SYNTHESIS OF POTENTIAL HSP90 AND HDAC MULTITARGET INHIBITORS

P. Kaziukonytė[1*], E. Kazlauskas[2], A. Zubrienė[2], A. Brukštus[1]

[1] *Vilnius University, Department of Chemistry and Geosciences, Naugarduko str. 24, LT-03225, Vilnius, Lithuania;*

[2] *Vilnius University, Life Sciences Center, Department of Biothermodynamics and Drug Design, Saulėtekio av. 7, LT- 10257 Vilnius, Lithuania.*

** E-mail: paulina.kaziukonyte@chf.stud.vu.lt*

Inhibition of histone deacetylases (HDACs) is a proven way to treat cancer [1] and compounds inhibiting HSP90 (Heat Shock Protein) shows promising anti-tumor properties as well [2]. We propose that it is possible to combine active fragments of inhibition to yield small-molecule drugs with improved therapeutic and side effect profile [3]. We chose known pharmacophores for the task - resorcinol moiety was selected to target HSP90 and hydroxamic acid functional group to target HDACs.

The first synthesis (Figure 1) was started from commercially available 2,4-dihydroxybenzoic acid **1**, which was converted to methyl ester **2**. In the following reactions compound **2** was substituted in the 5th position to give compounds **3**. Introduction of hydroxamic acid functional group gave desired products **4** in good yields.

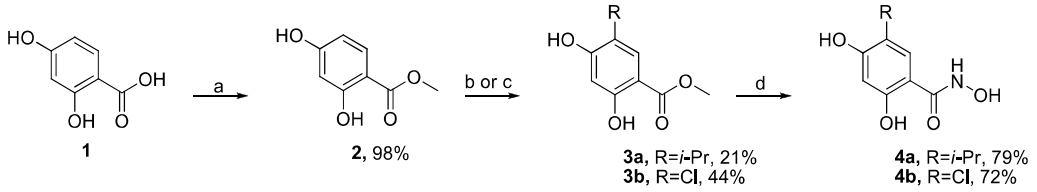

Figure 2. Syntheses of 5-substituted-2,4-dihydroxyphenylcarbohydroxamic acids. Reagents and conditions: a) H_2SO_4, MeOH, 30h, reflux, b) i-PrBr, $AlCl_3$, DCM, reflux, c) SO_2Cl_2, DCM, 2h 0°C, 20h 20°C, d) $NH_2OH{\cdot}HCl$, NaOH, H_2O, 3h 0°C, 12h 20°C.

The other structures we chose were benzimidazole derivatives **10** (Figure 2). Aldehydes **7** were made from starting materials **5** and **6**. Combination of **7** and **8** gave benzimidazole derivatives **9**. Compounds **9a**, **9b** were converted to hydroxamic acids **10a** and **10b** respectively.

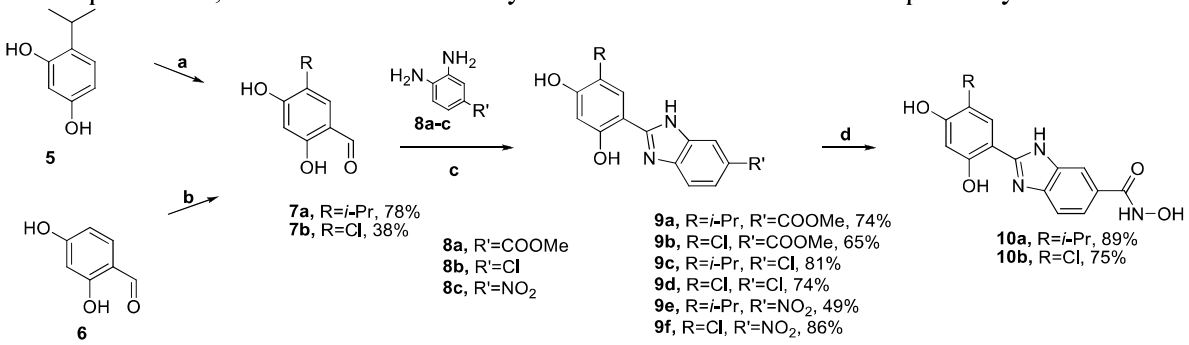

Figure 3. Syntheses of 2-arylbenzimidazo-5-carbohydroxamic acids. Reagents and conditions: a) $POCl_3$, DMF, 1h 0°C, 1h 50°C, b) NCS, HCl, $CHCl_3$, 4h, reflux, c) $Na_2S_2O_5$, DMF, 4h 80°C, d) $NH_2OH{\cdot}HCl$, NaOH, H_2O, 3h 0°C, 12h 20°C.

References

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