66TH INTERNATIONAL

OPEN READINGS

CONFERENCE FOR STUDENTS OF PHYSICS AND NATURAL SCIENCES

ANNUAL ABSTRACT BOOK | 2023

Vilnius University

VILNIUS UNIVERSITY PRESS

Editors

Martynas Keršys
Šarūnas Mickus

Cover and Interior design
Milda Stancikaitė

Vilnius University Press
9 Saulėtekio Av., III Building, LT-10222 Vilnius
info@leidykla.vu.lt, www.leidykla.vu.lt/en/
www.knygynas.vu.lt, www.journals.vu.lt

Bibliographic information is available
on the Lithuanian Integral Library Information System (LIBIS) portal ibiblioteka.lt.

ISBN 978-609-07-0883-5 (ePDF)

DOI: https://doi.org/10.15388/IOR2023

SYNTHETIC PATHWAY INVESTIGATION OF BENZIMIDAZOLE DERIVATIVES AS POTENTIAL INHIBITORS FOR HSP90

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Inhibition of Hsp90 (heat shock protein) has been explored as a potential therapeutic strategy for cancer, as many oncogenic client proteins rely on Hsp90 for their stability and activity. Several small-molecule inhibitors of Hsp90 have been developed and are currently being evaluated in clinical trials [1].

Due to the fact that the highest binding constant with the targeted protein is delivered by compounds containing 4-isopropyl-1,3-benzenediol moiety [2], various benzimidazole derivatives were synthesized as potential inhibitors of Hsp90, where 4-isopropyl-1,3-benzenediol moiety was connected by a different number of methylene linkers n = 0-1.

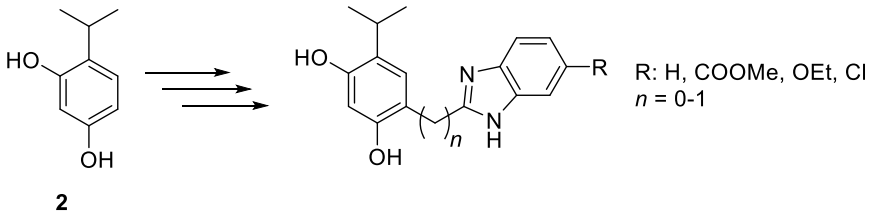

Fig. 1. Previously synthesized benzimidazole derivatives.

To investigate the dependency between methylene groups in synthesized benzimidazoles and the binding constant, we are looking for methods to synthesize benzimidazole derivatives containing double methylene linker (n = 2). Furthermore, double methylene linker can be synthesized as ethylene or ethene linker between benzimidazole and 4-isopropyl-1,3-benzenediol moiety by introducing double or triple bonds.

In all cases, the investigation of the synthesis pathways was started with commercially available 1-(2,4-dihydroxyphenyl)ethenone (**1**). Through a multi-step synthesis pathway, the starting material (**1**) was modified to 2,4-dihydroxy-5-isopropylbenzaldehyde (**3**) or ethyl 3-(2,4-dihydroxy-5-isopropylphenyl)propanoate (**4**) as critical starting materials for the investigation of the benzimidazole (**5**) formation (Fig. 2). By changing reaction conditions, the formation of the benzimidazole was investigated.

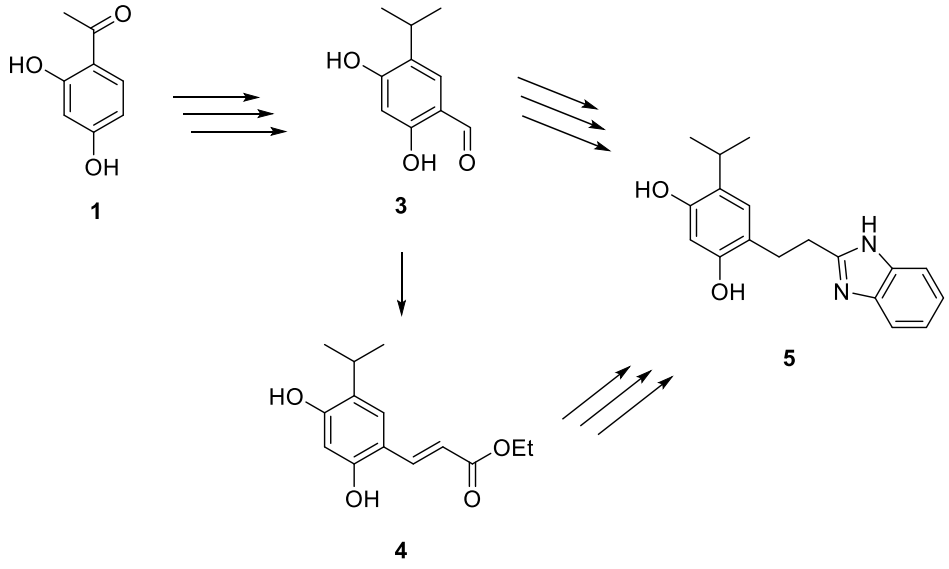

Fig. 2. Synthetic pathway of 4-(2-(1*H*-benzo[*d*]imidazol-2-yl)ethyl)-6-isopropylbenzene-1,3-diol.

Final product **5** is yet to be analyzed for inhibition properties for Hsp90.

[1] L. Neckers. Hsp90 inhibitors as novel cancer chemotherapeutic agents. *Trends Mol. Med.* **2002**, 55–61.
[2] E. Kazlauskas, A. Brukstus, H. Petrikas, et al. Improving the Hsp90 Inhibitors Containing 4-(2,4-Dihydroxyphenyl)-1,2,3-thiadiazole Scaffold: Synthesis, Affinity and Effect on Cancer Cells. *Anticancer. Agents Med. Chem.* **2017**.