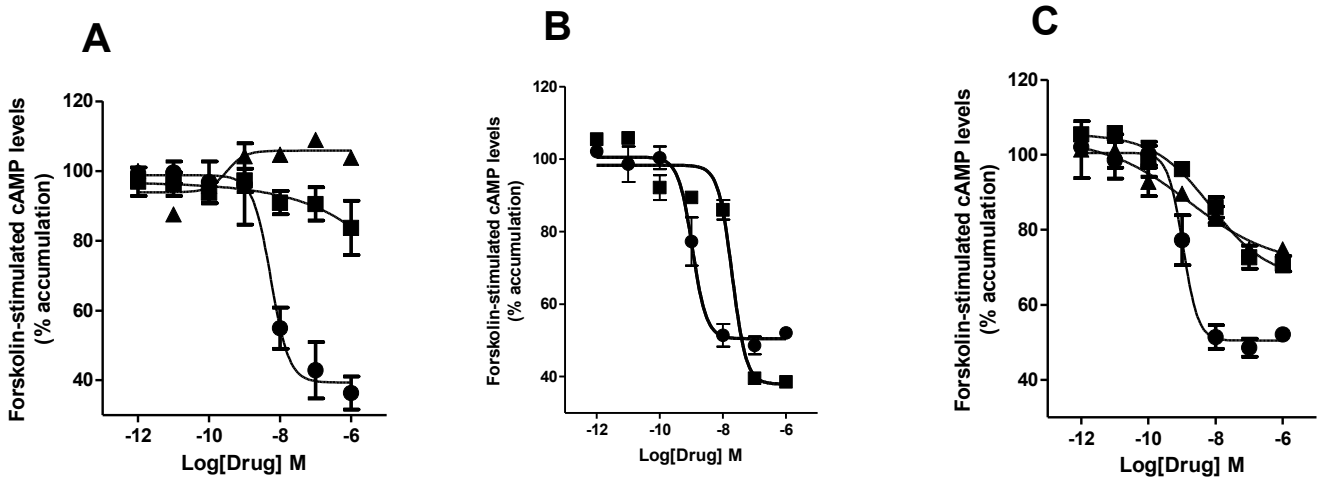

Fig. 1

Supplementary Fig 1. Cyclase assay: The classical cannabinoids, (A) L759656 (■) and L759633 (▲) failed to significantly affect cAMP levels, while (B) JWH133 (■) (EC_{50} 20 nM) was slightly more efficacious than CP55940 (●)(EC_{50} 5.5 nM) albeit with lower potency. (C) THC (■) (EC_{50} 7 nM) and KM233 (▲) (EC_{50} 1.6 nM) displayed lower efficacy but comparable potency to CP55940 in inhibiting adenylyl cyclase. EC_{50s} were obtained fitting the dose response curve (nonlinear regression) using GraphPad using GraphPad Prism 4.0. Data represent mean ± SEM of at least 3 experiments.

