Supporting Information to

Synthesis of novel fluorinated xanthine derivatives with high adenosine A_{2B} receptor binding affinity

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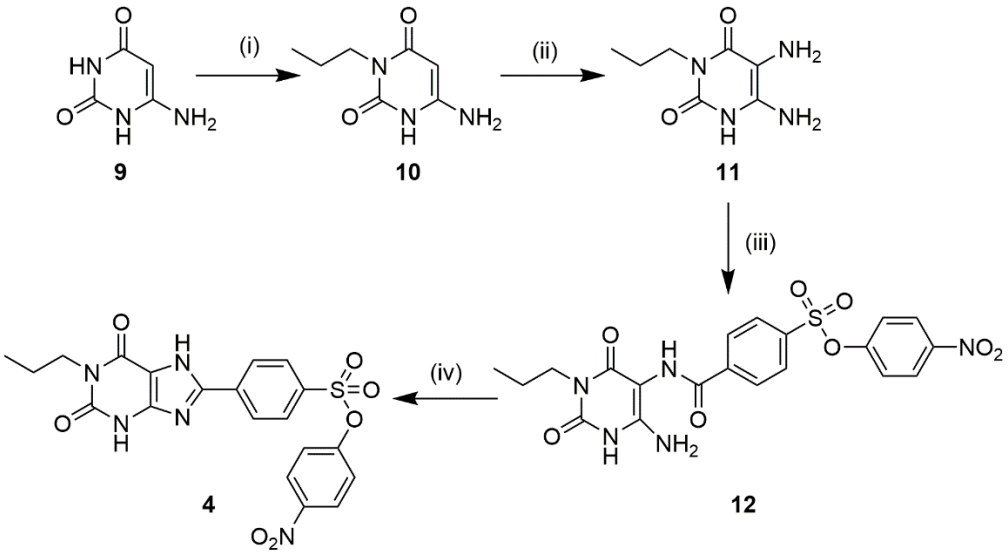
Content:

1. Synthesis of the precursor compound 4

Starting with 6-aminouracil **9** in a selective *N*-alkylation [1,2], nitrosylation and reduction with hydrogen and palladium on carbon to the diamine **11** was performed [2,3]. The 4-((4-nitrophenoxy)sulfonyl)benzoic acid was synthesized over a two-step approach starting from potassium 4-sulfobenzoate, which was chlorinated and converted to the final sulfonyl ester [4]. Instead of using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) [4], benzotriazolooxytris(dimethylamino)phosphoniumhexafluorophosphat (BOP) was used for the formation of the amide **12**, because it already showed good results in another study [5]. The reaction was performed in dichloromethane (DCM) with triethylamine (TEA) as base, to result in **12** with moderate yields of around 36%. The obtained amide **12** was intramolecular cyclized to result in the xanthine backbone precursor **4** with a yield of 91% [4].



Scheme S1. Synthesis of xanthine backbone **4**. Reaction conditions: (i) a) cat. $(NH_4)_2SO_4$, 1,1,1,3,3,3-hexamethyldisilazan, reflux, 2 h, b) toluene, 1-iodopropane, reflux, 16 h, c) sat. aq. $NaHCO_3$, 71%; (ii) a) 50% aq. HOAc, $NaNO_2$, 70 °C, 30 min, b) H_2/Pd/C, ethanol, room temperature, 5 h, 85%; (iii) BOP, TEA, 4-((4-nitrophenoxy)sulfonyl)benzoic acid, DCM, room temperature, 2 d, 36%; (iv) polyphosphoric acid trimethylsilyl ester, 145 °C, 8 h, 91%.

