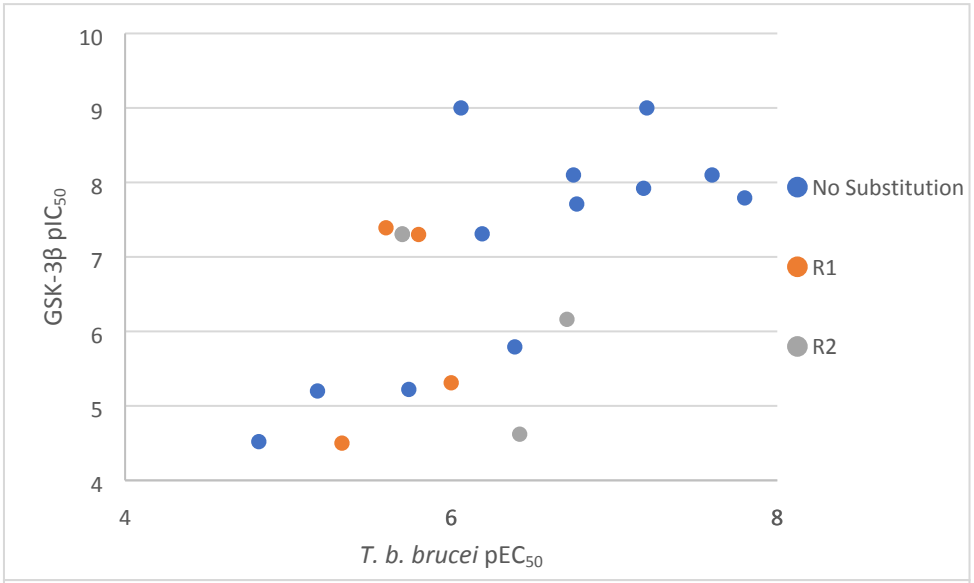
8.37 (dd, *J*=4.39, 1.95 Hz, 1 H) 8.24 (dd, *J*=9.28, 1.95 Hz, 1 H) 7.47 - 7.51 (m, 2 H) 7.38 - 7.42 (m, 2 H) 7.16 - 7.20 (m, 1 H) 7.14 (dd, *J*=9.28, 4.39 Hz, 1 H) 1.72 (s, 6 H) 1.34 (s, 9 H). LC-MS (m/z): 403.1 [M+1].



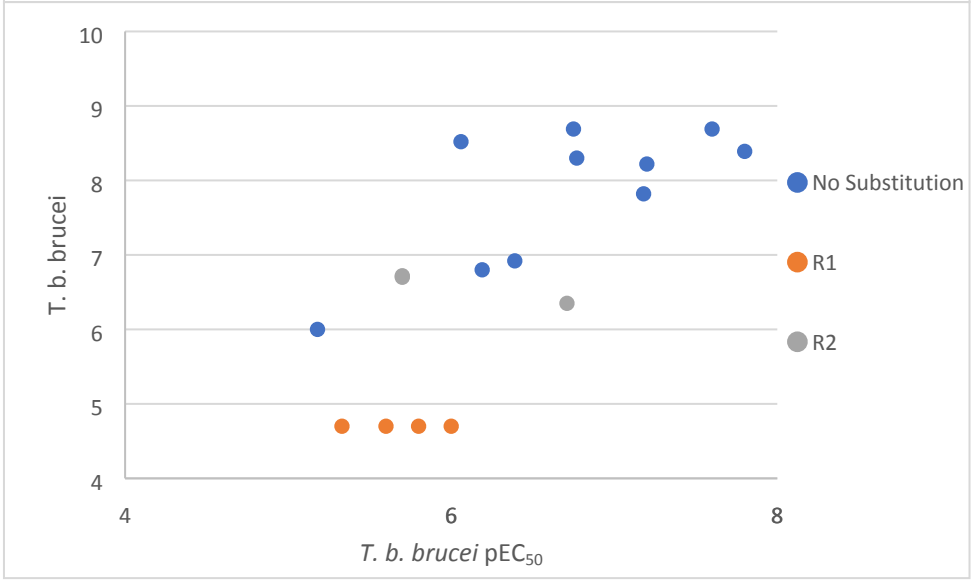
2-(3-(2-((4-Methoxybenzyl)amino)pyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol (S2a). To an oven-dried flask containing a solution of 2-(3-(2-chloropyrimidin-4-yl)pyrazolo[1,5-*b*]pyridazin-2-yl)propan-2-ol **7g** (20 mg, 69 µmol) in *n*-BuOH, 4-methoxybenzylamine (18 µL, 138 µmol) was added and the reaction was heated to 115 °C for 16 h. The reaction mixture was concentrated to dryness and purified by column chromatography using EtOAc: hex, 50-100 % 12 CV to afford the title compound as a yellow solid (0.014 g, 51%). ^{1}H NMR (500 MHz, CHLOROFORM-*d*) δ ppm 8.24 - 8.40 (m, 2 H) 8.17 (dd, *J*=9.28, 1.95 Hz, 1 H) 7.28 - 7.32 (m, 2 H) 7.14 (dd, *J*=9.28, 4.39 Hz, 1 H) 6.95 (br. s, 1 H) 6.86 - 6.90 (m, 2 H) 4.60 (d, *J*=5.37 Hz, 2 H) 3.78 - 3.84 (m, 3 H) 1.72 (s, 6 H). LC-MS (m/z): 391.1 [M+1].

Figure S1. Comparison of *T. b. brucei* pEC_{50} inhibition data to literature values for **a.** GSK-3β pIC_{50}; **b.** CDK-2 pIC_{50}; **c.** CDK-4 pIC_{50}. Colored on whether there was no substitution at R^1 and R^2 (blue), substitution at R^1 (orange), or substitution at R^2 (grey).

a.



b.



c.

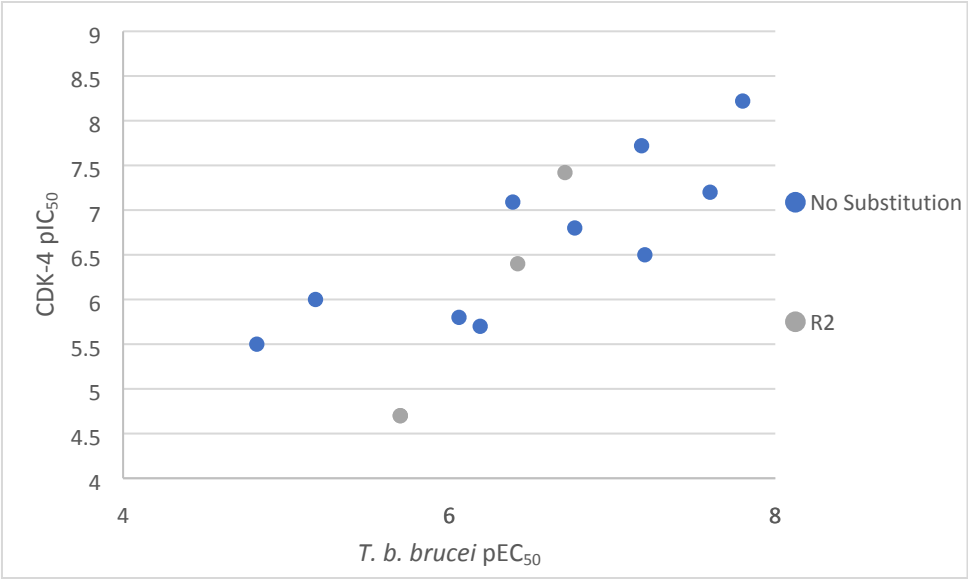


Table S3. Mouse plasma stability in CD-1 mouse cells. Compounds were dosed at 5µM and incubated for 2 h, with CD-1 cells and K2-EDTA as an anticoagulant.

	% Compound Remaining					
Incubation Time (min)	**0**	**10**	**20**	**30**	**60**	**120**
20r	100 %	99 %	101 %	104 %	104 %	105 %
20g	100 %	100 %	105 %	109 %	115 %	116 %

Table S4. Measured % Stability of the compounds and fold induction of hydroxylation of testosterone to hydroxytestosterone in cytochrome P450 (CYP450) isozymes 3A4 after 2 h. Both compounds were deemed to not induce or be substrates of CYP450 3A4.

Cpd	Fold Induction	% Stability
20r	0.32	87
20g	0.078	102

Table S5. Measured permeability between Apical (A) and Basal (B) plasma membrane domains of Caco-2 cells. Compounds were dosed either in the A or B receiver compartment, then measured after 2 h. The apparent permeability (P_{app}) is equal to $dQ/(dt*X*C_0)$ where dQ/dt = amount of product present in basal (A-B) or apical (B-A) in function of time (nmol/s), X = area of transwell (cm^2) and C_0 = initial concentration of product (nmol/ml) applied in apical or basal compartment. Compounds with a $P_{app} > 1*10^{-6}$ (cm/s) are deemed highly permeable. Compounds with an efflux ratio > 2 are deemed to be effluxed.

Cpd	Mean P_{app} A-B (10^{-6} cm/s)	Mean P_{app} B-A (10^{-6} cm/s)	Mean (B-A/A-B) Efflux Ratio
20r	42	53	1.3
20g	32	33	1.0

Table S6. Measured pEC_{50} values at different time points against *T. b. brucei*. Compounds with a $pEC_{50} \geq 6$ at 18 h were deemed fast acting. The washout value was obtained after incubating *T. b. brucei* with the compound for 18 h, then washing out the compound, and incubating the parasite for 72 h; compounds with a $pEC_{99} \geq 6$ were deemed cidal.