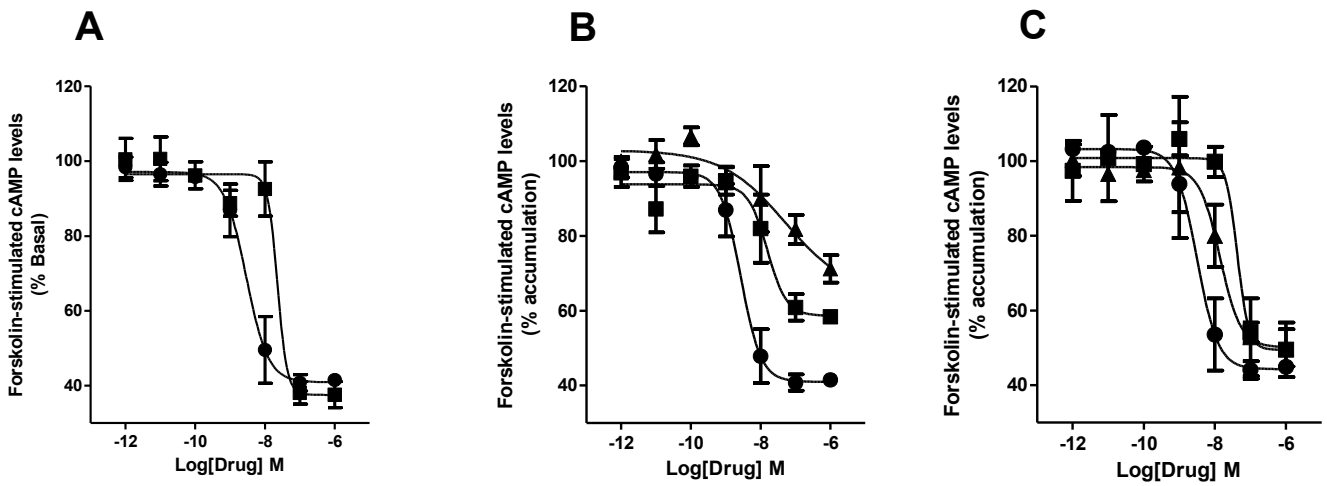

Fig. 2

Supplementary Fig 2. Cyclase assay: (A) The non-classical cannabinoid, HU308 (■) (EC_{50} 30 nM) was less potent than its congener, CP55940 (●) (EC_{50} 3 nM). (B) Aminoalkylindoles, WIN55212-2 (■) (EC_{50} 20 nM) and STS135 (▲) (EC_{50} 52 nM) displayed lower potencies and efficacies compared to CP55940 in the cyclase assay (C) A836339 (■) (EC_{50} 43 nM) and GP1a (▲) (EC_{50} 14 nM) displayed comparable efficacies as CP55940 in inhibiting adenylyl cyclase but were less potent. EC_{50s} were obtained by fitting the dose response curve (nonlinear regression) using GraphPad Prism 4.0. Data represent mean ± SEM of at least 3 experiments.

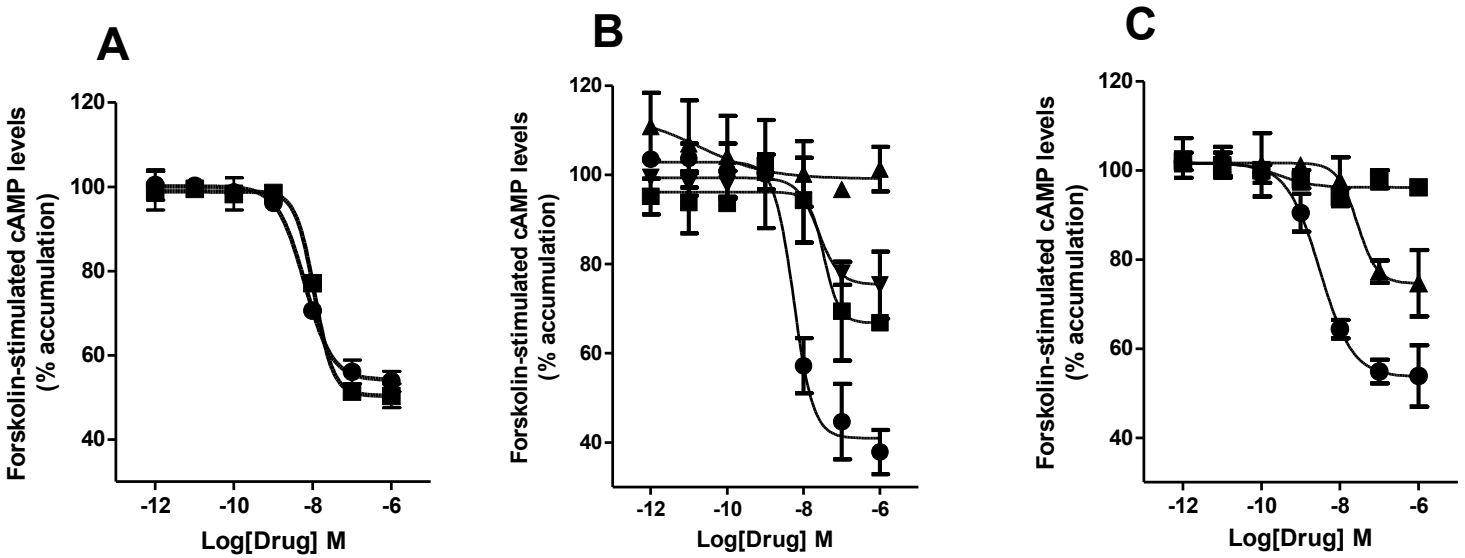

Fig. 3

Supplementary Fig. 3. Cyclase assay: (A) The cannabilactone, AM1710 (■) (EC_{50} 11nM) was as potent and efficacious as CP55940 (●)(EC_{50} 6 nM) in inhibiting the accumulation of cAMP. (B) The carboxamide SER601 (■) (EC_{50} 40 nM) and the pyrimidine GW833972A (▼) (EC_{50} of 28 nM) were less potent and efficacious than CP55940, while 4Q3C (▲) failed to elicit any response in cyclase assay (C) The natural product, 4-O-methylhonokiol (■) failed to inhibit accumulation of cAMP, while β caryophyllene (▲) (EC_{50} 30 nM) was a low efficacy agonist. EC_{50s} were obtained by fitting the dose response curve (nonlinear regression) using GraphPad Prism 4.0. Data represent mean ± SEM of at least 3 experiments.