2. ^{1}H, ^{13}C, ^{19}F NMR and mass spectra of compounds 5 and 6

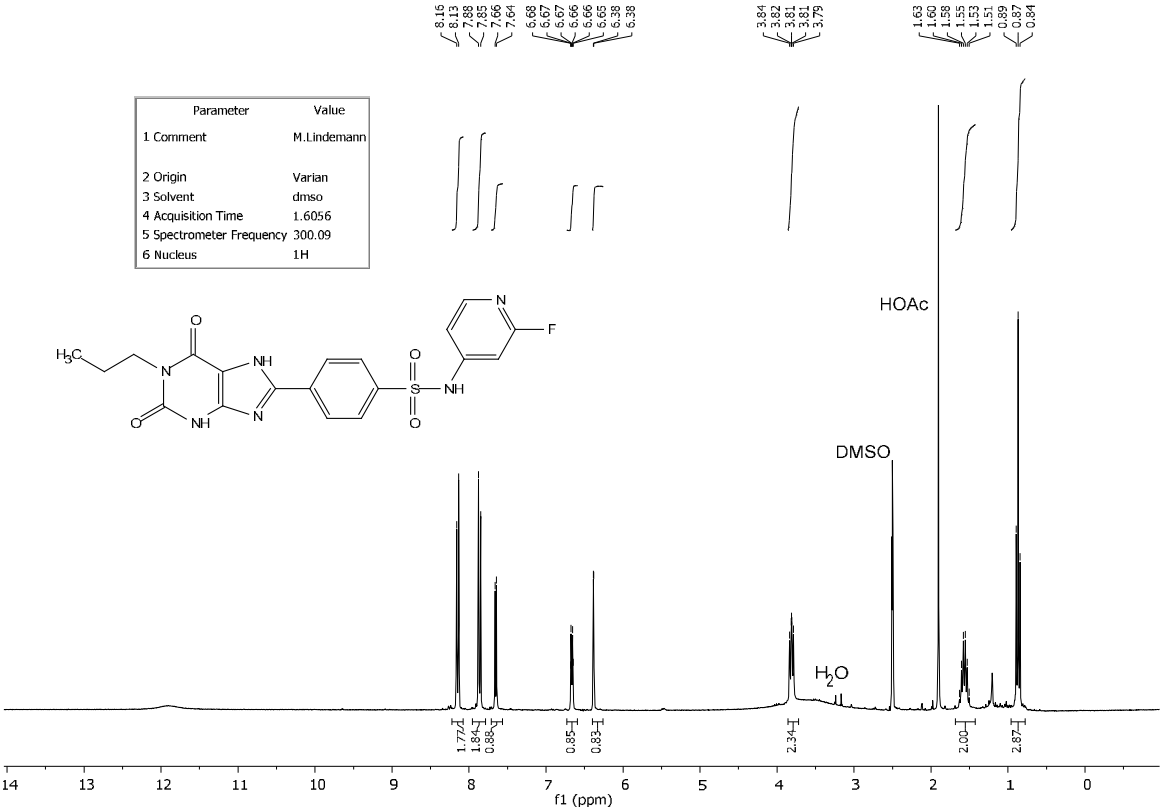


Figure S1. ^{1}H NMR spectrum of compound **5**.

