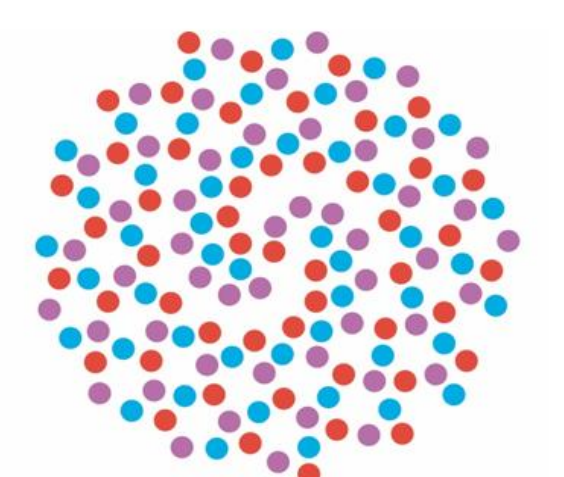




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Covalent Chromenopyrazole probes for Cannabinoid type 2 Receptor

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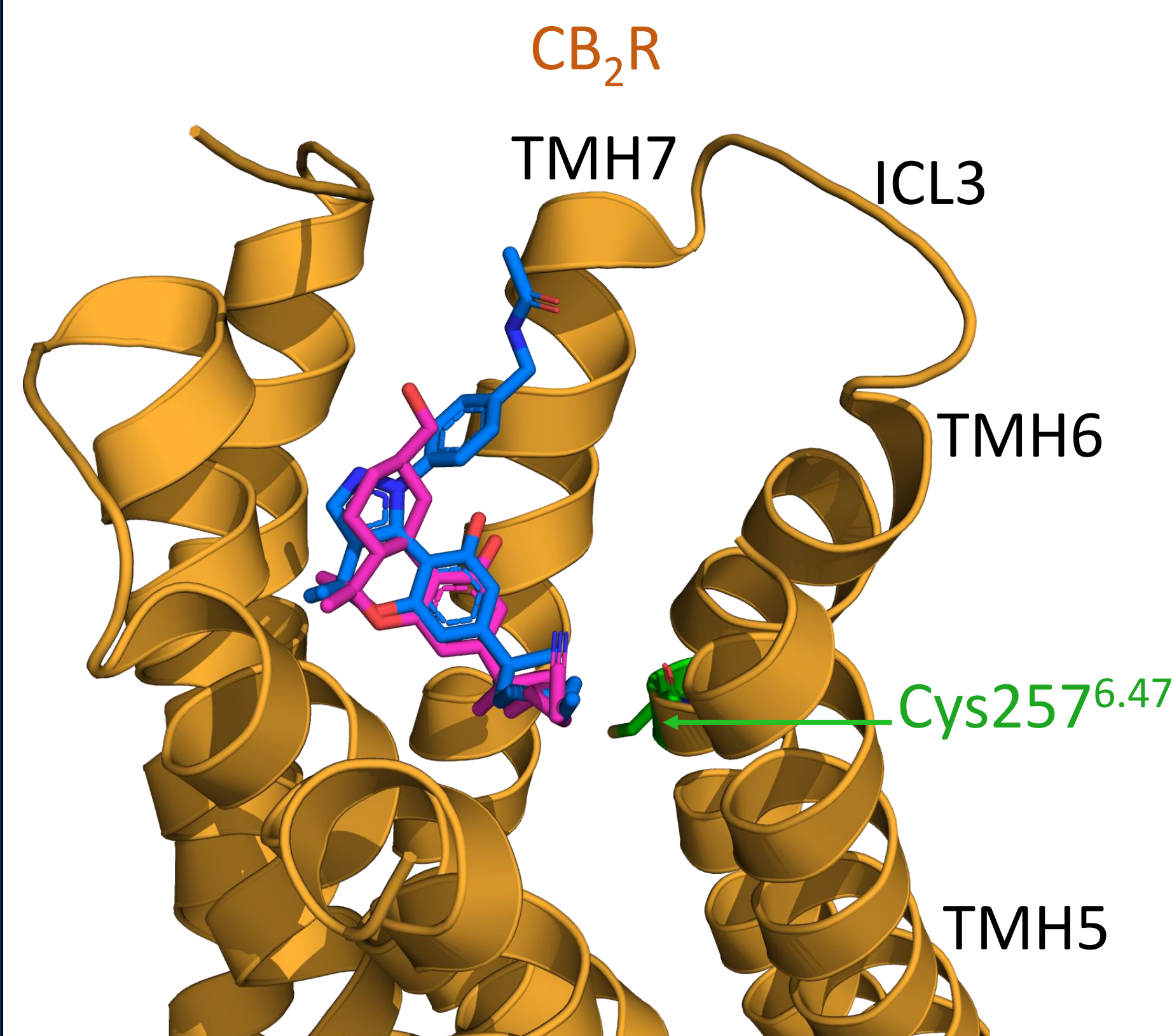
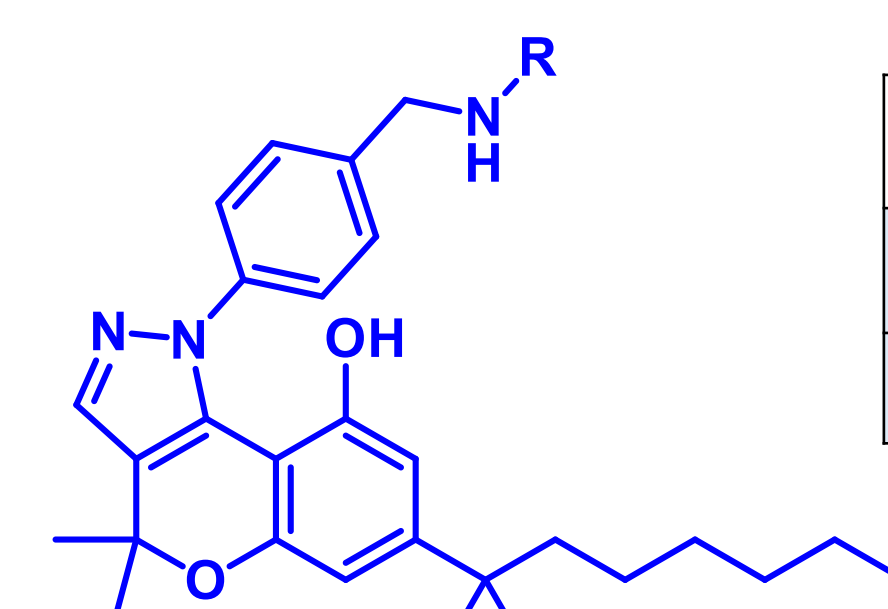
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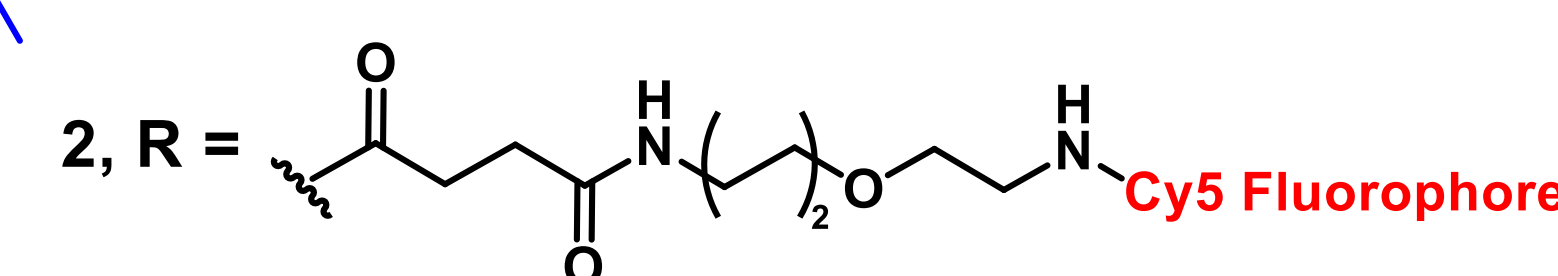
Introduction