Cpd	6 h	12 h	18h	24 h	Washout pEC_{50}	Washout pEC_{99}
12d	< 4.4 ± 0.0	< 4.9 ± 0.0	< 5.4 ± 0.0	6.6 ± 0.15	6.7 ± 0.06	6.5 ± 0.14
22a	5.7 ± 0.07	6.3 ± 0.12	6.8 ± 0.10	6.8 ± 0.05	7.1 ± 0.08	6.8 ± 0.25
22b	5.7 ± 0.04	6.1 ± 0.08	6.8 ± 0.17	6.9 ± 0.11	7.2 ± 0.06	6.2 ± 0.44
22c	6.0 ± 0.24	7.1 ± 0.16	7.8 ± 0.14	8.4 ± 0.20	8.2 ± 0.09	7.2 ± 0.4
20r	5.3 ± 0.03	5.5 ± 0.20	5.9 ± 0.22	6.1 ± 0.11	6.4 ± 0.09	5.8 ± 0.31
20c	5.4 ± 0.07	6.1 ± 0.20	6.9 ± 0.08	6.7 ± 0.10	6.9 ± 0.09	6.4 ± 0.07
20g	5.9 ± 0.06	6.7 ± 0.12	7.1 ± 0.10	7.3 ± 0.08	7.4 ± 0.08	7.0 ± 0.11

Figure S2. Peripheral blood levels of **20r** after IP administration to female NMRI mice (n=3) at a target dose 10 mg/kg in 1% DMSO, 20% Captisol® in water. Individual values for each time point are represented in the plot.

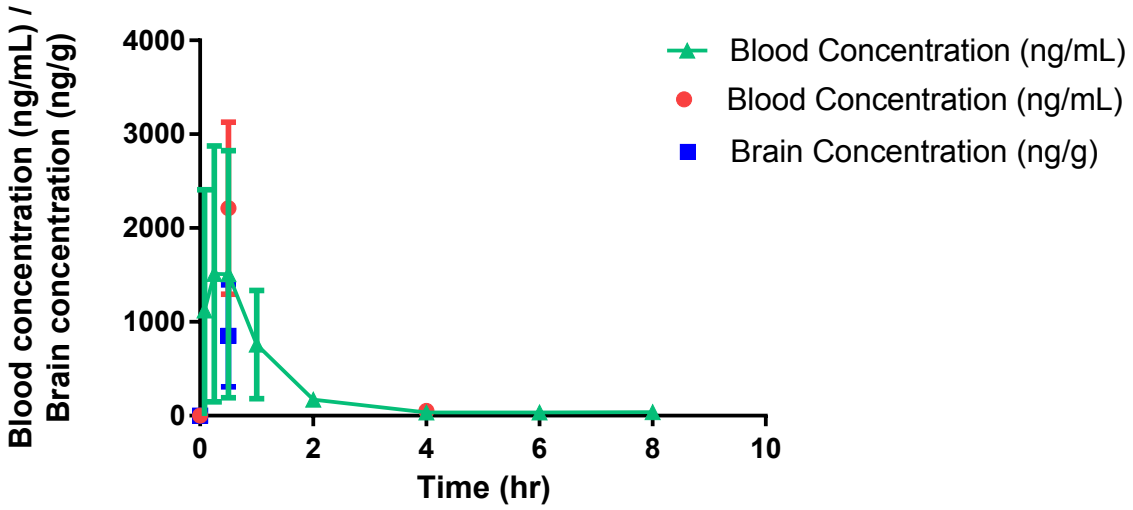


Table S7. Blood and brain levels of **20r**, after IP administration of 10 mg/kg single dose (target dose) to female NMRI mice (n=3). LLOQ=10 ng/mL(blood); 50 ng/g (brain).

Sampling Time (h)	Matrix	N1	N2	N3	Mean	SD
0.5	Blood	1150	2790	2690	2210	919
	Brain	223	1180	1150	851	544
	Brain/Blood Ratio	0.19	0.42	0.43	0.35	0.13

4	Blood	53	24	82	53	29
	Brain	<LLOQ	<LLOQ	<LLOQ	-	-
	Brain/Blood Ratio	-	-	-	-	-

Table S8. Blood and brain levels of **20g**, after IP administration of 10 mg/kg single dose (target dose) to female NMRI mice (n=3).

Sampling Time (h)	**Matrix**	**N1**	**N2**	**N3**	**Mean**	**SD**
0.5	Blood	1360	1110	360	943	520
	Brain	1900	1120	292	1104	804
	Brain/Blood Ratio	1.4	1.0	0.8	1.1	0.30
4	Blood	63	160	81	101	52
	Brain	42	258	94	130	113
	Brain/Blood Ratio	0.67	1.6	1.2	1.1	0.47

Table S9. Percentage inhibition of **20g** against human kinase panel (Eurofins) at 1 μM.

ASSAY NAME	**Inhibition at 1 μM (%)**
Abl kinase (h)	11
Akt1/PKBalpha (h)	-26
AurA/Aur2 kinase (h)	37
c-Met kinase (h)	11
CaMK2alpha (h)	3.7
CDC2/CDK1 (h) (cycB)	100
CDK2 (h) (cycA)	100
CDK2 (h) (cycE)	98
CDK4 (h) (cycD3)	103.
CHK1 (h)	-7.9
CHK2 (h)	2.6
EGFR kinase (h)	-0.1
EphA2 kinase (h)	32
EphA3 kinase (h)	11
EphB4 kinase (h)	5.3
ERK2 (h) (P42mapk)	60
FGFR1 kinase (h)	8.1
FGFR2 kinase (h)	31
FGFR3 kinase (h)	30
GSK3beta (h)	94
HGK (h) (MAP4K4)	67
IKKalpha (h)	72

IRAK4 (h)	51
IRK (h) (InsR)	-1.2
JAK3 (h)	73
JNK1 (h)	83
KDR kinase (h) (VEGFR2)	67
Lck kinase (h)	8.4
MAPKAPK2 (h)	-3.5
MARK1 (h)	9.3
MNK2 (h)	47
NEK2 (h)	11.7123
p38alpha kinase (h)	-41
PAK2 (h)	10
PAK4 (h)	-0.11
PDK1 (h)	6.6
Pim2 kinase (h)	19
PKA (h)	9.4
PKCbeta 2 (h)	4.9
PLK1 (h)	5.3
RAF-1 kinase (h)	52
ROCK1 (h)	1.8
SGK1 (h)	8.3
SIK (h)	22
Src kinase (h)	19
TAOK2 (TAO1) (h)	86
TRKA (h)	5.3

Table S10. Parasitemia levels (measured as parasites per milliliter) of *T. b. brucei* STIB795 from efficacy study of **20g** dosed at 10 mg/kg/day during 5-day treatment of mice.

	Infection	**Treatment**					**Post Treatment**
Mouse	Day 0	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
1	1×10^4	9.5×10^6	2.1×10^7	5.6×10^4	ND[a]		
2	1×10^4	9.0×10^6	1.2×10^7	ND	ND[a]		
3	1×10^4	1.4×10^7	4.0×10^7	1.1×10^5	ND	ND	[a]
4	1×10^4	7.5×10^6	1.4×10^8	1.4×10^9	[a]		
5	1×10^4	1.3×10^7	5.6×10^4 [a]				
6	1×10^4	2.0×10^6	2.7×10^7	4.5×10^7	3.2×10^8	7.3×10^8 [a]	

ND = Not Detected (parasitemia levels < 5.6×10^4 p/mL).

[a]Dead

Table S11. Measured activity of compounds against *Trypanosoma cruzi*, and *Leishmania donovani* as well as L6 and THP-1.

Cpd	*T. cruzi* pEC_{50}	*L. donovani* pEC_{50}	L6 pTC_{50}	THP-1 pTC_{50}
1	*nt*	*nt*	> 6.2 ± 0.00	> 6.7 ± 0.00
10e	> 9.0 ± 0.00	*nt*	> 6.2 ± 0.00	> 6.7 ± 0.00
10i	*nt*	*nt*	> 6.2 ± 0.00	> 6.7 ± 0.00
20m	5.3 ± 0.11	*nt*	*nt*	4.7 ± 0.031
20a	< 5.0 ± 0.00	< 5.0 ± 0.00	*nt*	4.6 ± 0.00
20l	< 5.0 ± 0.00	nt	*nt*	5.7 ± 0.06
10b	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.8 ± 0.00	4.7 ± 0.01
10s	5.2 ± 0.055	< 5.3 ± 0.00	< 5.3 ± 0.00	4.9 ± 0.03
S1h	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	4.3 ± 0.00
10d	4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	4.3 ± 0.01
10a	< 4.7 ± 0.00	< 5.7 ± 0.00	*nt*	4.7 ± 0.03
S1i	*nt*	*nt*	5.2 ± 0.055	> 5.5 ± 0.00
S1k	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00
S1g	< 4.7 ± 0.00	< 5.3 ± 0.00	*nt*	< 4.3 ± 0.00
S2a	< 4.7 ± 0.00	< 5.3 ± 0.00	*nt*	< 4.3 ± 0.00
S1c	5.1 ± 0.10	< 5.3 ± 0.00	< 4.8 ± 0.00	< 4.3 ± 0.00
S1e	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00
S1f	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00
10g	5.1 ± 0.035	< 6.3 ± 0.00	5.5 ± 0.033	5.1 ± 0.07
S1d	< 4.7 ± 0.00	< 5.3 ± 0.00	*nt*	< 4.6 ± 0.00
S1j	< 4.7 ± 0.00	< 5.3 ± 0.00	*nt*	< 4.3 ± 0.00
10f	< 4.7 ± 0.00	5.7 ± 0.032	4.6 ± 0.094	4.9 ± 0.02
12c	< 4.7 ± 0.00	< 6.3 ± 0.00	5.4 ± 0.091	5.3 ± 0.07
12d	< 4.7 ± 0.00	< 5.3 ± 0.00	4.3 ± 0.009	> 6.2 ± 0.00
S1b	5.6 ± 0.045	5.8 ± 0.20	4.3 ± 0.082	< 4.3 ± 0.00
12b	5.8 ± 0.034	< 5.3 ± 0.00	5.5 ± 0.011	5.8 ± 0.11
12a	5.0 ± 0.008	< 5.3 ± 0.00	4.5 ± 0.043	4.8 ± 0.06
S1a	5.8 ± 0.063	6.1 ± 0.19	< 4.3 ± 0.00	< 4.3 ± 0.00
21a	5.4 ± 0.026	5.9 ± 0.20	< 4.9 ± 0.00	< 4.9 ± 0.00
22a	5.5 ± 0.015	< 5.3 ± 0.00	5.2 ± 0.079	< 5.3 ± 0.00
22b	< 4.7 ± 0.00	< 5.3 ± 0.00	5.4 ± 0.099	5.3 ± 0.003
22c	6.1 ± 0.013	*nt*	> 6.0 ± 0.00	6.1 ± 0.004
20r	6.4 ± 0.027	*nt*	> 6.2 ± 0.068	6.2 ± 0.011
20c	7.2 ± 0.081	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
20p	5.6 ± 0.071	< 5.7 ± 0.00	5.5 ± 0.038	5.4 ± 0.12
10h	*Nt*	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
23j	5.0 ± 0.014	< 6.3 ± 0.00	5.0 ± 0.075	5.1 ± 0.035
22d	< 4.7 ± 0.00	< 5.6 ± 0.00	< 4.3 ± 0.00	< 4.6 ± 0.00
21d	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00
18c	< 4.7 ± 0.00	< 5.3 ± 0.00	4.4 ± 0.015	4.5 ± 0.19
18a	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.015	< 4.3 ± 0.00
16a	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00