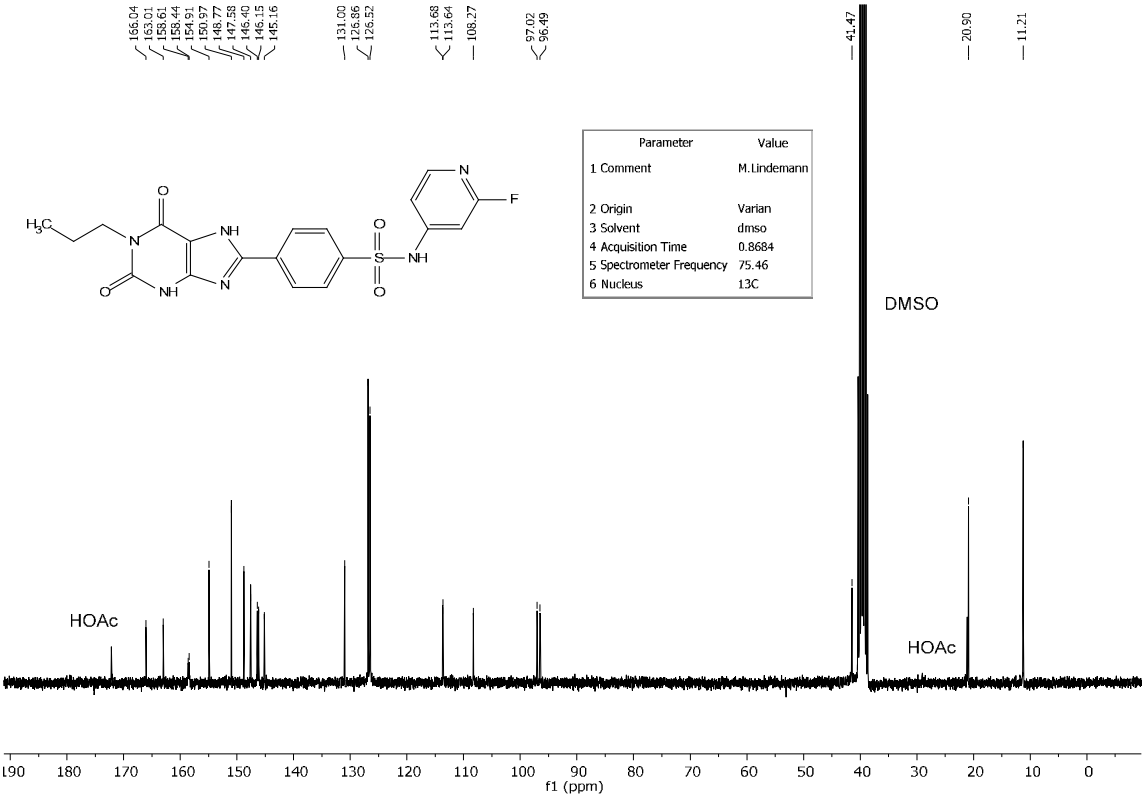


Figure S2. ^{13}C NMR spectrum of compound **5**.