- The Cannabinoid type 2 receptor (CB₂R) is a class A G protein – coupled receptors (GPCR) and plays a central to endogenous cannabinoid system. CB₂R is predominately expressed in the peripheral nervous and has been implicated in several chronic diseases.
- Currently, there is a lack of selective, covalent probes for studying CB₂R
- Based on a chromenopyrazole scaffold the Vernall group has developed a high affinity, CB₂R selective agonists such as **1** (Singh et al.) and the fluorescent, inverse agonist (**2**).
- PROJECT AIMS:** By introducing an electrophilic group (covalent warhead) to compounds such as **1** and **2** we aim to develop fluorescent and non-fluorescent covalent ligands that are CB₂R selective

Ligand Design



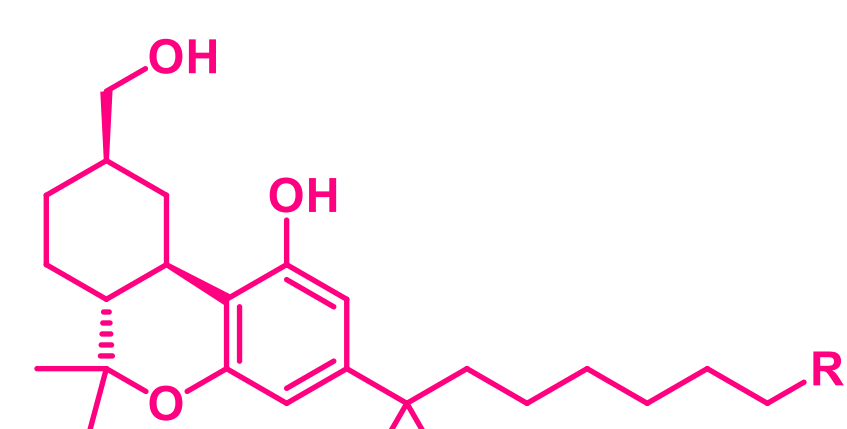
1, R = Ac



2, R =

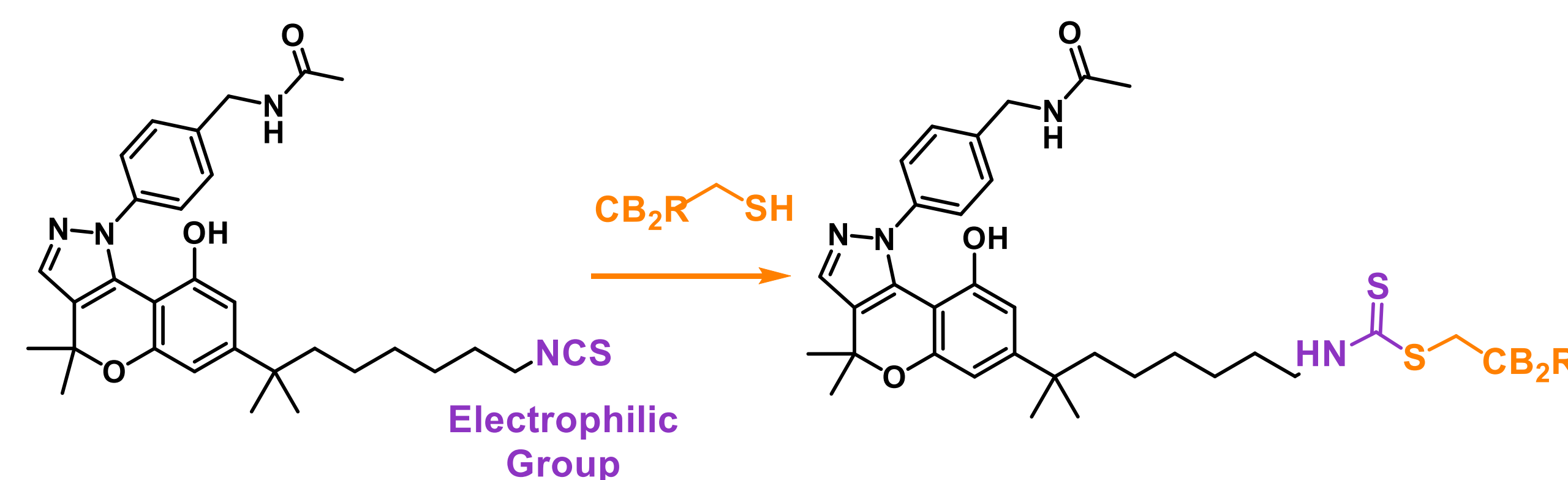
Cmp.	hCB ₁ R pK _i	hCB ₂ R pK _i	hCB ₂ R EC ₅₀ or IC ₅₀	hCB ₂ R selectivity
1	<5.30	7.91	EC ₅₀ 7.92	407
2	5.26	7.38	IC ₅₀ 6.93	131