21e	5.0 ± 0.009	*nt*	4.9 ± 0.034	< 4.3 ± 0.00
21f	< 4.7 ± 0.00	*nt*	*nt*	< 4.3 ± 0.00
20g	*nt*	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
21g	5.1 ± 0.020	*nt*	4.7 ± 0.025	4.3 ± 0.043
21h	5.6 ± 0.061	*nt*	4.9 ± 0.024	< 4.3 ± 0.00
20q	*nt*	< 5.3 ± 0.00	5.3 ± 0.085	6.1 ± 0.01
23b	< 4.7 ± 0.00	< 5.3 ± 0.00	*nt*	< 4.3 ± 0.00
18d	6.0 ± 0.028	< 5.3 ± 0.00	5.7 ± 0.29	5.7 ± 0.06
23a	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
10n	< 4.7 ± 0.00	*nt*	4.3 ± 0.00	< 4.3 ± 0.00
20d	*nt*	*nt*	6.2 ± 0.13	> 6.2 ± 0.00
20e	6.3 ± 0.047	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
20h	< 4.8 ± 0.00	< 5.4 ± 0.00	< 4.4 ± 0.00	< 4.4 ± 0.00
20n	4.8 ± 0.020	< 5.3 ± 0.00	5.0 ± 0.046	5.4 ± 0.07
20o	4.7 ± 0.00	< 5.3 ± 0.00	4.6 ± 0.031	5.1 ± 0.03
20f	5.4 ± 0.015	< 5.3 ± 0.00	5.4 ± 0.055	5.6 ± 0.03
18b	< 4.7 ± 0.00	< 5.3 ± 0.00	< 4.3 ± 0.00	< 4.3 ± 0.00
23h	5.4 ± 0.015	*nt*	4.4 ± 0.038	< 4.3 ± 0.00
23d	5.5 ± 0.039	*nt*	4.5 ± 0.029	< 4.3 ± 0.00
23i	5.6 ± 0.20	*nt*	5.1 ± 0.045	*nt*
23c	5.4 ± 0.045	< 5.3 ± 0.00	4.7 ± 0.041	< 4.3 ± 0.00
17	4.9 ± 0.038	< 5.3 ± 0.00	4.6 ± 0.016	< 4.3 ± 0.00
20k	6.9 ± 0.014	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
19a	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
19b	*nt*	*nt*	> 6.2 ± 0.00	> 6.2 ± 0.00
20i	6.4 ± 0.051	*nt*	< 5.6 ± 0.00	6.2 ± 0.14
20j	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
23f	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
23e	5.3 ± 0.029	*nt*	< 4.3 ± 0.00	4.8 ± 0.14
23k	5.4 ± 0.023	*nt*	4.5 ± 0.019	4.9 ± 0.10
23l	4.9 ± 0.026	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
23g	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00
23m	< 4.7 ± 0.00	*nt*	< 4.3 ± 0.00	< 4.3 ± 0.00

nt = not tested

Table S.12. Measured severity score of compounds (10 μM) against adult *Schistosoma mansoni* at the indicated time points. Compounds were scored based on the non-mutually exclusive phenotypic responses of the parasite that involved changes in translucency, motility and ability to adhere to the substratum. Each response was awarded a score of 1 and added up to the maximum score of 4. Degeneracy or damage to the outer surface of the worm was scored as 4. The anthelmintic, niclosamide, which causes degeneracy, tegumental (surface) damage and eventually death, was used as a positive control.

ID	3 h	6 h	24 h	48 h
1	0	0	0	0
10i	0	0	0	2
10b	0	0	0	0
10s	2	2	2	2
S1h	0	0	0	0
S1i	0	0	0	0
S1k	2	2	2	2
S1g	0	0	0	0
20r	1	1	0	0
21e	0	0	0	0
21f	1	0	0	0
Niclosamide (positive control)	4	4	4	4

Table S.13. SEM measurements for *T. b. brucei* and MRC5 activity.

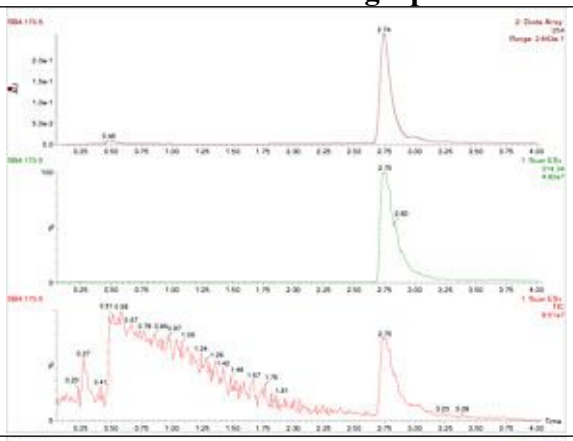
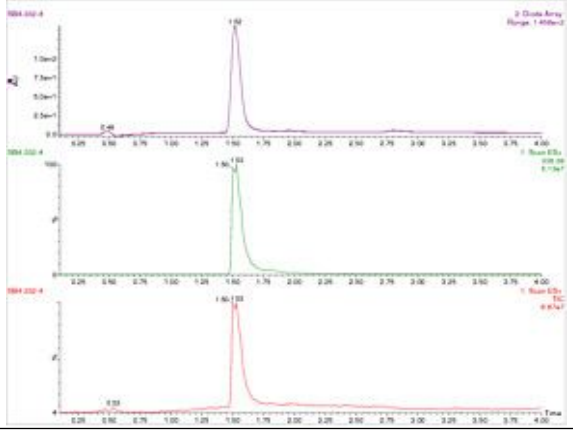
ID	*T. b. brucei* pEC_{50}	MRC5 pTC_{50}
10a	5.2 ± 0.08	< 4.3 ± 0.00
10b	4.8 ± 0.01	< 4.3 ± 0.00
10c	6.4 ± 0.11	*nt*
10d	6.4 ± 0.09	*nt*
10e	7.4 ± 0.07	< 4.3 ± 0.00
10f	5.3 ± 0.07	< 4.3 ± 0.00
10g	5.7 ± 0.02	< 4.3 ± 0.00
1	8.2 ± 0.02	< 4.3 ± 0.00
10h	8.2 ± 0.03	*nt*
10i	7.6 ± 0.07	*nt*
10j	5.7 ± 0.11	*nt*
10k	7.2 ± 0.01	*nt*
10l	6.1 ± 0.1	*nt*
10m	6.8 ± 0.06	*nt*
10n	6.1 ± 0.07	*nt*
10o	7.2 ± 0.05	*nt*
10p	5.8 ± 0.13	*nt*
10q	6.0 ± 0.17	*nt*

