SYNTHESIS OF 2''-(2-(PHENYLAMINO)ETHOXY)-PAROMOMYCIN

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The Human Immunodeficiency Virus (HIV) is a causative agent of Acquired Immune Deficiency Syndrome (AIDS). To become infectious, viral particles must undergo maturation (i.e. cleavage of viral polyproteins – Gag and Gag Pol – into functional proteins). This process is mediated by HIV protease (HIV PR): several sites in the Gag region are cleaved in cis, then the HIV PR can be cleaved off from the precursor and complete the polyprotein cleavage into functional proteins giving rise to mature, infectious viral progeny [1].

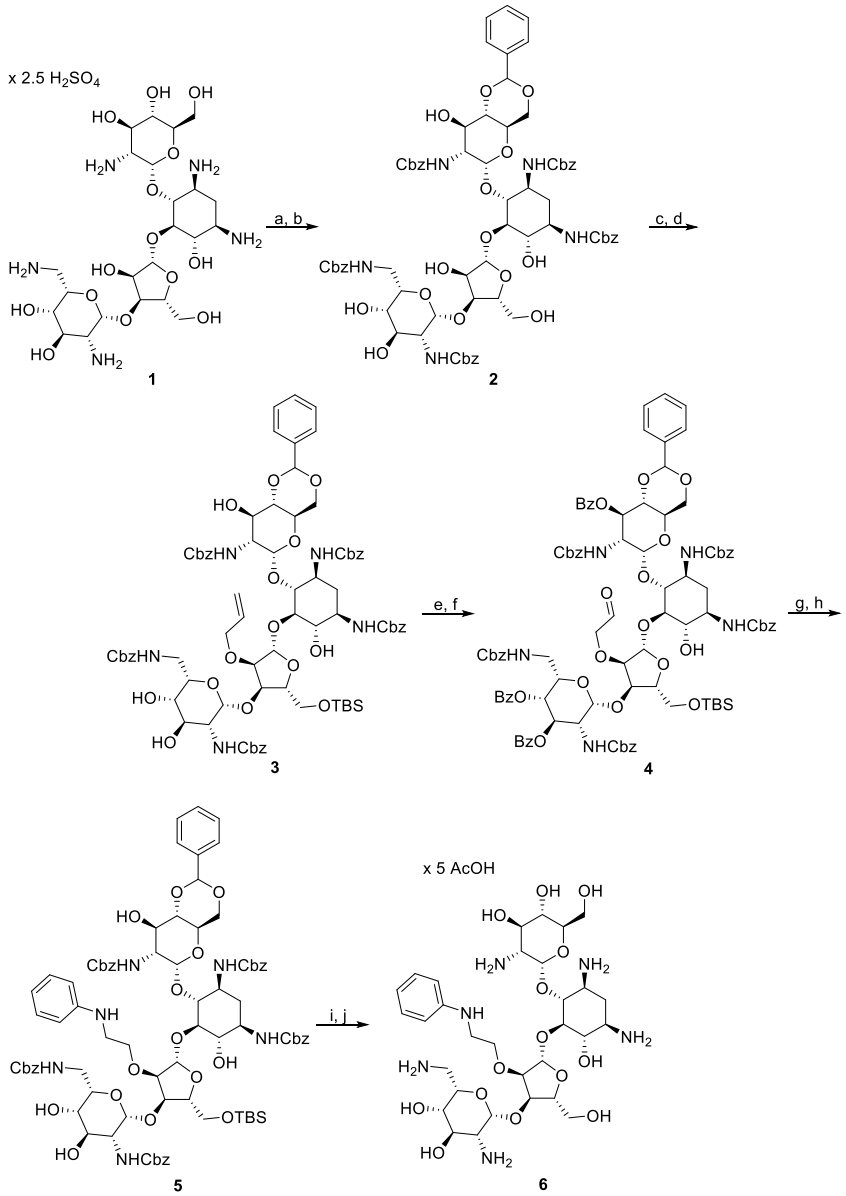

Fig. 1. Scheme of 2''-(2-(phenylamino)ethoxy)-paromomycin **6** synthesis: (a) CbzCl, Na_2CO_3, $NaHCO_3$, THF/H_2O, RT, 3 h; (b) benzaldehyde, TFA, RT, 14 h; (c) TBDMSOTf, 2,4,6,-trimethylpyridine, THF/H_2O, RT, 24 h, (d) allyl iodine, KHMDS, THF, RT, 24 h; (e) BzCl, Py, RT, 14 h; (f) 1. O_3, CH_2Cl_2, –78 °C, 2. Me_2S, CH_2Cl_2, from –78 °C to RT, 72 h.; (g) benzylamine, AcOH, $NaBH_3CN$, THF, RT, 24 h; (h) MeONa/MeOH; (i) 80% AcOH, 60 °C, 3 h; (j) H_2, $Pd(OH)_2$/C, 80% AcOH

Competitive HIV PR inhibitors are used clinically against HIV infection. Development of drug resistance against these compounds is a common problem and novel compounds are sought after. Allosteric modulators which bind to a site outside the enzyme active site represent an interesting alternative. Thus, the aim of this project is to identify a lead compound targeted beyond the active site of HIV PR.

Virtual screening method was used to find ligands binding out of the HIV PR active site**.** The screening was performed with Schrodinger Glide (v. 2015.4) HIV-1 PR was screened against drugbank database (ver. 4.3) in high throughput mode (HTVS). Highest ranked 300 hits were taken for a next round of docking with a standard precision option. 25 compounds were selected manually and evaluated by Glide XP scoring function. Based on experimental data, analogs of positive hits were selected from ZINC15 database (Tanimoto index threshold of 0.6). These analogs were scored via Glide XP scoring function. The virtual screening (VS) yielded several hits with significantly higher score than for original ligand-receptor complex. One of them – 2''-(2-(phenylamino)ethoxy)-paromomycin – was selected for organic synthesis and further testing.

To obtain the chosen product commercially available paromomycin sulfate **1** (*fig. 1*) was firstly protected with the use of benzyl chloroformate that selectively protects amines. The reaction was performed in mixture of THF and water with sodium carbonate/sodium bicarbonate buffer for 3 h [2]. The product was recrystallized from hexane and used in protection with benzaldehyde, which was performed with trifluoracetic acid to yield the compound **2** [3]. Further reaction was performed to protect the only remaining primary hydroxyl of **2** with *tert*-butyldimethylsilyl to obtain the corresponding product compatible to functional modification performed with allyl iodine and KHMDS, which allows us to selectively protect only 2"-hydroxyl, to yield ether **3** [4]. The next step was performed to protect the remaining free hydroxyls from reduction, to which purpose benzoyl chloride was used [4]. After that, protected compound was ozonated at –78°C and treated with MeS_2 afterwards to obtain the aldehyde **4** [4]. On the next step, sequentially reductive amination with benzylamine and deprotection with MeONa in MeOH were performed to yield benzylamine derivative **5**, which was to be further deprotected with acetic acid and then reduced with hydrogen on $Pd(OH)_2/C$ in acidic conditions to yield the final product **6** in form of acetic acid salt [4].

Thus, in this work, 2''-(2-(phenylamino)ethoxy)-paromomycin **6** was synthesized. Its sample was send to further examination as a ligand for allosteric modification of HIV PR in Czech Academy of Sciences.

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