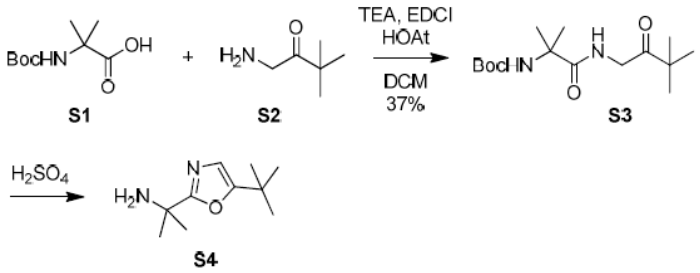
Supplementary Material

Design and Synthesis of Novel Arylketo-containing P1-P3 Linked Macrocyclic BACE-1 Inhibitors

Veronica Sandgren[1], Oscar Belda[2], Ingemar Kvarnström[1], Jimmy Lindberg[2], Bertil Samuelsson[2] and Anders Dahlgren[1,*]

[1]*Department of Chemistry, Linköping University, S-581 83 Linköping, Sweden;* [2]*Medivir AB, Lunastigen 7, S-141 44 Huddinge, Sweden*

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 Et_3N (4.4. mL, 31.4 mmol) in CH_2Cl_2 (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. $NaHCO_3$ and the organic phase was dried (Na_2SO_4) 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. ^{1}H-NMR ($CDCl_3$, 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 H_2SO_4 (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 CH_2Cl_2 (3 times) after which the aq. phase was made basic (pH = 12) with 2 M NaOH and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to give the product **S4** as a colorless oil in 40% yield. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 9H), 1.60 (s, 6H), 6.57 (s, 1H); ^{13}C-NMR ($CDCl_3$, 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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[2] Hom, R.; Toth, G.; Probst, G.; Bowers, S.; Troung, A.; Tung, J. S.; Patent WO2007/47306.