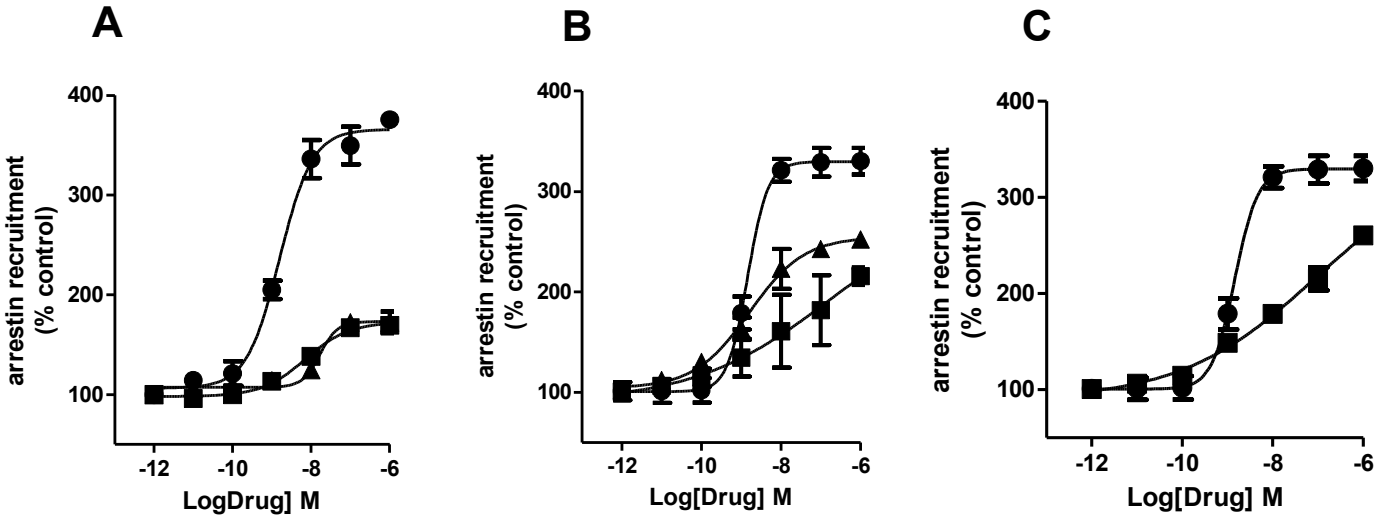

Fig. 4

Supplementary Fig. 4. Arrestin recruitment assay: (A) Aminoalkylindoles WIN55212-2 (■) (EC_{50} 7.2 nM) and JWH015 (▲) (EC_{50} 160 nM); (B) STS135 (▲) (EC_{50} 1.5 nM) and AM1248 (■) (EC_{50} 71 nM); and (C) UR144 (■) (EC_{50} 95 nM) were low efficacy agonists (with variable potencies and efficacies) compared to CP55940 (●) for arrestin recruitment by the CB2 cannabinoid receptor. EC_{50s} were obtained by fitting the dose response curve (nonlinear regression) using GraphPad Prism 4.0. Data represent mean ± SEM of at least 3 experiments.