- Cys257^{6,47}CB₂R is the site of covalent attachment for the non – selective cannabinoid receptor agonist **AM841**.
- Ligand docking to the **CB₂R** (orange, PDB: 6KPF) crystal structure with compound **1** (blue carbons) overlaps significantly with the native ligand **AM12033** (pink carbons, an AM841 analogue) suggesting a suitable attachment point to target.
- Our ligand design contains an electrophilic group at C1' position of the geminal dimethyl heptyl chain to facilitate covalent binding.

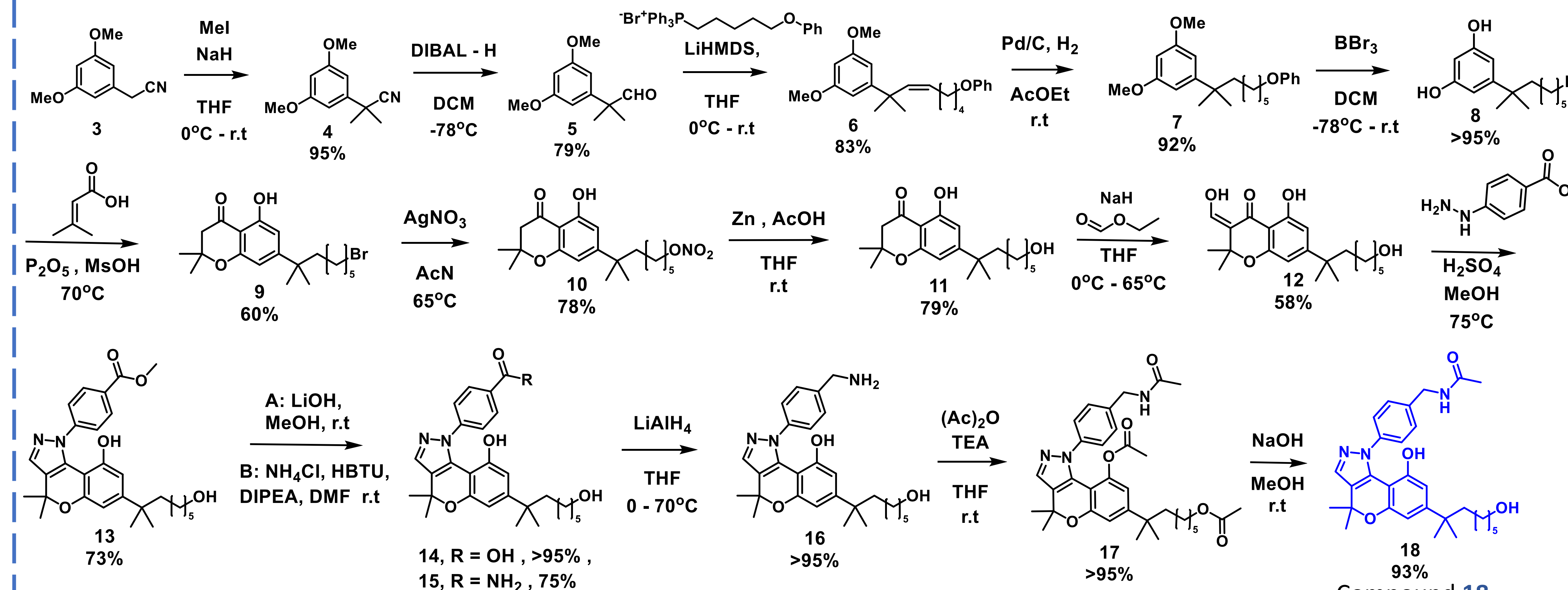


AM841 R = NCS

