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Supplementary Material

Development of chromenopyrazole-based selective cannabinoid 2 receptor agonists

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Figure S1. ^{1}H NMR spectrum of *N*-[(1*S*)-1-{[(1*S*)-1-[(2-aminoethyl)carbamoyl]ethyl]carbamoyl}ethyl]-4-{4-[9-hydroxy-4,4-dimethyl-7-(2-methyloctan-2-yl)-1*H*,4*H*-chromeno[4,3-c]pyrazol-1-yl]phenyl}butanamide.

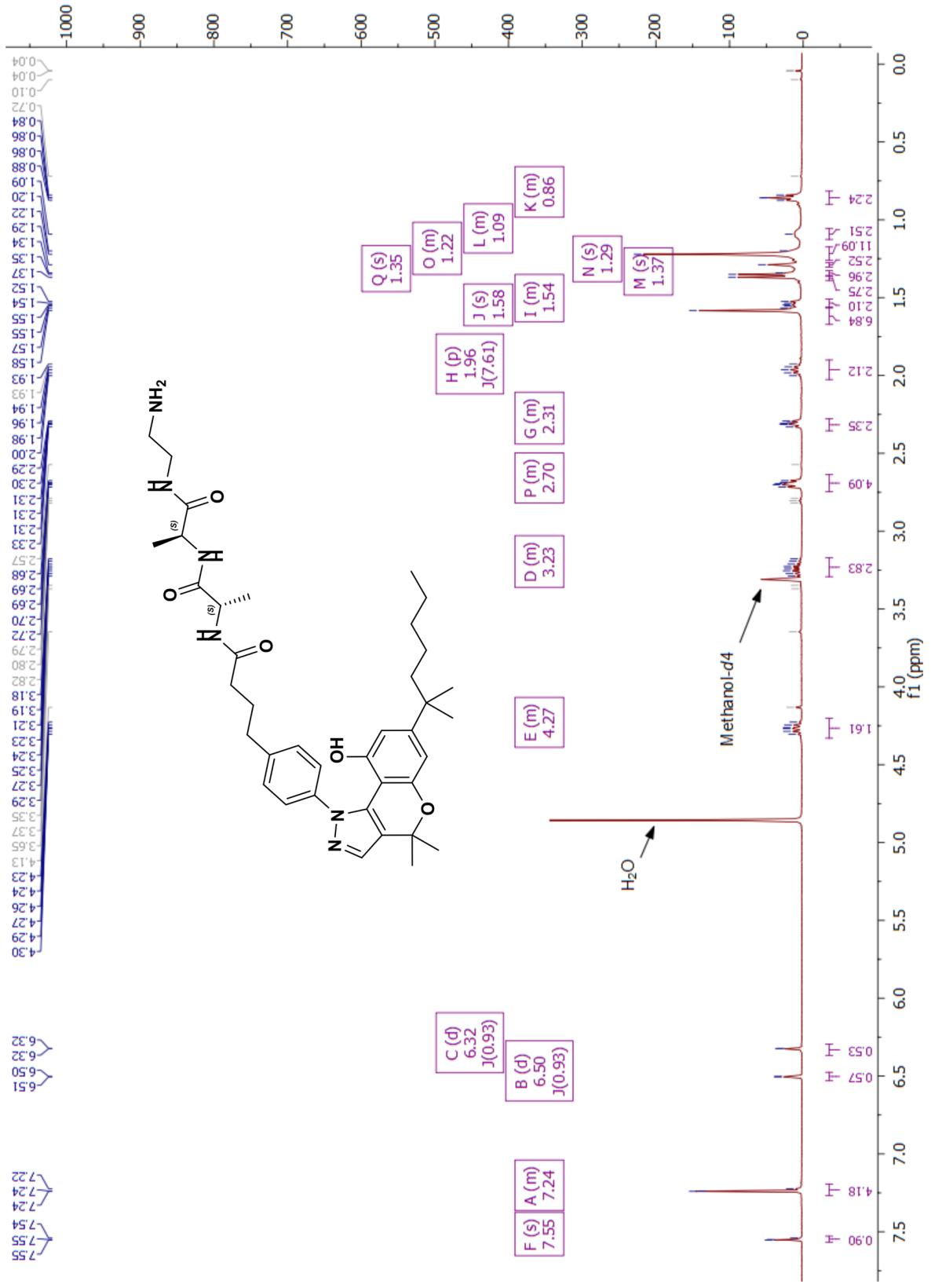

Figure S2. ^{13}C NMR spectrum of *N*-[(1*S*)-1-{[(1*S*)-1-[(2-aminoethyl)carbamoyl]ethyl]carbamoyl}ethyl]-4-{4-[9-hydroxy-4,4-dimethyl-7-(2-methyloctan-2-yl)-1*H*,4*H*-chromeno[4,3-c]pyrazol-1-yl]phenyl}butanamide.