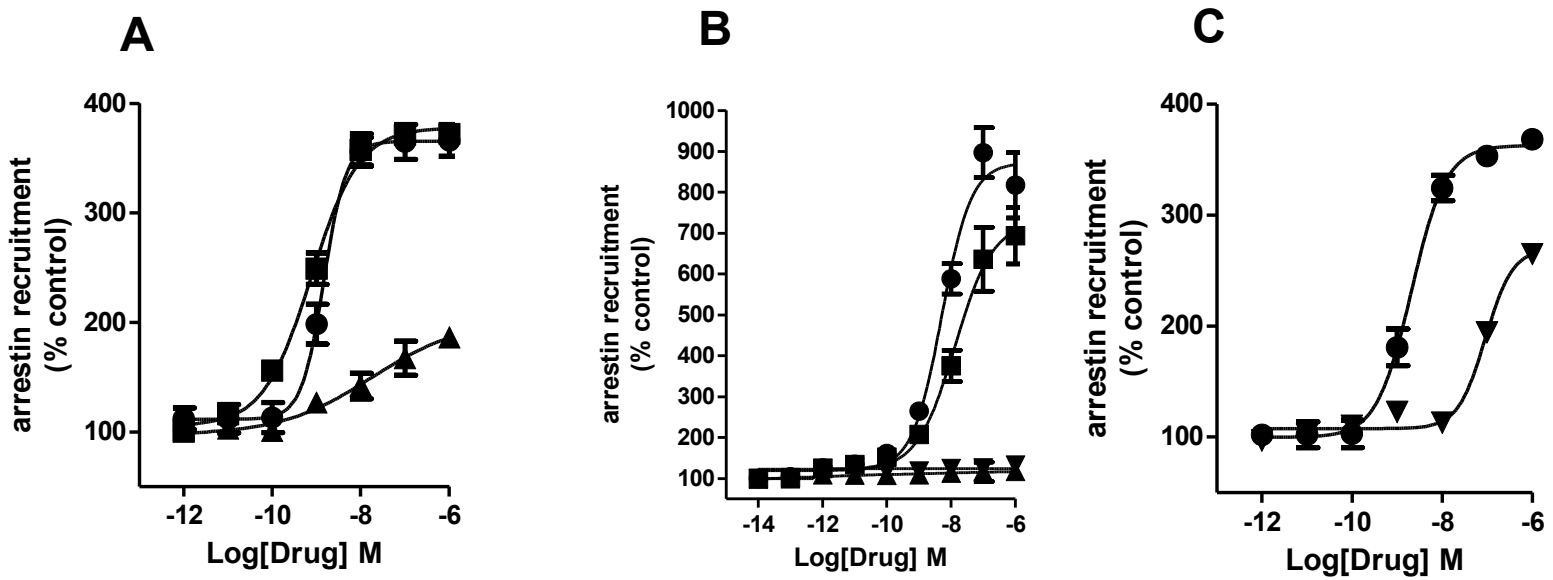

Fig. 5

Supplementary Fig. 5. Arrestin recruitment assay: (A) A836339 (■) (EC_{50} 0.7 nM) was equipotent and equi-efficacious to CP55940 (●) (EC_{50} 1.5 nM) in recruiting arrestins while, GP1a (▲) (EC_{50} 17 nM) was a low efficacy agonist. (B) AM1710 (■) (EC_{50} 6.7 nM) was as potent and efficacious as CP55940 in recruiting arrestins, but SER601 (▼) and 4Q3C (▲) were inactive. (C) The pyrimidine analogue, GW833972A (▼) (EC_{50} 90 nM), was moderately efficacious, albeit with low potency relative to CP55940, in recruiting arrestins. EC_{50s} were obtained by fitting the dose response curve (nonlinear regression) using GraphPad Prism 4.0. Data represent mean ± SEM of atleast 3 experiments.

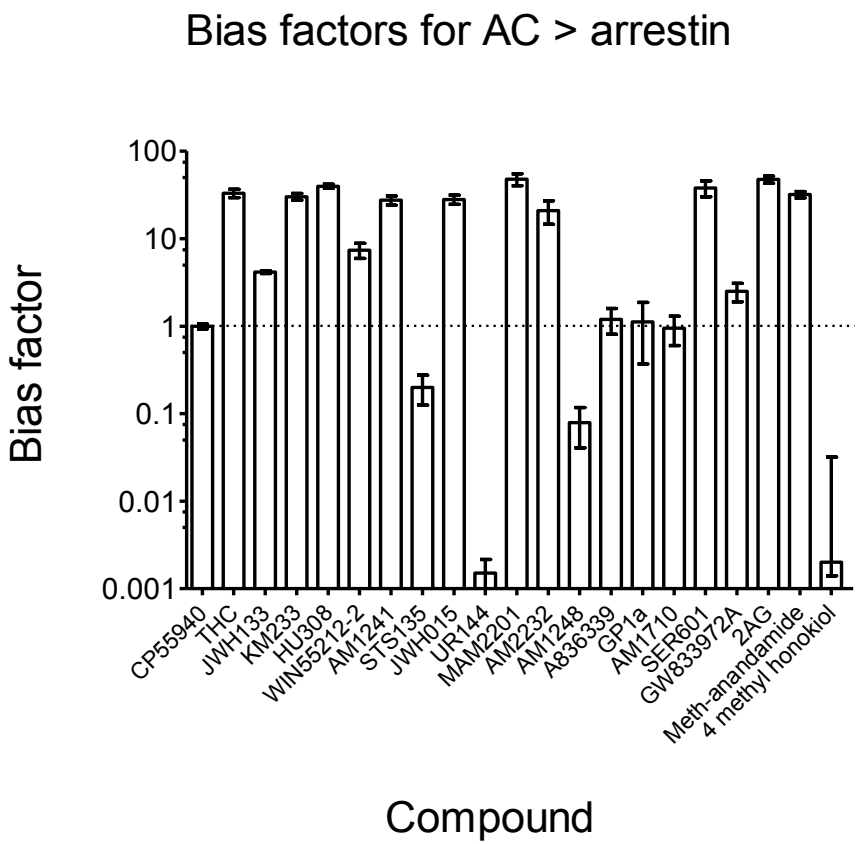

Fig. 6

Supplementary Fig. 6 Bar graph depicting bias factors for select active compounds for inhibition of adenylyl cyclase compared to β arrestin recruitment