SYNTHESIS OF 4,6-DISUBSTITUTED BENZENE-1,3-DIOLES CONTAINING HYDROXAMIC ACIDS

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Inhibition of histone deacetylases (HDACs) is a proven way to treat cancer, as four drugs are already approved by the United States Food and Drug Administration [1]. Meanwhile, compounds inhibiting HSP90 (Heat Shock Protein) shows promising anti-tumor properties as well, acting as a single agent or in combination with additional drugs [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 HDAC. Some of the created and fulfilled syntheses of designed molecules are given below.

Syntheses of 5-chloro- and 5-isopropyl-2,4-dihidroxyphenylcarbohydroxamic acids (figure 1) were started with commercially available compound **1**. Esterification reaction was carried out to give compound **2**, which in the following reaction were substituted in the 5th position to give compounds **3**. Lastly, hydroxamic acid functional group was introduced.

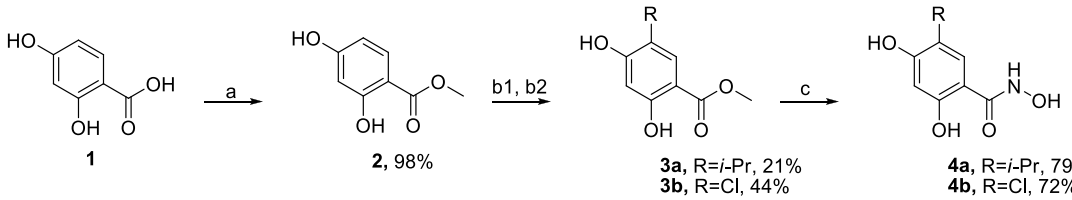

Figure 1. Syntheses of 5-substituted-2,4-dihydroxyphenylcarbohydroxamic acids. Reagents and conditions: a) H_2SO_4, MeOH, 30h, reflux, b1) i-PrBr, $AlCl_3$, DCM, reflux, b2) SO_2Cl_2, DCM, 2h 0°C, 20h 20°C, c) $NH_2OH{\cdot}HCl$, NaOH, H_2O, 3h 0°C, 12h 20°C.

Further syntheses to benzimidazole derivatives (figure 2) were started from compounds **5** and **6**. Vilsmeier–Haack reaction was carried out to give compound **7a** and substitution reaction gave product **7b**. Combination of compounds **7** and **8** gave compounds **9**, which were converted to hydroxamic acids.

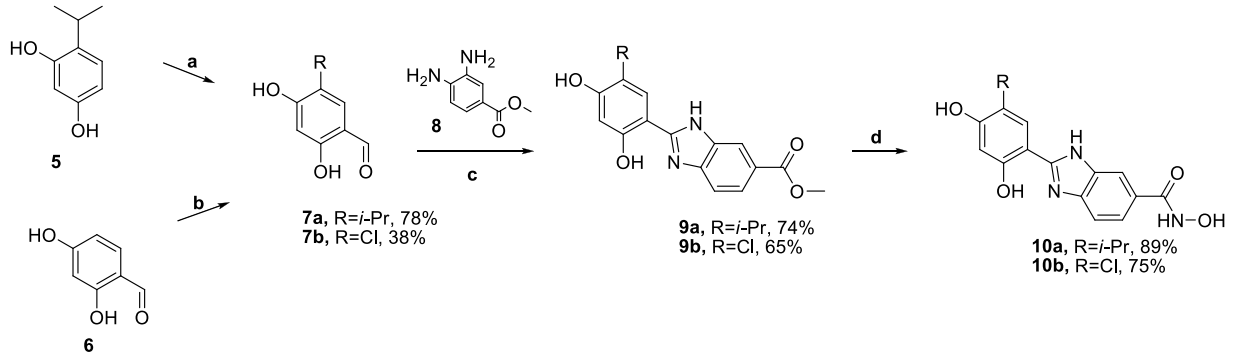

Figure 2. Syntheses of 2-arylbenzimidazo-5-carbohydroxamic acids. Reagents and conditions: a) $POCl_3$, DMF, 1h 0°C, 1h 20°C, 1h 50°C, b) NCS, HCl, $CHCl_3$, 4h, reflux, c) $Na_2S_2O_5$, DMF, 4h 80°C, d) $NH_2OH{\cdot}HCl$, NaOH, H_2O, 3h 0°C, 12h 20°C

Inhibition activities of compounds **4** and **10** are yet to be analyzed.

[1] T. Eckschlager, J. Plch, M. Stiborova, J. Hrabeta, Histone Deacetylase Inhibitors as Anticancer Drugs, International Journal of Molecular Sciences **18**, 1414 (2017);
[2] Y. Li, T. Zhanga, S. J. Schwartz, D. Suna, New Developments in Hsp90 Inhibitors as Anti-cancer Therapeutics: Mechanisms, Clinical Perspective and More Potential, Drug Resistance Updates **12**, 17-27 (2009);
[3] N. Dessalew, W. Mikre, On the Paradigm Shift Towards Multitarget Selective Drug Design, Current Computer-Aided Drug Design **4**, 76-90 (2008).