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神経変性疾患分子イメージングを目指す TLR4 阻害剤 resatorvid を基盤とする新規 ^{18}F 標識 PET プローブの開発研究

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[Background] Resatorvid (TAK-242) (Fig. 1), which was developed as a TLR-4 inhibitor, was recently shown to be potential as a therapeutic agent for stroke since TLR4-NOX4 signaling may be the predominant causal pathway (Suzuki, Y. *et al.*, *Sci. Rep.* 2012). Due to the highly specificity of resatorvid towards TLR4, we envisaged that it has potential usefulness as a PET probe for imaging of TLR4 during ischemia reperfusion injury in brain. In this study, we develop a PET probe, ^{18}F-resatorvid ([^{18}F]**1**) to figure out the function of TLR4 in brain diseases intrigued by ischemia and reperfusion.

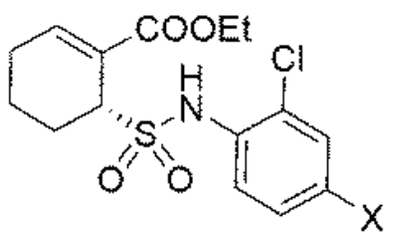
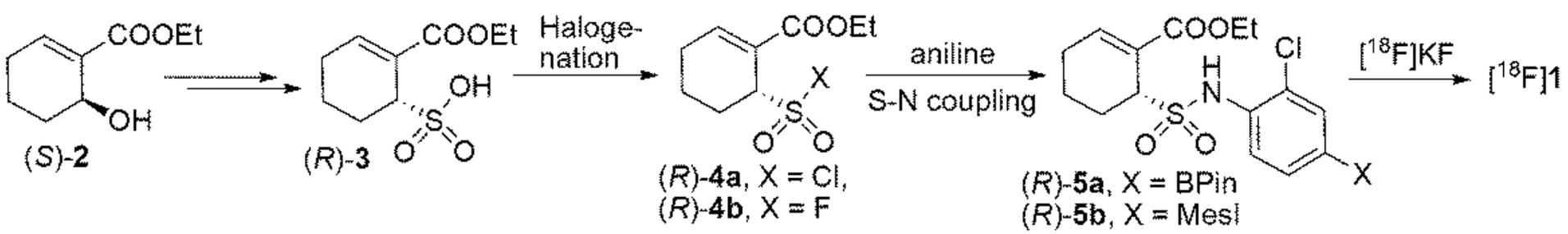


Figure 1: Resatorvid (**1**, X: F) and ^{18}F-resatorvid ([^{18}F]**1**, X: ^{18}F).

[Results] In order to get access of [^{18}F]**1**, we adapted synthetic route as shown in scheme 1. Cyclohexenol (*S*)-**5** was synthesized with >95% ee (Takano, S. *et al. Tetrahedron: Asymmetry* 1992). Alcohol (*S*)-**2** was transformed to sulfonic acid (*R*)-**3** in good yield. Efforts to gain access of sulfonyl chloride (*R*)-**4a** were ended up with failure whereas sulfonyl fluoride (*R*)-**4b** was obtained with moderate yield. Coupling of (*R*)-**4b** with aniline derivative provided (*R*)-**5a** which was then converted to (*R*)-**5b**. We are now optimizing reaction condition to prepare [^{18}F]**1** using obtained precursors.



Scheme 1: Synthetic route for synthesis of ^{18}F-resatorvid [^{18}F]**1**.