AM12033 R = CN

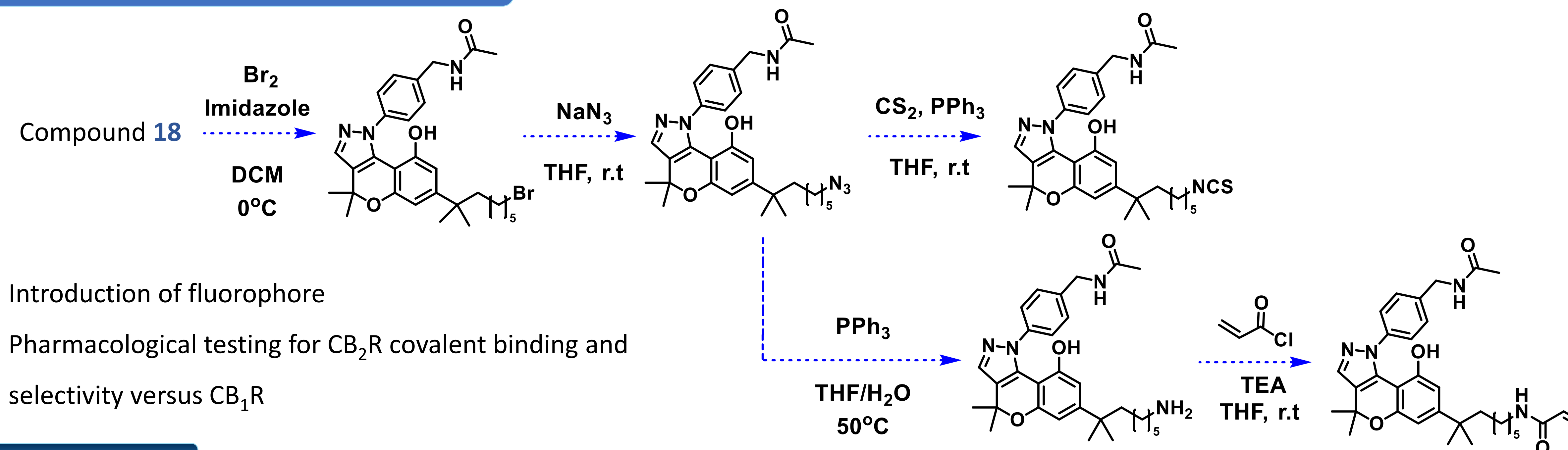


Synthesis



Compound **18**
Key intermediate for covalent group introduction

Future Directions



- Introduction of fluorophore
- Pharmacological testing for CB₂R covalent binding and selectivity versus CB₁R

References

Singh et al. Chromenopyrazole-based High Affinity, Selective Fluorescent Ligands for Cannabinoid Type 2 Receptor. *ACS Med. Chem. Let.* 2019. **10**, 209 – 14.
Hua et al. Activation and Signaling Mechanism Revealed by Cannabinoid Receptor-Gi Complex Structures. *Cell*. 2020. **180**.