CHEMISTRY & CHEMICAL TECHNOLOGY

CONFERENCE 2023 VILNIUS

Conference Book
International Conference
Chemistry and Chemical technology

CCT-2023

The conference is dedicated to prof. Edvardas Ramanauskas 100th anniversary

https://doi.org/10.15388/CCT.2023

ISBN 978-609-07-0833-0 (Leidinio forma: Elektroninis - PDF)

Vilnius, Lithuania 2023

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Synthesis of 5-(2,4-Dihydroxyphenyl)imidazole Derivatives as Potential Hsp90 Inhibitors

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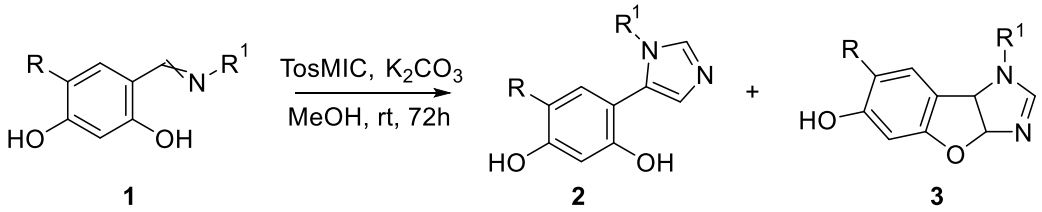
Heat Shock Protein 90 (Hsp90) is an ATP-dependent molecular chaperone, responsible for the folding, correction, activation, and deactivation of its client proteins. [1] Despite Hsp90 having an important role in normal cell cycle regulation, it is also involved in the stabilization of oncogenic proteins. [2] Therefore, it is proposed that inhibiting ATP binding site with small-molecule inhibitors could lead to effective cancer therapy, with some synthetic compounds already going through clinical trials. [3]

A promising class of inhibitors is compounds containing 1,3-benzenediol moiety, based on the natural compound Radicicol. Active structures are usually composed of aromatic substitutes linked to 1,3-benzenediol by a 5-membered heterocyclic ring. Continuing our previous research on 4-(2,4-dihydroxyphenyl)-1,2,3-thiadiazoles as potential Hsp90 inhibitors [4], we decided to synthesize a series of 5-(2,4-dihydroxyphenyl)imidazoles (**2**).

Van Leusen reaction was employed to obtain imidazoles **2** from imines **1** and toluenesulfonylmethyl isocyanide (TosMIC). The reaction was held in methanol and basic conditions at room temperature for 72 hours. Additionally, an unexpected formation of compounds **3** was observed and investigated further.



Scheme 1

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