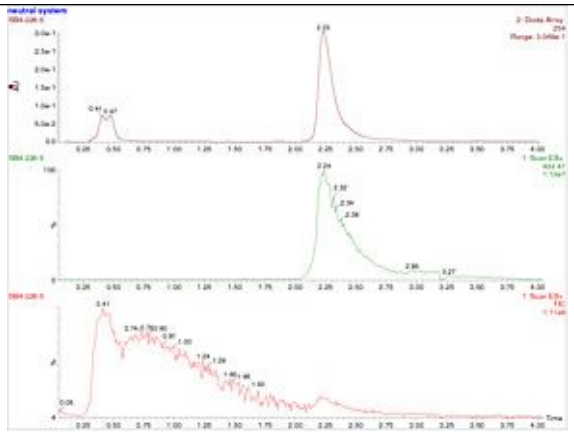
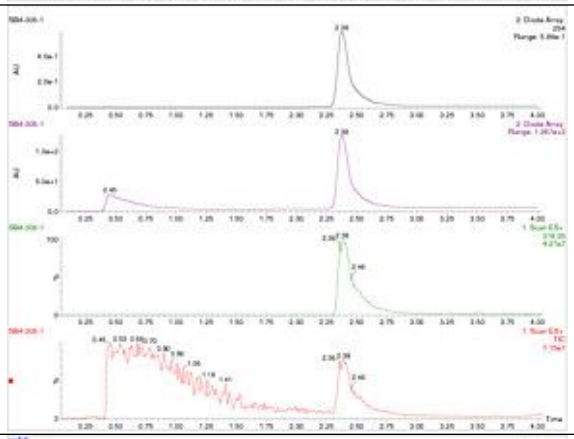
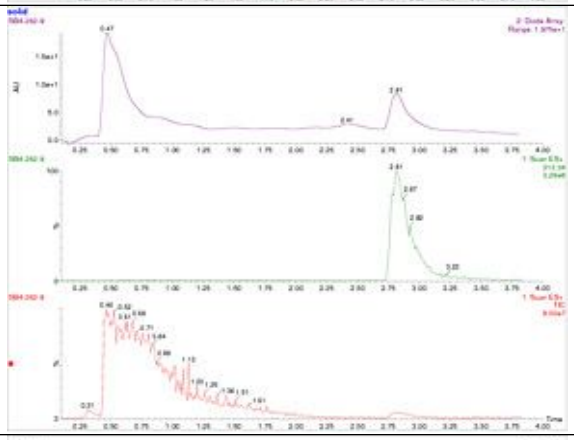
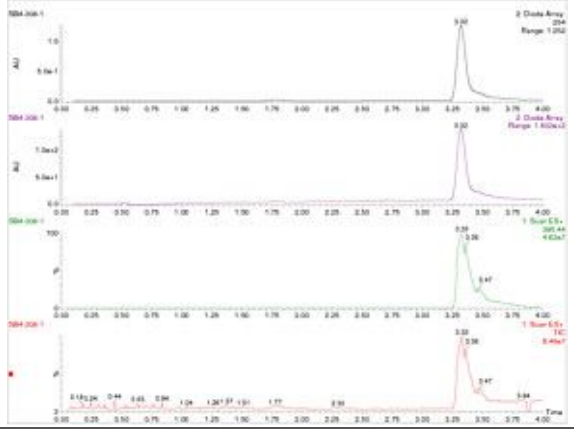
10r	7.8 ± 0.06	*nt*
10s	6.2 ± 0.08	5.7 ± 0.17
10t	5.6 ± 0.08	*nt*
9	6.7 ± 0.01	*nt*
12a	6.0 ± 0.02	< 4.3 ± 0.00
12b	6.6 ± 0.02	< 4.3 ± 0.00
12c	6.6 ± 0.05	< 4.3 ± 0.00
12d	7.0 ± 0.02	< 4.3 ± 0.00
16a	< 4.4 ± 0.00	< 4.3 ± 0.00
17	5.4 ± 0.04	4.7 ± 0.02
18a	< 4.4 ± 0.00	< 4.3 ± 0.00
18b	6.2 ± 0.02	< 4.3 ± 0.00
18c	< 4.4 ± 0.00	< 4.3 ± 0.00
18d	6.6 ± 0.08	< 4.3 ± 0.00
19a	< 4.4 ± 0.00	< 4.3 ± 0.00
19b	7.0 ± 0.09	< 4.3 ± 0.00
20a	< 4.7 ± 0.00	< 4.3 ± 0.00
20b	5.9 ± 0.10	< 4.6 ± 0.00
20c	7.6 ± 0.09	< 4.3 ± 0.00
20d	7.2 ± 0.05	< 4.3 ± 0.00
20e	7.3 ± 0.01	< 4.3 ± 0.00
20f	6.0 ± 0.02	< 4.3 ± 0.00
20g	7.7 ± 0.05	< 4.3 ± 0.00
20h	5.3 ± 0.01	< 4.4 ± 0.00
20i	7.0 ± 0.05	< 4.6 ± 0.00
20j	5.2 ± 0.13	< 4.3 ± 0.00
20k	7.7 ± 0.02	< 4.3 ± 0.00
20l	5.9 ± 0.14	< 4.3 ± 0.00
20m	5.3 ± 0.17	< 4.3 ± 0.00
20n	4.8 ± 0.05	< 4.3 ± 0.00
20o	5.3 ± 0.03	< 4.3 ± 0.00
20p	6.3 ± 0.11	< 4.3 ± 0.00
20q	6.8 ± 0.02	< 4.3 ± 0.00
20r	6.8 ± 0.06	< 4.3 ± 0.00
21a	5.9 ± 0.01	< 4.9 ± 0.00
21b	6.2 ± 0.08	< 4.3 ± 0.00
21c	4.9 ± 0.04	< 4.3 ± 0.00
21d	6.5 ± 0.05	< 4.3 ± 0.00
21e	6.2 ± 0.07	< 4.3 ± 0.00
21f	6.1 ± 0.07	< 4.3 ± 0.00
21g	6.2 ± 0.04	4.5 ± 0.03
21h	6.7 ± 0.05	< 4.3 ± 0.00
22a	7.5 ± 0.08	< 4.3 ± 0.00
22b	7.7 ± 0.06	< 4.3 ± 0.00
22c	8.3 ± 0.13	< 4.6 ± 0.00
22d	7.1 ± 0.03	< 4.3 ± 0.00
23a	7.2 ± 0.06	< 4.3 ± 0.00
23b	6.8 ± 0.01	< 4.3 ± 0.00
23c	7.1 ± 0.10	< 4.3 ± 0.00

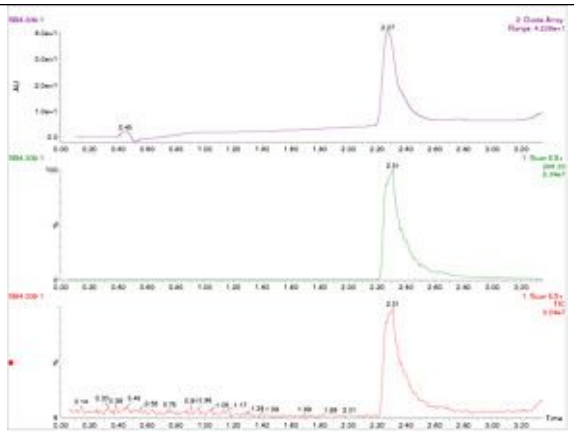
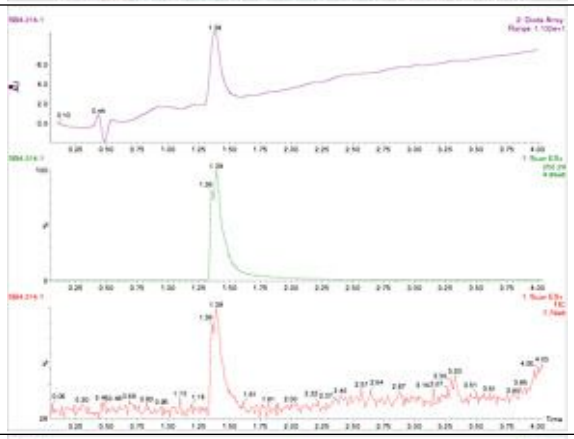
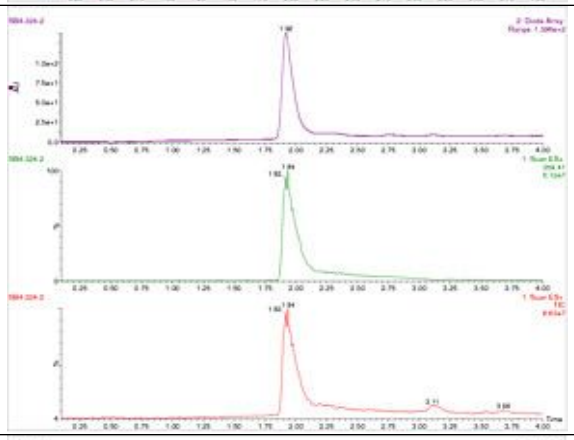
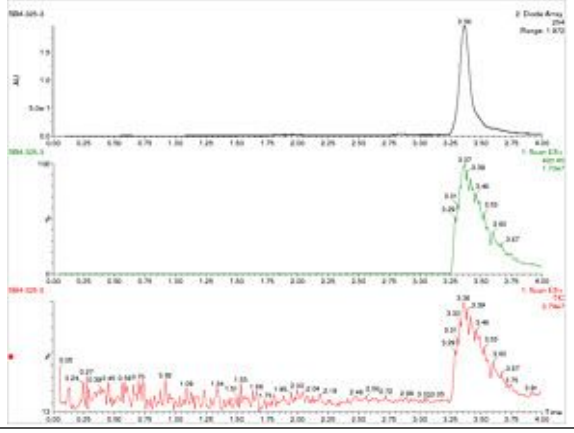
23d	6.8 ± 0.13	< 4.3 ± 0.00
23e	7.2 ± 0.04	< 4.3 ± 0.00
23f	6.6 ± 0.03	< 4.3 ± 0.00
23g	7.2 ± 0.05	< 4.3 ± 0.00
23h	6.8 ± 0.03	< 4.3 ± 0.00
23i	7.9 ± 0.08	< 4.3 ± 0.00
23j	6.8 ± 0.07	< 4.3 ± 0.00
23k	6.3 ± 0.04	< 4.3 ± 0.00
23l	6.3 ± 0.04	< 4.3 ± 0.00
23m	5.3 ± 0.03	< 4.3 ± 0.00

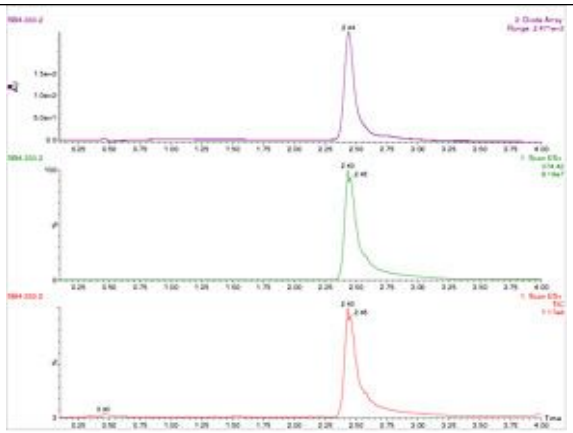
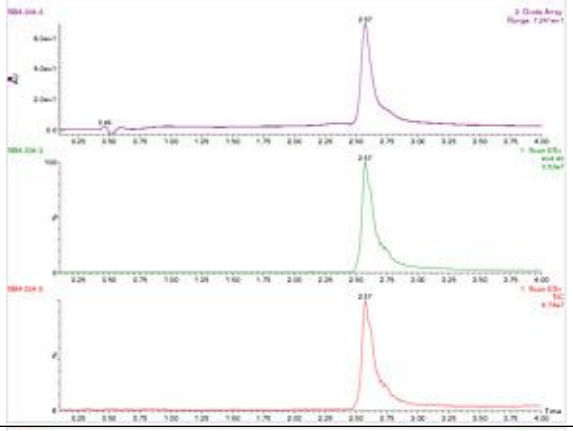
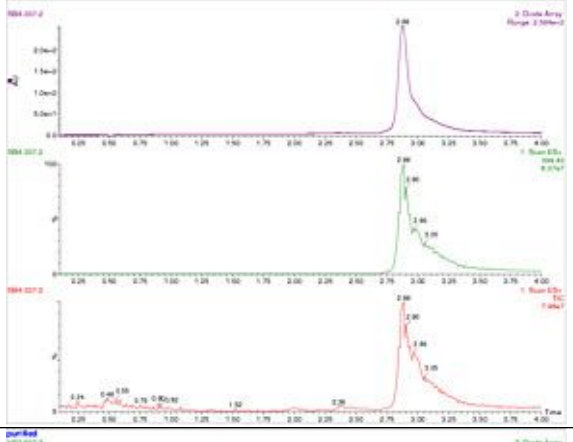
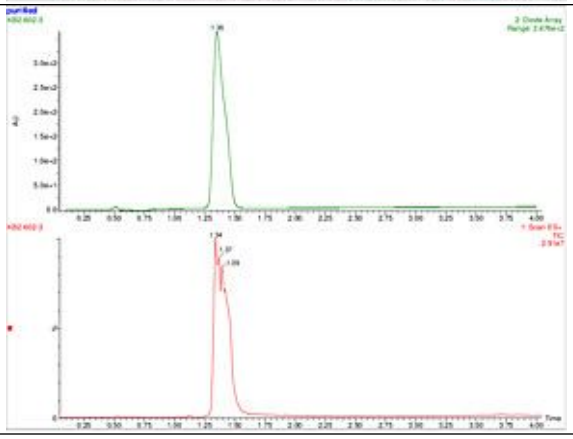
nt = not tested.