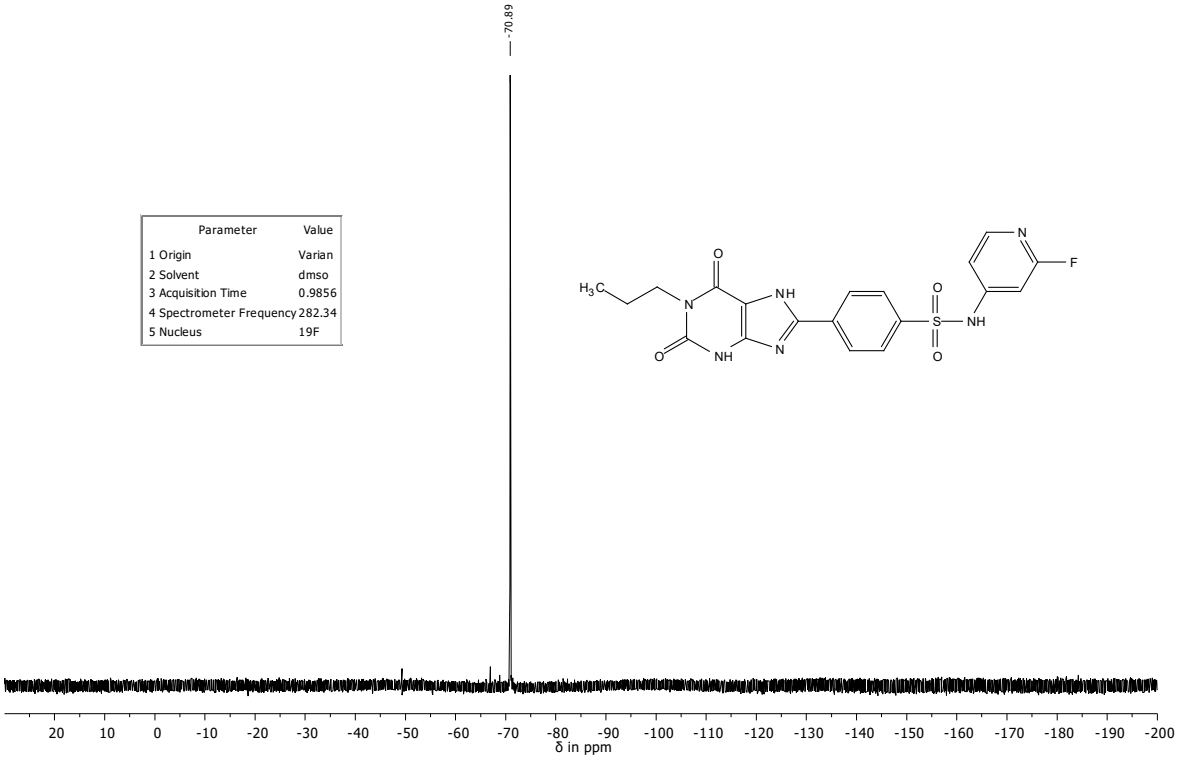


Figure S3. ^{19}F NMR spectrum of compound **5**.

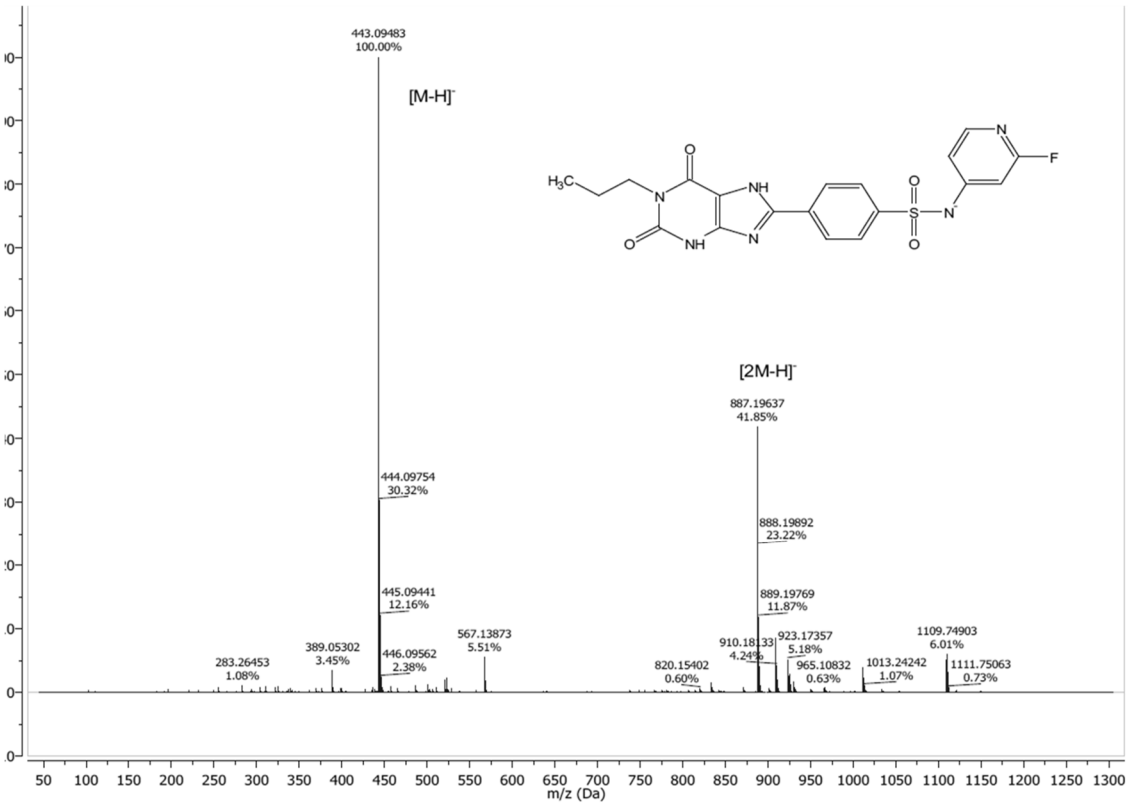


Figure S4. Mass spectrum of compound **5**.

