

DEPARTMENT OF CHEMISTRY PONDICHERRY UNIVERSITY

Invites you to the lecture on

"Structural Consequences of the Imidate Isosteres for the Peptide bond and Development of Small Molecule Inhibitors for Human Histone Deacetylases, Epidermal Growth Factor Receptors and Bacterial Growth"

Ву

Dr. Damodara Reddy
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09th Nov. 2015 (Monday)

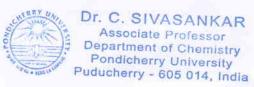
Time: 3.30 pm

Venue: Department of Chemistry, PU

(Prof. K. Tharanikkarasu)

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(Dr. C. Sivasankar) (Seminar Coordinator)



Structural Consequences of the Imidate Isosteres for the Peptide bond and Development of Small Molecule Inhibitors for Human Histone Deacetylases, Epidermal Growth Factor Receptors and Bacterial Growth

Abstract

The first embodiment of the imidate isosteres for the peptide bond is described. Simple synthetic methods for introducing the imidate isostere in the form of 5,6-dihydro-4H-1,3-oxazines and corresponding 1,3-thazines along the peptide sequence are provided. As a result of such amide \rightarrow imidate (A \rightarrow I) modifications two local short range interactions namely, the $n \rightarrow \sigma^*$ and the $n_i \rightarrow \pi_{i-1}^*$ interactions are introduced along the peptide chains. These interactions form 5-membered ring structures that render first access to several unusual conformations in peptides.

Histone Deacetylases (HDAC)-isoform selectivity and potency remains an unattained goal. Using the largazole macrocyclic depsipeptide structure as a starting point for developing new HDACI inhibitors with increased selectivity, a combination of four different simplified largazole analog (SLA) scaffolds with diverse zinc-binding groups (for a total of 60 compounds) were designed, synthesized and biologically evaluated against class I HDACs 1, 3 and 8, and class II HDAC6. Experimental evidence as well as molecular docking poses converged to establish the cyclic tetrapeptides (CTPs) as the primary determinant of both potency and selectivity. We have also worked on channel peptides. Helical peptidomimetics having a wide central pore have been designed to mimic gramicidin A channels. Molecular modeling focused on oligomers of heterochiral dipeptides of proline analogs, in particular azaproline (AzPro). MD simulations in explicit water confirmed the stability of the designed helices. A sixteen-residue formyl-(AzPro-Pro)₈-ethanolamine helical pores was synthesized as well as full thirty-two residue (AzPro-Pro)₁₆ and (Pro-AzPro)₁₆ channels. The ability to lyse liposomes was established suggesting channel formation. These peptidomimetics did not hemolyze red blood cells, unlike gramicidin A. Finally, we are also developing selective and potent dimerisation inhibitors for Epidermal Growth Factor receptors (EGFR).

References

- 1) Reddy, D. N.; Thirupathi, R.; Prabhakaran, E. N. Chem. Commun. 2011, 47, 9417.
- 2) Reddy, D. N.; Prabhakaran, E. N. J. Org. Chem. 2010, 76, 680.
- 3) Reddy, D. N.; Thirupathi, R.; Tumminakatti, S.; Prabhakaran, E. N. Tetrahedron Lett. 2012, 53, 4413.
- 4) Reddy, D. N.; George G.; Prabhakaran, E. N. Angew. Chem. Int. Ed. 2013, 52, 3935.
- 5) Reddy, D. N.; Prabhakaran, E. N. Biopolymers 2013, 101, 66.
- 6) Tumminakatti, S.; Reddy, D. N.; Lakshmi, A. N.; Prabhakaran, E. N. Tetrahedron Lett. 2014, 55, 4731
- 7) Tumminakatti, S.; Reddy, D. N.; Prabhakaran, E. N. J. Pept. Sci. 2015, 104, 21.
- 8) Marshall, G.; Reddy, D. N. US patent App No.: 2015-015092.
- 9) Reddy, D. N.; Ballante, F.; Chuang, T; Pirolli, A.; Marrocco, B.; Marshall, G. R. (2015) Design and Synthesis of Simplified Largazole Analogs as Isoform-Selective Human Lysine Deacetylase Inhibitors. Manuscript submitted to *J. Med. Chem.* for publication.