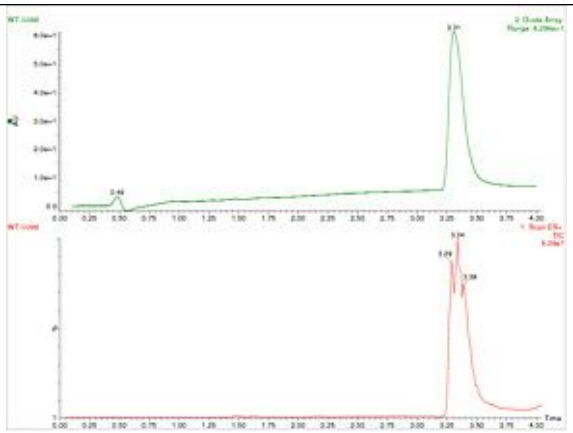
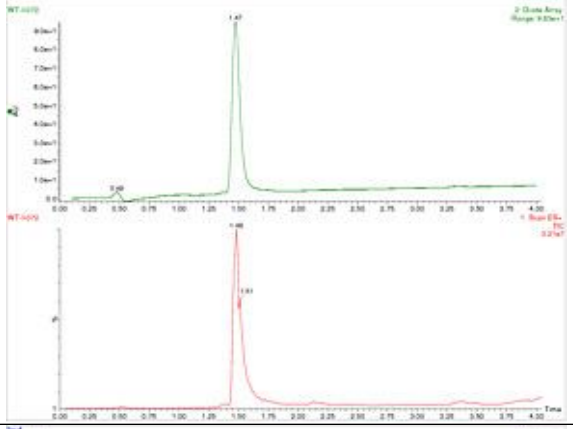
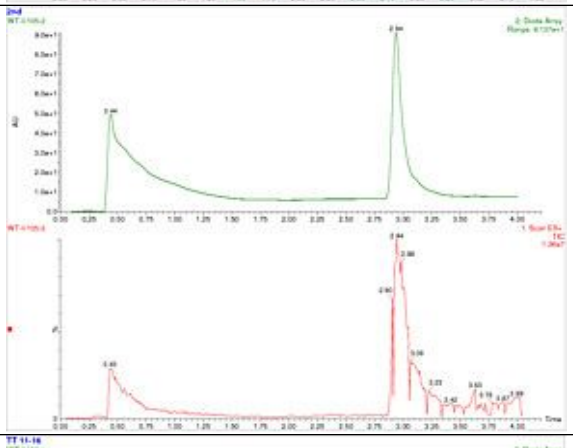
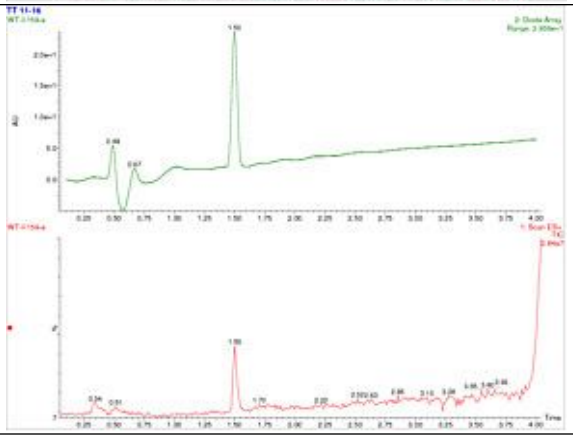
Table S14. HPLC trace of key compounds.

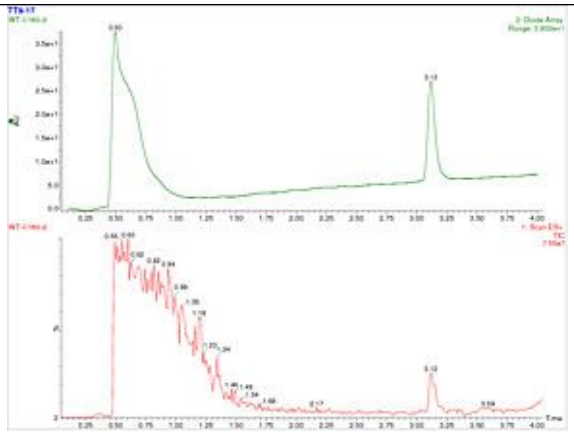
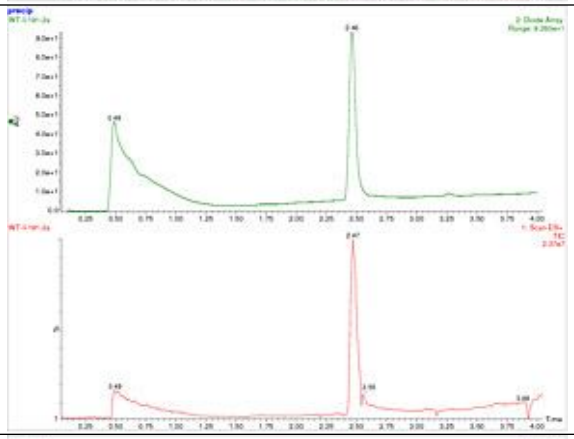
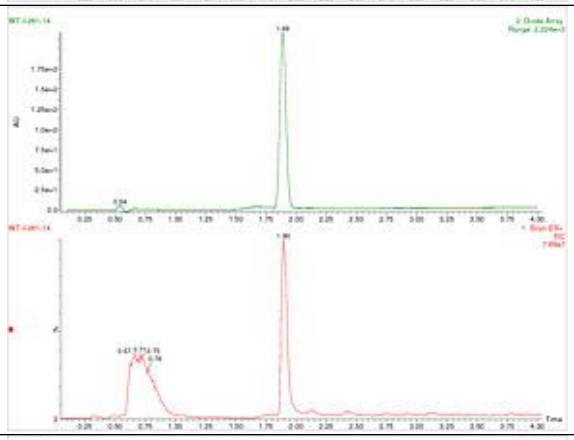
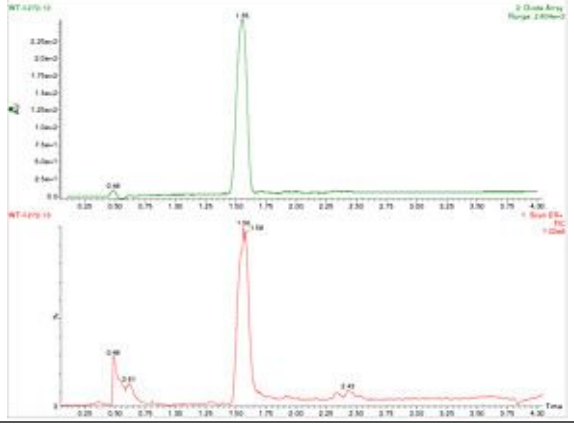
ID	HPLC Chromatograph
10i	
10d	

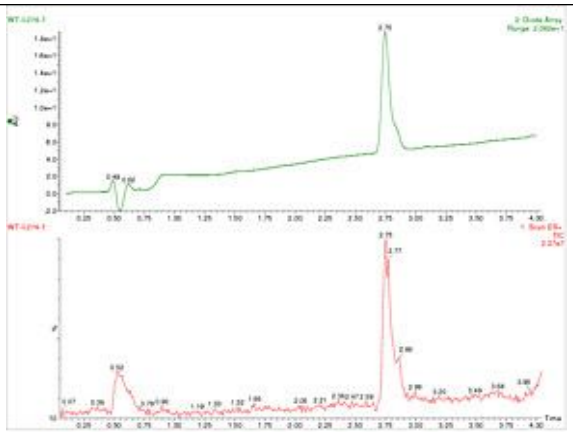
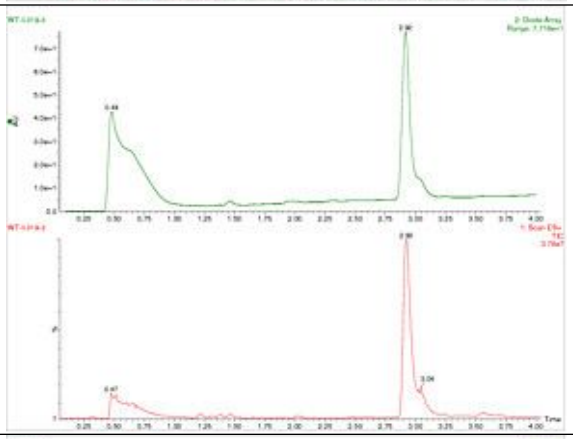
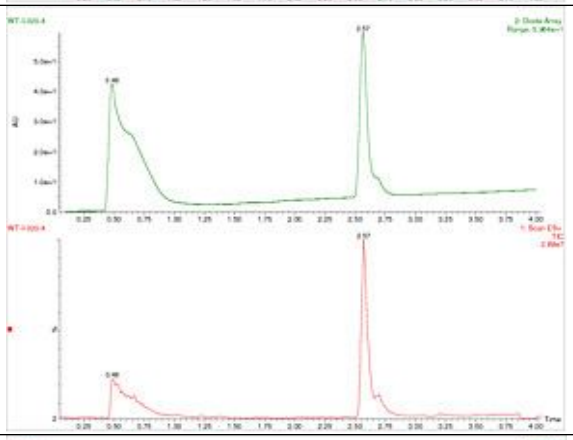
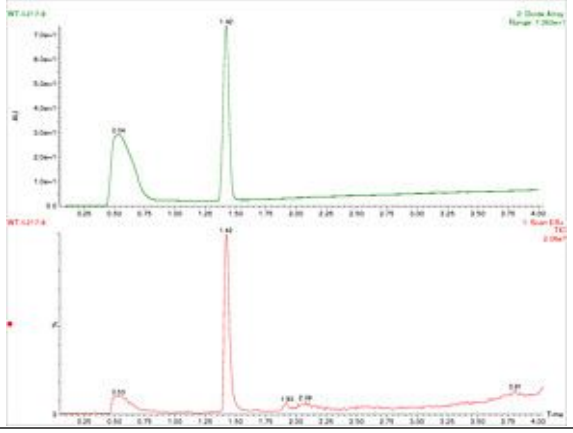
10f	
12c	
12d	
S1b	