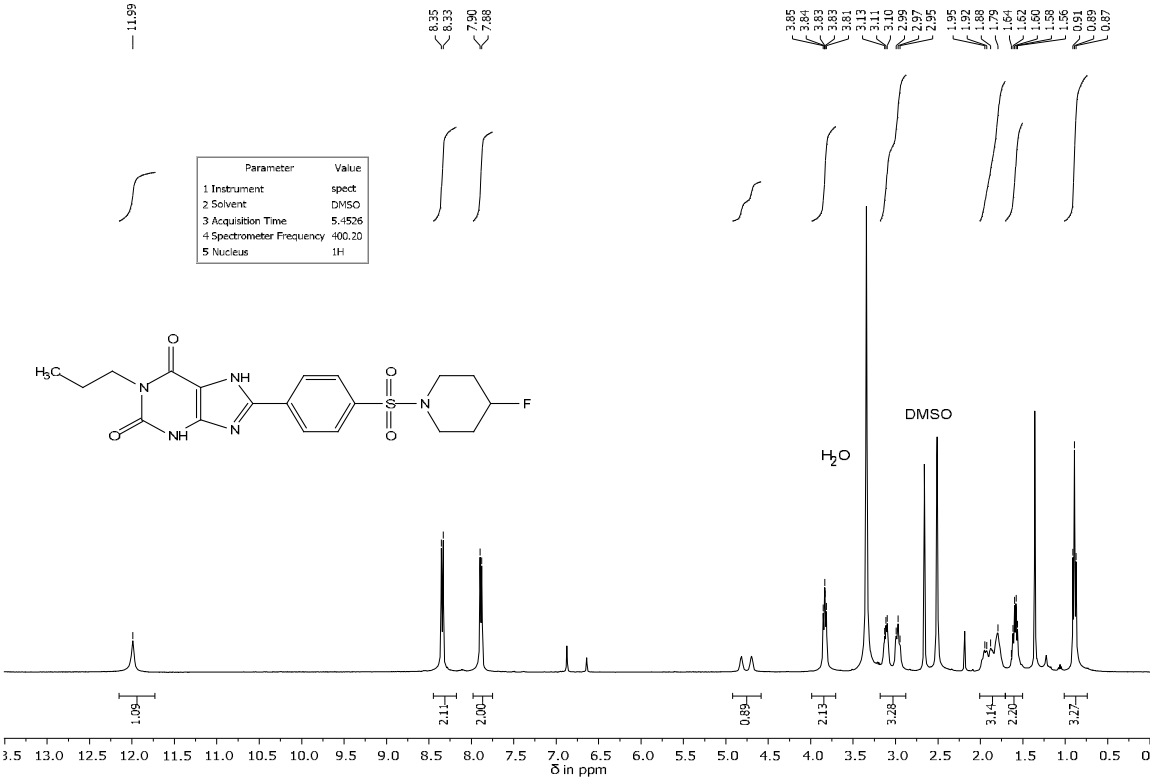


Figure S5. [1]H NMR spectrum of compound **6**.

