**Supplementary Material**

**Design and Synthesis of Novel Arylketo-containing P1-P3 Linked Macro-cyclic BACE-1 Inhibitors**

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**Synthesis of the amine 2-(5-(tert-butyl)oxazol-2-yl)propan-2-amine**

1-Amino-3,3-dimethylbutan-2-one (S2) was synthesized according to a published procedure [1]. The synthesis of amine S4 was performed according to a reported synthetic procedure [2]. tert-Butyl (1-((3,3-dimethyl-2-oxobutyl)amino)-2-methyl-1-oxopropan-2-yl)carbamate (S3). Commercially available S1 (2.1 g, 10.33 mmol) was added to a slurry of S2 (1.6 g, 10.44 mmol) and Et3N (4.4 mL, 31.4 mmol) in CH2Cl2 (20 mL). EDCI (2.4 g, 12.5 mmol) and HOAt (142 mg, 1.04 mmol) were added and the suspension was stirred at rt for 16 h. The reaction mixture was washed with sat. aq. NaHCO3 and the organic phase was dried (Na2SO4) and the solvent evaporated. The crude product was purified using flash column chromatography (heptane:EtOAc 10:1 to 2.5:1) to give 1.15 g (37%) of S3 as a white solid. 1H-NMR (CDCl3, 400 MHz) δ 1.19 (s, 9H), 1.43 (s, 9H), 1.51 (s, 6H), 4.26 (d, J = 4.3 Hz, 2H). MS (M-55) + calcd: 245.2; found: 245.2.

2-(5-(tert-butyl)oxazol-2-yl)propan-2-amine (S4). Compound S3 (497 mg, 1.66 mmol) was added to H2SO4 (1.5 mL) and the reaction mixture was stirred at 85 °C for 25 minutes. Ice was added and the mixture was adjusted to pH = 3-4 with 2 M aqueous NaOH. The aqueous phase was washed with CH2Cl2 (3 times) after which the aq. phase was made basic (pH = 12) with 2 M NaOH and extracted with CH2Cl2. The organic phase was dried (Na2SO4) and evaporated to give the product S4 as a colorless oil in 40% yield. 1H-NMR (CDCl3, 300 MHz) δ 1.27 (s, 9H), 1.60 (s, 6H), 6.57 (s, 1H); 13C-NMR (CDCl3, 75.5 MHz) δ 28.8, 29.2, 31.6, 50.7, 119.2, 141.0, 146.7. MS (M+H) + calcd: 183.1; found: 183.1.

**REFERENCES**

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