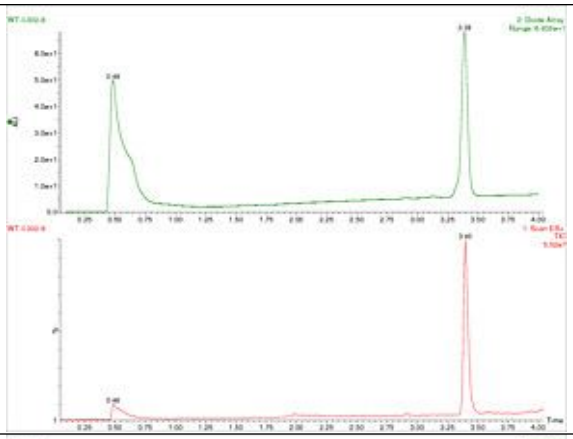
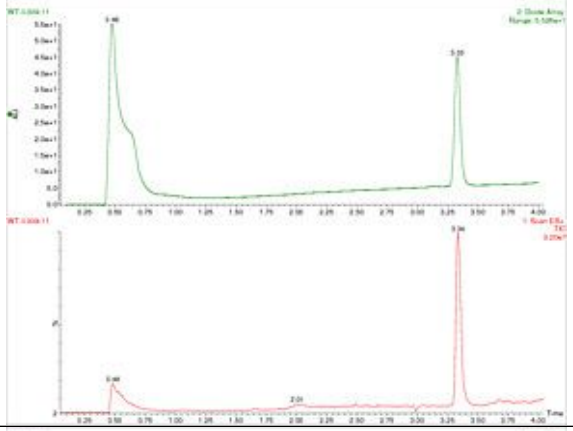
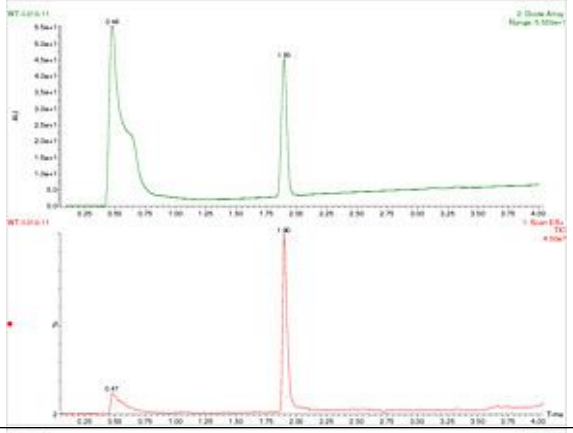
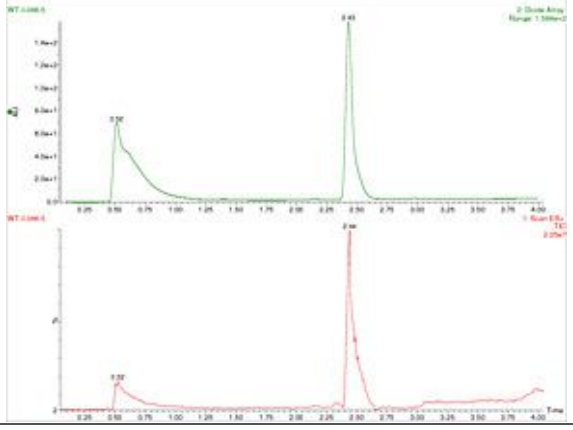
12b	
12a	
S1a	
21a	

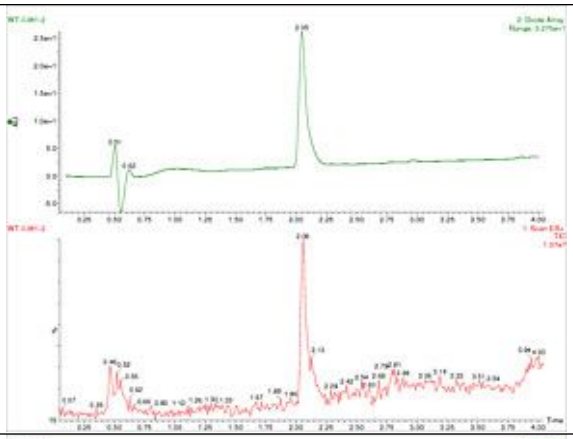
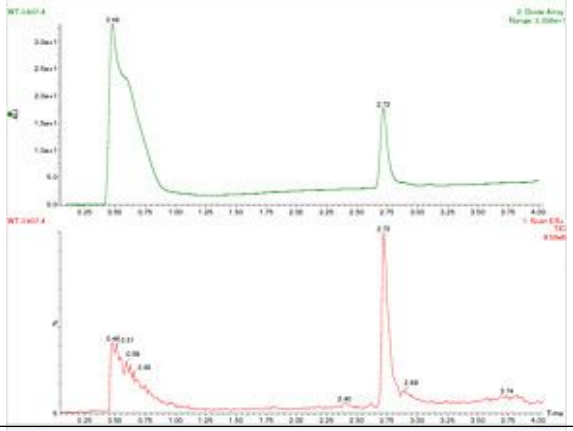
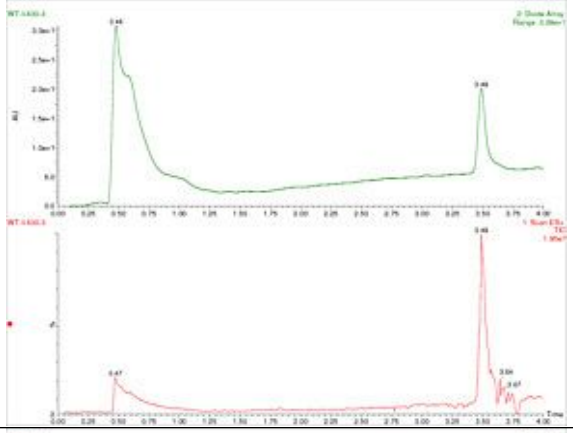
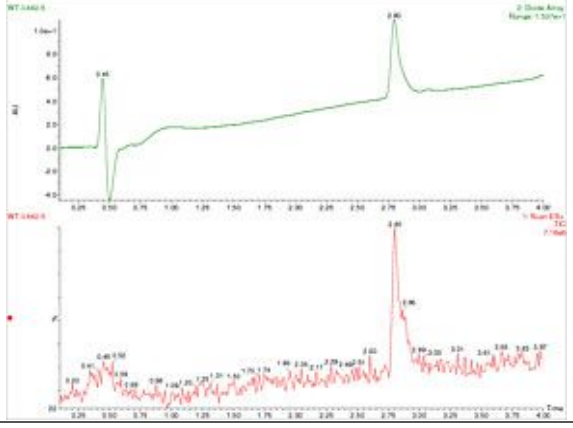
22a	
21f	
22c	
20r	

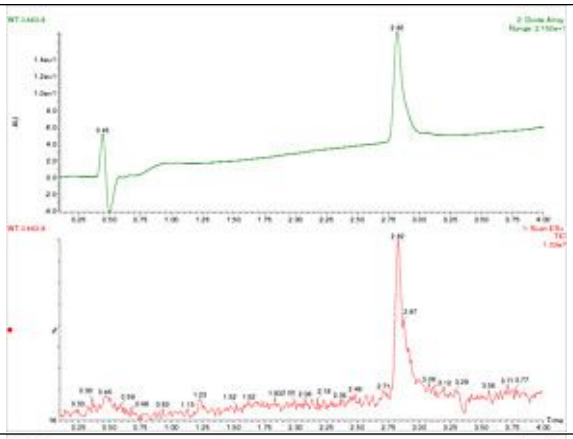
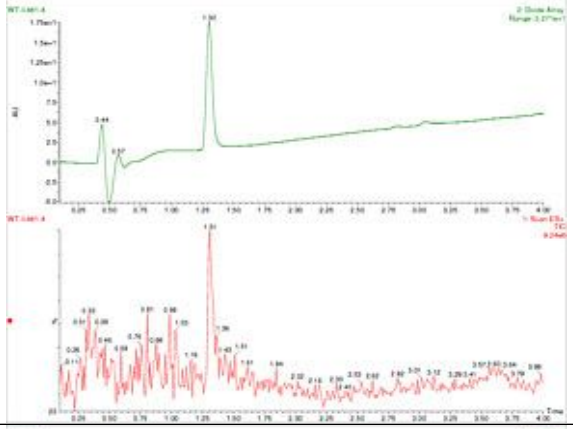
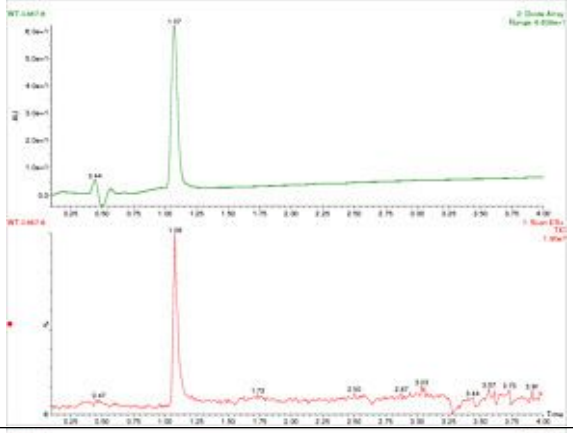
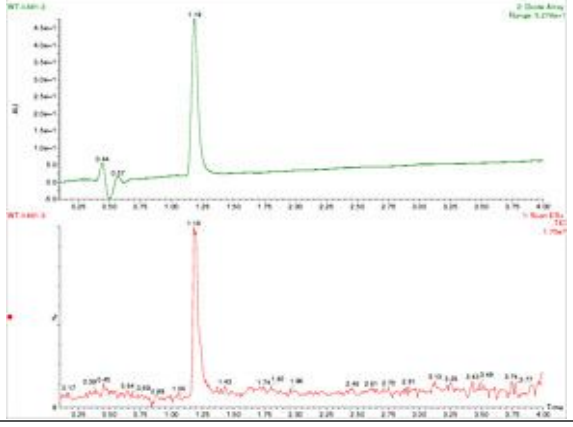
20c	
20p	
10h	
23j	