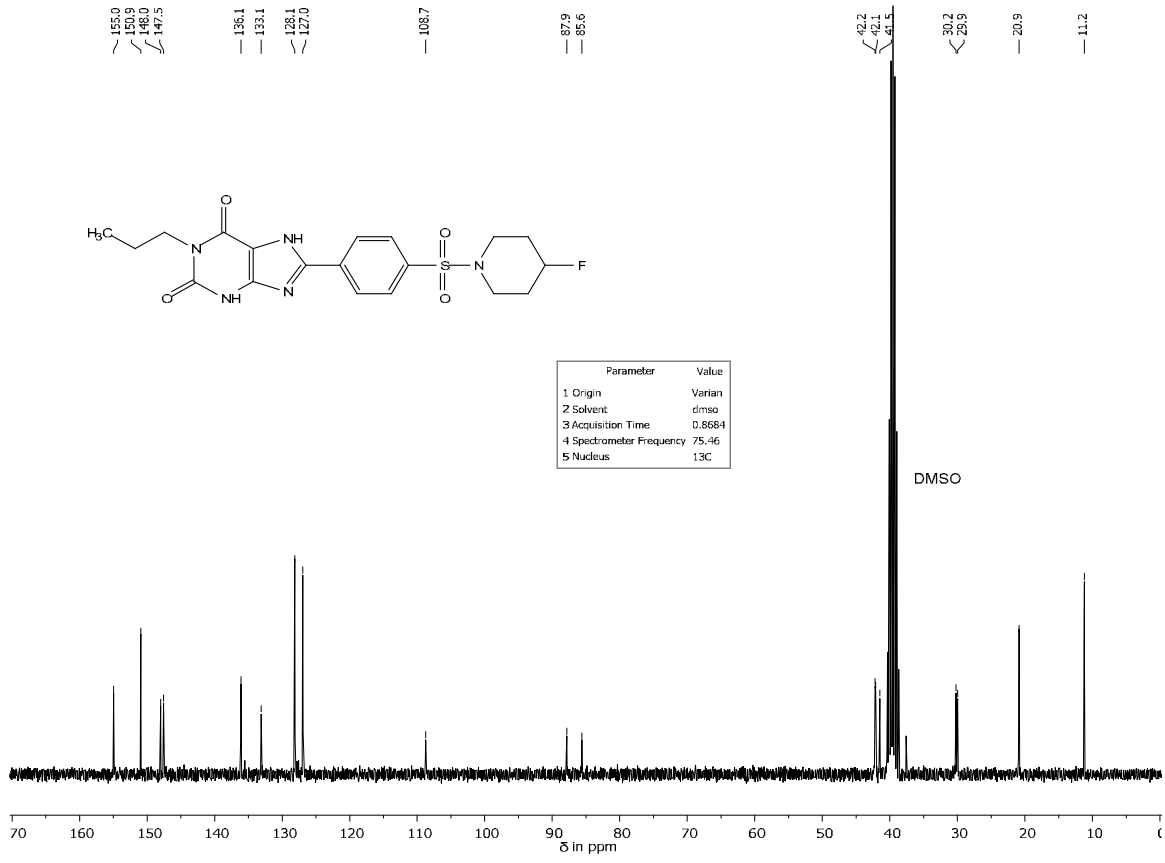


Figure S6. [13]C NMR spectrum of compound **6**.