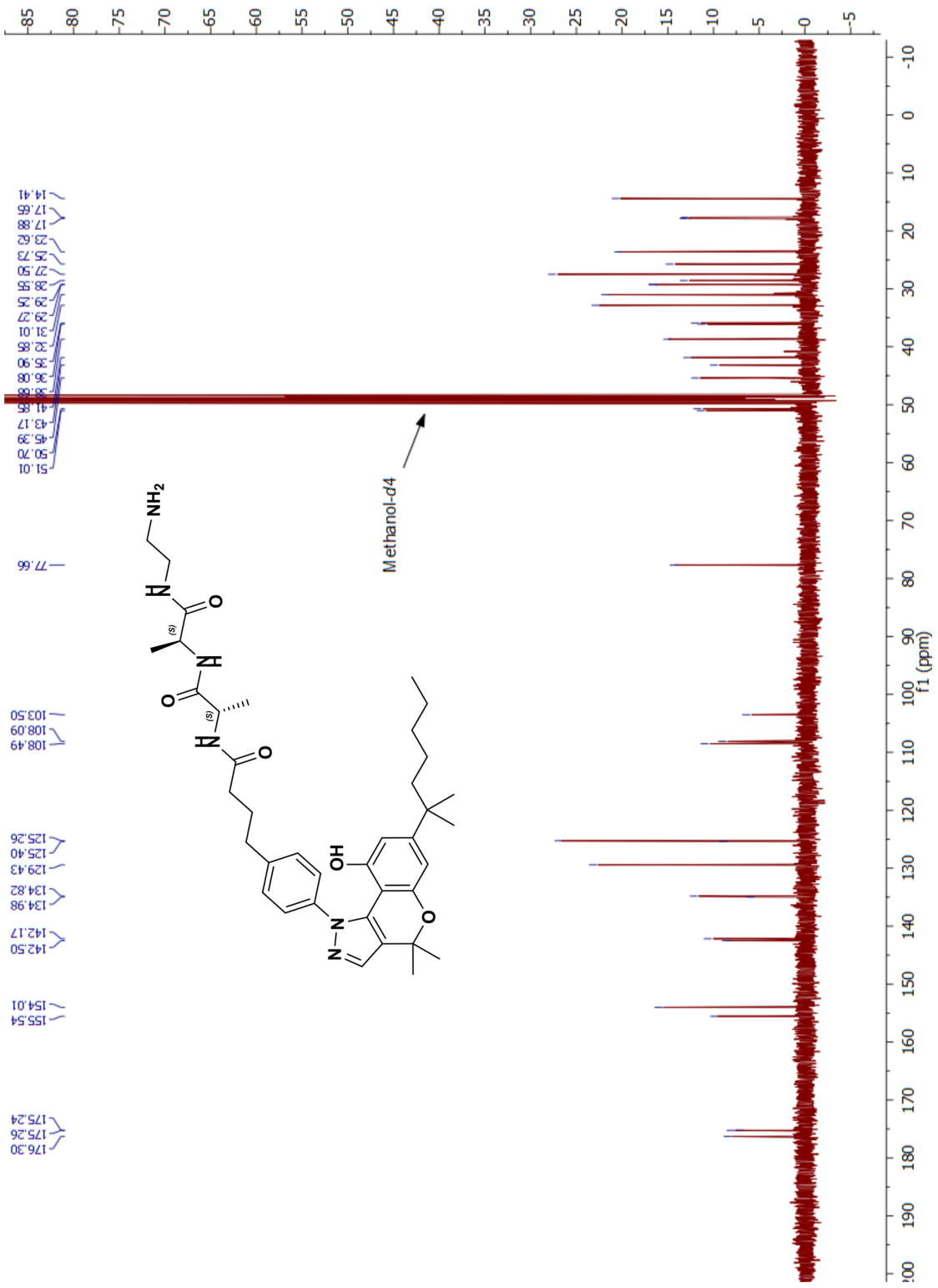

Table S1 Forskolin stimulated % response in cAMP BRET assay at wild type HEK-293 cells.

Compound	% FSK Response ± SEM[a]
2	102.40 ± 4.05
3	98.28 ± 1.64
5	104.51 ± 1.07
6	101.70 ± 1.77
7	105.86 ± 7.29
8	98.33 ± 3.73

Compounds **(2** - **3, 5** - **8)** tested in the cAMP BRET assay at WT-HEK-293 cells at 10 μM concentration. All data is from two individual experiments performed in duplicate, raw data[a] is normalised to forskolin response (100 %) and vehicle response (0 %) and is expressed as mean ± SEM. One-way ANOVA was carried out to check for statistically significant differences in comparison with the forskolin-only control. No significant difference was detected in the overall ANOVA ($P<0.01$).

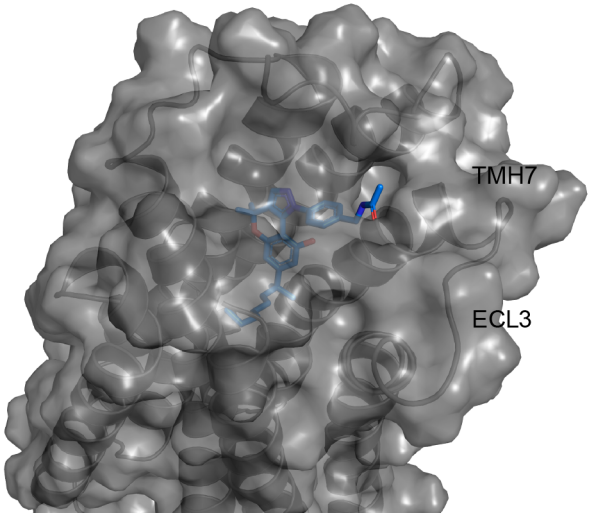

Figure S3. Highest ranked pose of ACS-18 (blue carbons) in CB_2R (grey Connolly surface). A tunnel is visible in the crystal structure that will allow an exit point for dipeptide attachment.