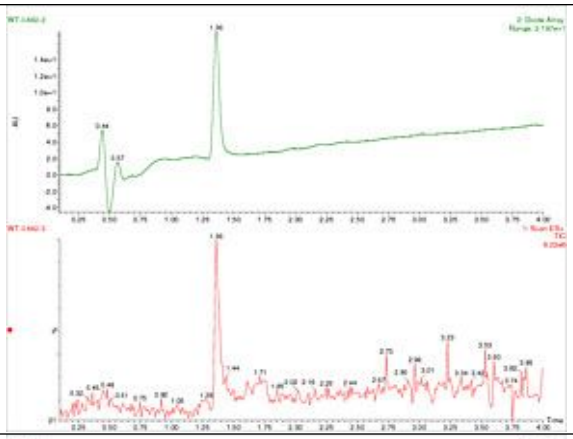
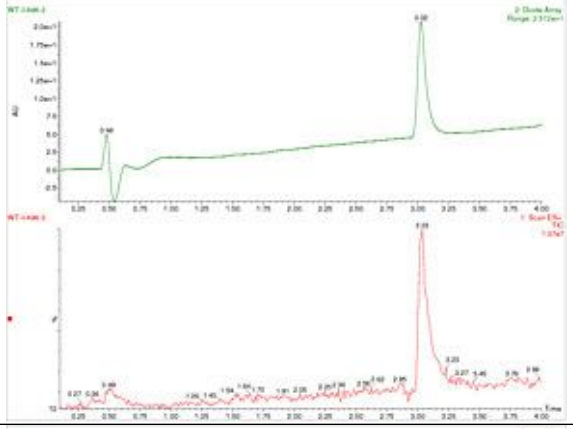
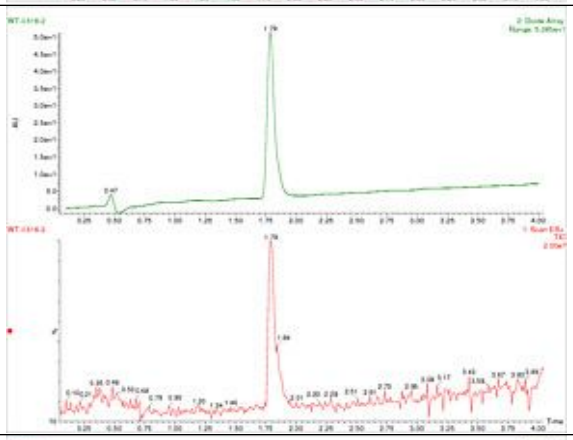
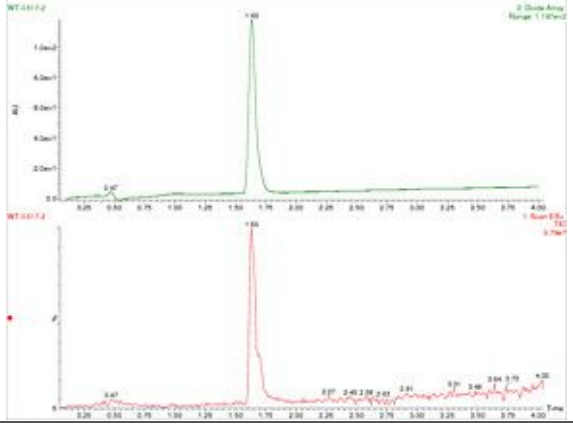
22d	
21d	
18c	
18a	

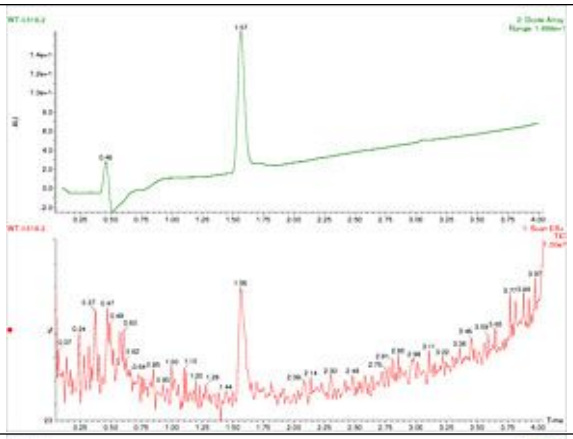
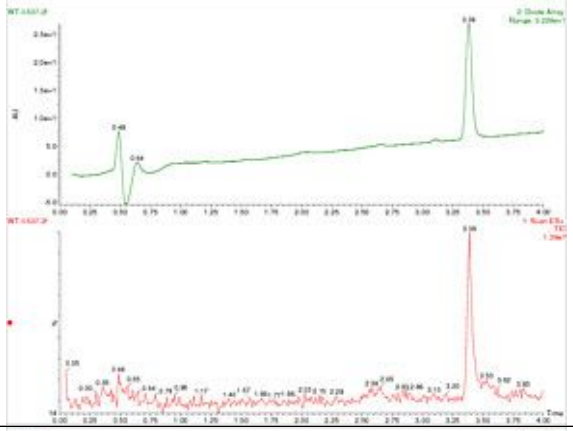
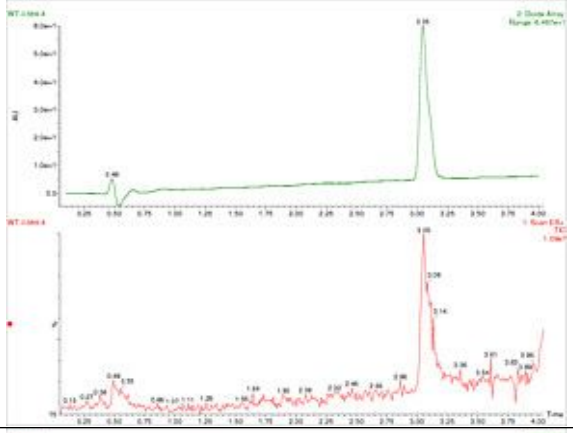
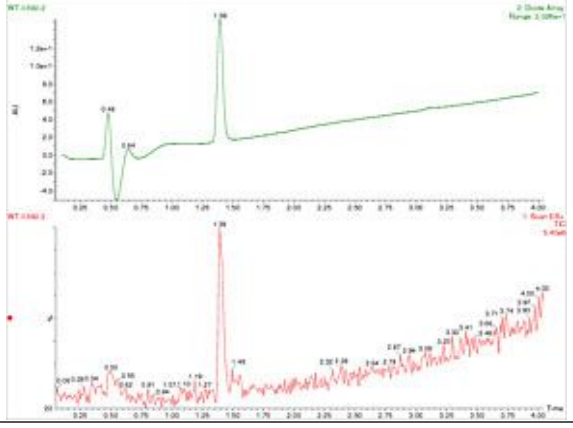
16a	
21e	
21f	
20g	

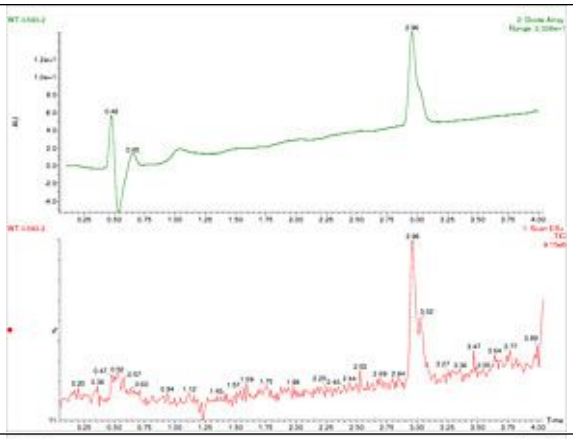
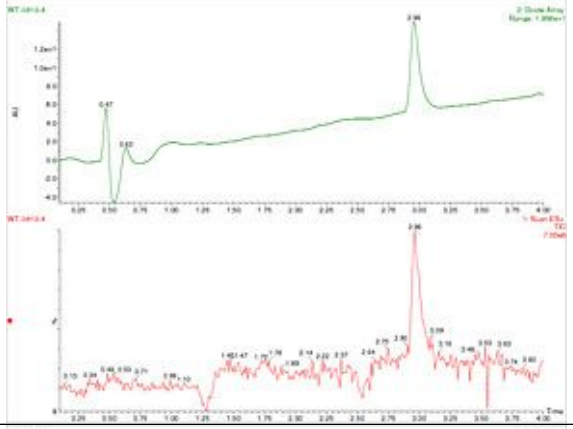
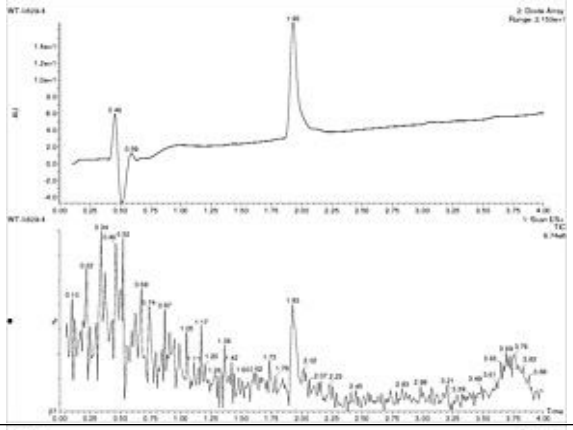
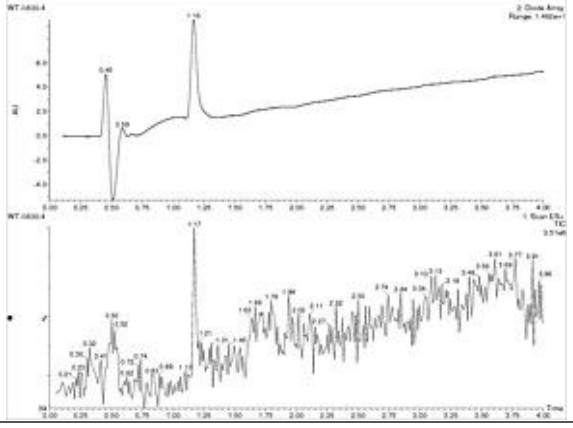
21g	
21h	
20q	
23b	