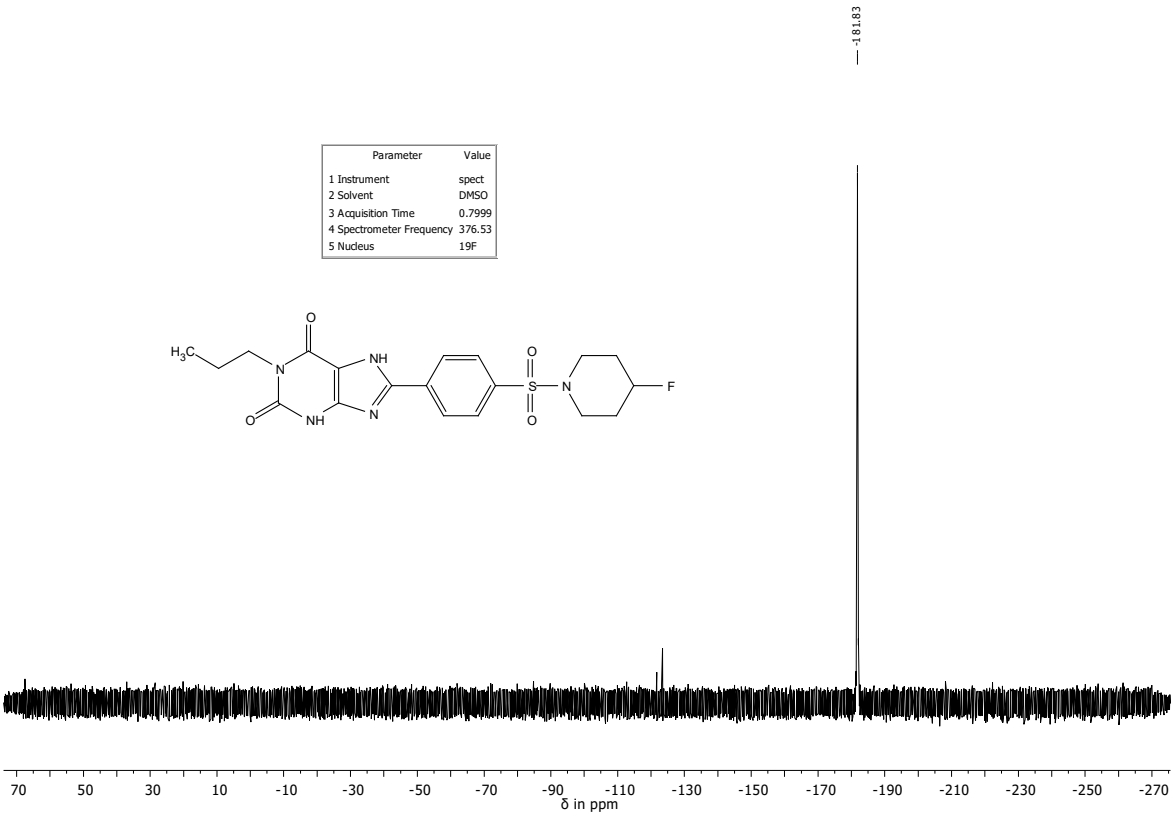


Figure S7. ^{19}F NMR spectrum of compound **6**.

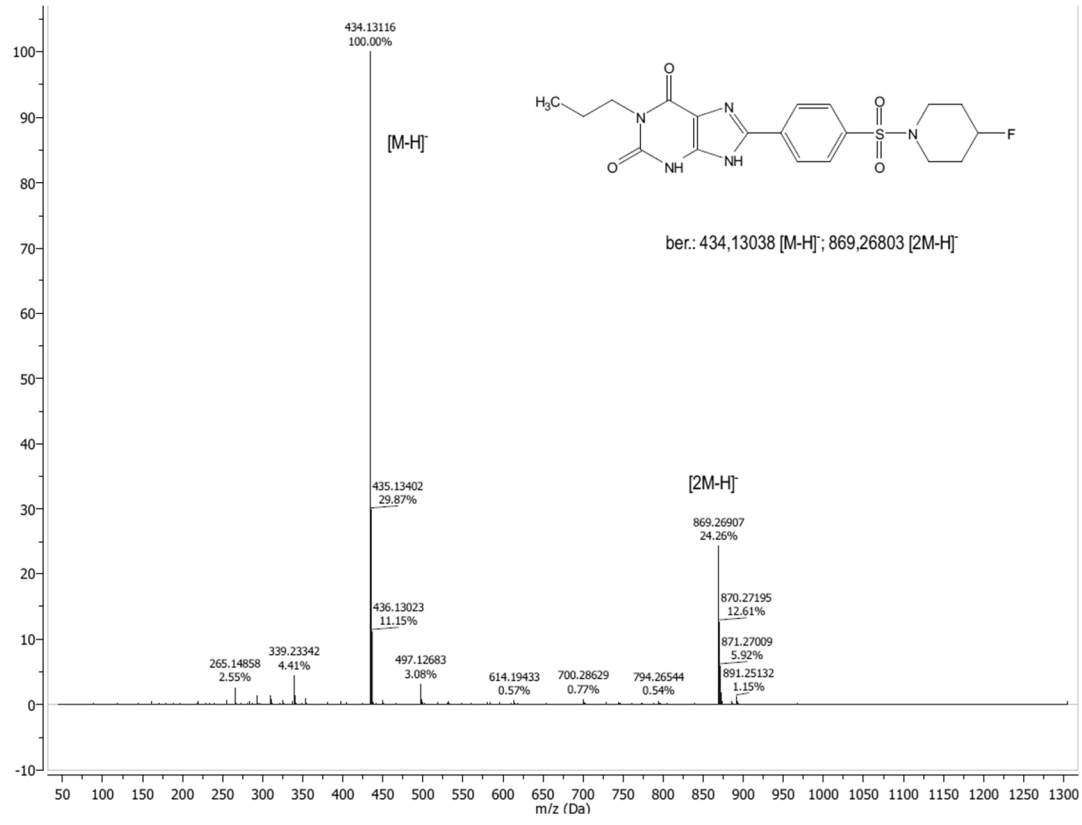


Figure S8. Mass spectrum of compound **6**.

3. References

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