**A *N*-propionylsulfonamide prodrug of K-5a2** **provided improved aqueous solubility and hERG inhibition**

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**Graphical Abstract**

**HM-1**, a N-propionylsulfonamide prodrug of **K-5a2**, exhibited high potency against HIV-1NL4-3 strain (EC50 = 7.99 nM) in TZM-bl cells, HIV-1IIIB strain (EC50 = 2.9 nM) and HIV-1Y181C strain (EC50 = 5.5 nM) in MT-4 cells. Besides, **HM-1** showed a >70-fold improvement in aqueous solubility and 50 times lower hERG inhibition (IC50 = 6.39 μM) than **K-5a2** (IC50 = 0.13 μM). **HM-1** appeared to be free of most of the drawbacks associated with **K-5a2** and has been selected for further development as an oral anti-HIV-infection agent.