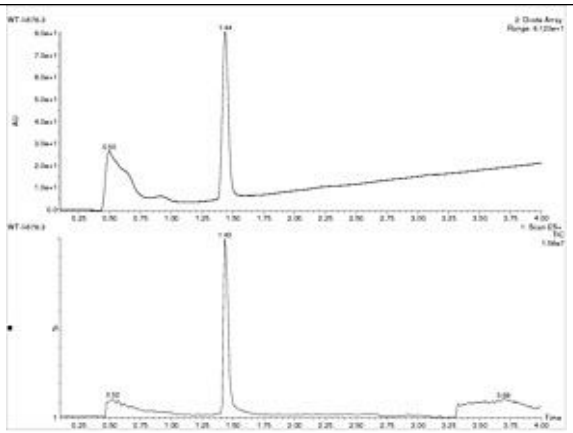
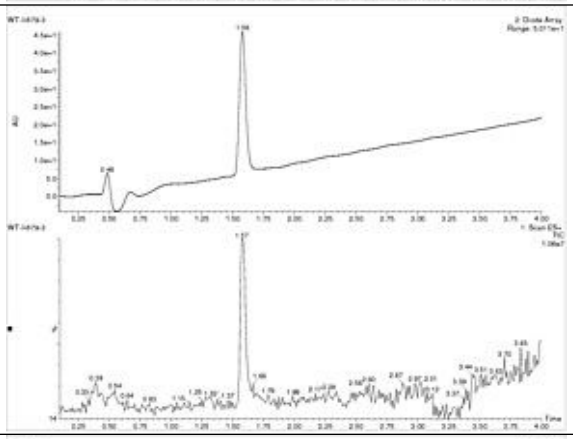
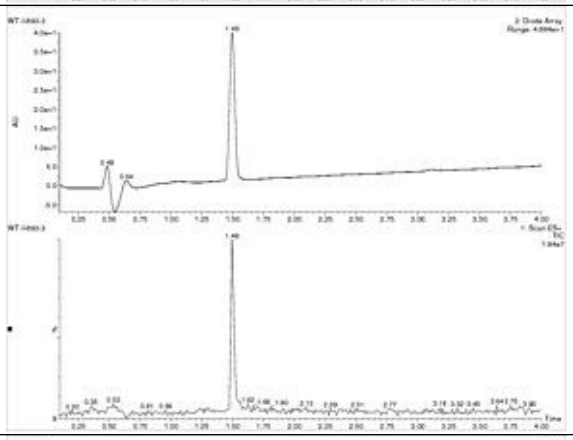
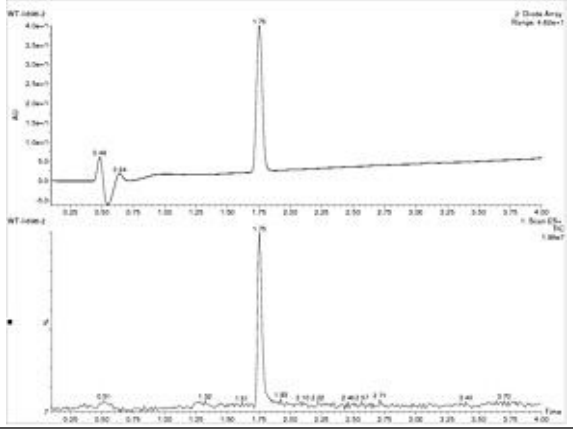
18d	
23a	
10n	
20d	

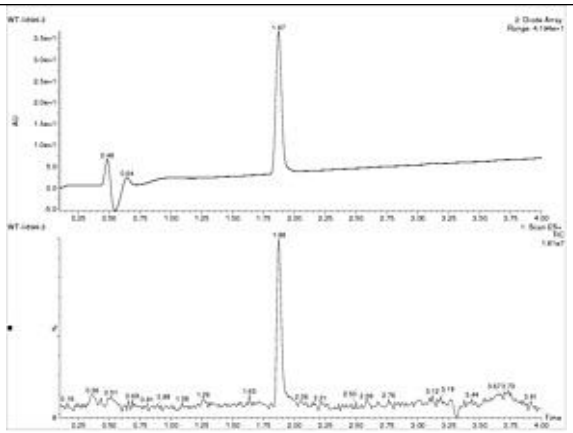
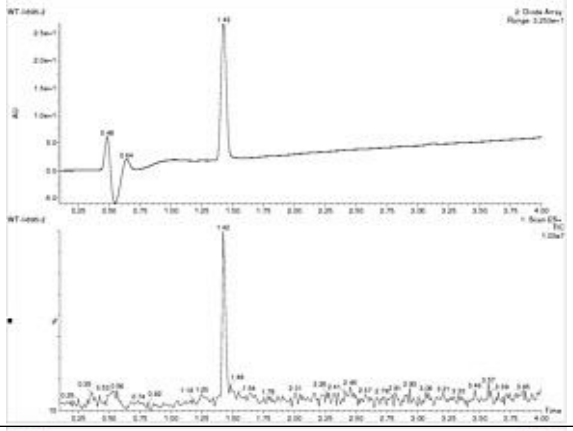
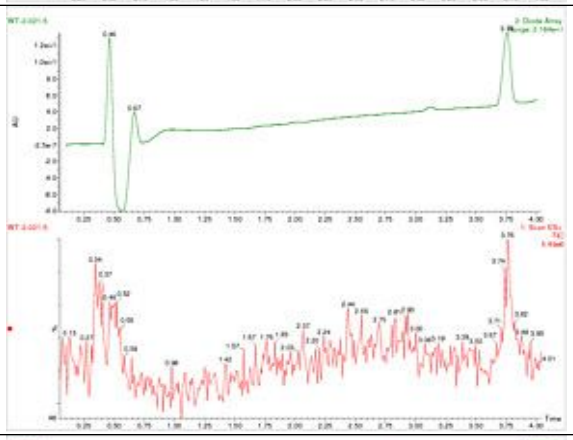
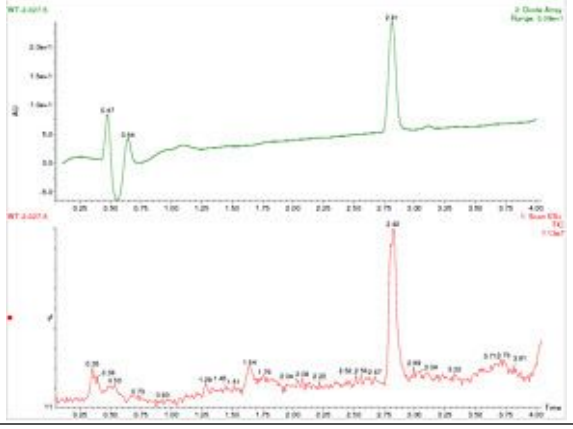
20e	
20h	
20n	
20o	

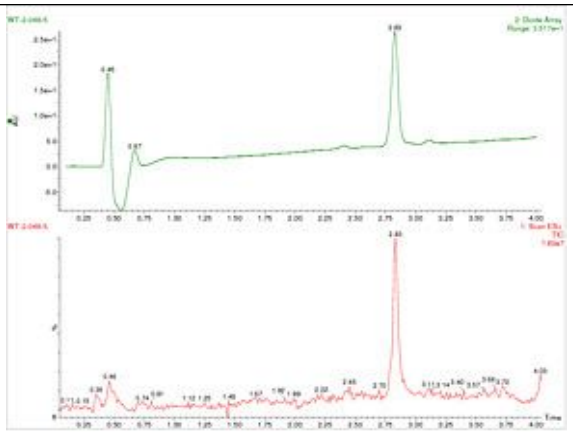
20f	
18b	
23h	
23d	

23i	
23c	
17	
20k	

19a	
19b	
20i	
20j	

23f	
23e	
23k	
23l	

23g	
23m	
21b	
21c	

20b	

1. Diaz, R.; Luengo-Arratta, S. A.; Seixas, J. D.; Amata, E.; Devine, W.; Cordon-Obras, C.; Rojas-Barros, D. I.; Jimenez, E.; Ortega, F.; Crouch, S.; Colmenarejo, G.; Fiandor, J. M.; Martin, J. J.; Berlanga, M.; Gonzalez, S.; Manzano, P.; Navarro, M.; Pollastri, M. P., Identification and characterization of hundreds of potent and selective inhibitors of Trypanosoma brucei growth from a kinase-targeted library screening campaign. *PLoS Negl Trop Dis* **2014,** *8* (10), e3253.