

INVESTIGATION OF SYNTHETIC PATHWAYS FOR REZORCINOL COMPOUNDS WITH SULFUR-CONTAINING NITROGEN HETEROCYCLES

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Hsp90 is a heat shock protein whose inhibition has excellent potential in cancer treatment. More than 400 client proteins rely on Hsp90 for maturation, activation, and stabilization [1], it is also essential in cell cycle control, protein folding, and degradation [2]. Various diseases, including cancer, are associated with the stability and overexpression of this protein, which influences cancer development. Understanding the link between the overexpression of Hsp90 and cancer is crucial to finding better cancer treatments by exploiting the differences between normal and tumor cells in terms of Hsp90 mRNA and protein induction, protein activation, and the number of post-translational modification (PTM) sites. Clinical trials have been initiated with various Hsp90 inhibitors, but none have yet been approved as monotherapy medication [3]. This work aims to synthesize resorcinol as lead compounds with combined structures that could be potential Hsp90 inhibitors and may fight against cancer.

To investigate benzimidazole's influence on the effectiveness of resorcinol inhibition, we connected these two fragments using different strategies. For this purpose, we selected 2,4-dihydroxybenzaldehyde as the starting compound. The hydroxyl groups of resorcinol were protected by adding methoxy substituents to prevent side reactions. To create the direct connection, we condensed the aldehyde with diaminobenzene. Simultaneously, to form the thiomethylene bridge, we reduced benzaldehyde to an alcohol and introduced a suitable leaving group. The connection between the fragments via sulfur was achieved using the Ullmann reaction involving the appropriate iodobenzene and thiobenzimidazole. We optimized the reaction conditions using analogous, readily available resorcinol derivatives.

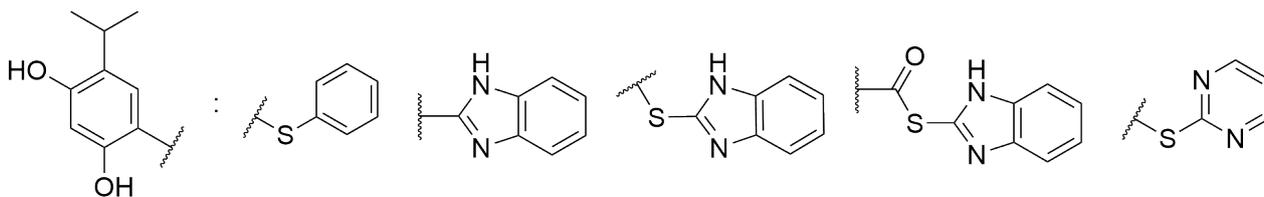


Fig. 1. Structures of targeted compounds

[1] X. Liang, et al., *J. Med. Chem.*, 2024, 67, 15968-15995.
[2] B. Birbo, et al., *Int. J. Mol. Sci.*, 2001, 22 (19), 10317.
[3] Y. Li, et al., *Eur. J. Med. Chem.*, 2024, 275, 116562.