Bis-1,3,4-Oxadiazole Derivatives as Novel and Potential Urease Inhibitors; Synthesis, *In Vitro*, and *In Silico* Studies

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ABSTRACT

Aims: Synthesis of bis-1,3,4-oxadiazole derivatives as novel and potential urease inhibitors.

Background: Despite of many important biological activities associated with oxadiazoles, they are still neglected by medicinal chemists for their possible urease inhibitory activity. Keeping in view the countless importance of urease inhibitors, we have synthesized a new library of substituted bis-oxadiazole derivatives (**1-21**) in order to evaluate their urease inhibitory potential.

Objective: Synthesis of substituted bis-oxadiazole derivatives (**1-21**) in order to evaluate their urease inhibitory potential.

Method: *Bis*-1,3,4-oxadiazole derivatives **1-21** were synthesized through sequential reactions using starting material isophthalic acid (**a**). Esterification reaction was done by refluxing in methanol for 2 h in the presence of catalytic amount of concentrated H_2SO_4 till dissolution. In second step, dimethyl isophthalate (**b**) and hydrazine hydrate in excess (**1**:5) were refluxed in methanol to afford isophthalicdihydrazide (c). Then, isophthalicdihydrazide (**c**) was treated with different substituted benzaldehydes in 1:2 ratio under acidic conditions.

Result: *In vitro* urease inhibitory activity of the synthesized compounds were evaluated and results demonstrated good activities with IC_{50} values in the range of 13.46 ± 0.34 to 74.45 ± 3.81 µM as compared to the standard thiourea (IC_{50} = 21.13 ± 0.415 µM). Most of the compounds were found to be more potent than the standard. Structure-activity relationship (SAR) suggested that the variations in the inhibitory activities of the compounds were due to different substitutions. Furthermore; *in silico* study was also performed.

Conclusion: Current study identified a new class of urease inhibitors. All synthetic compounds **1-21** showed potent as well as good to moderate urease inhibitory activities except **3**. SAR suggested that hydroxy bearing analogs were identified exceptionally good. Molecular docking revealed many important interactions made by compounds with the active site of urease enzyme.