Accepted Manuscript

Applications of parallel synthetic lead hopping and pharmacophore-based virtual screening in the discovery of efficient glycine receptor potentiators

Nagasree Chakka, Kristin L. Andrews, Loren M. Berry, Howard Bregman, Hakan Gunaydin, Liyue Huang, Angel Guzman-Perez, Matthew H. Plant, Jeffrey R. Simard, Jacinthe Gingras, Erin F. DiMauro

PII: S0223-5234(17)30397-5

DOI: 10.1016/j.ejmech.2017.05.036

Reference: EJMECH 9466

To appear in: *European Journal of Medicinal Chemistry*

Received Date: 23 March 2017

Revised Date: 9 May 2017

Accepted Date: 11 May 2017

Please cite this article as: N. Chakka, K.L. Andrews, L.M. Berry, H. Bregman, H. Gunaydin, L. Huang, A. Guzman-Perez, M.H. Plant, J.R. Simard, J. Gingras, E.F. DiMauro, Applications of parallel synthetic lead hopping and pharmacophore-based virtual screening in the discovery of efficient glycine receptor potentiators, *European Journal of Medicinal Chemistry* (2017), doi: 10.1016/j.ejmech.2017.05.036.

Applications of Parallel Synthetic Lead Hopping and Pharmacophore-Based Virtual Screening in the Discovery of Efficient Glycine Receptor Potentiators

Nagasree Chakka[†], Kristin L. Andrews[‖], Loren M. Berry[‡], Howard Bregman[†,┤], Hakan Gunaydin[‖,┤], Liyue Huang[‡,┤], Angel Guzman-Perez[†], Matthew H. Plant[#], Jeffrey R. Simard[§,┤], Jacinthe Gingras[§], and Erin F. DiMauro*[,†,┤]

[†]Department of Medicinal Chemistry, Amgen Inc., 360 Binney Street, Cambridge, MA 02142, USA

[‖]Department of Molecular Engineering, Amgen Inc., 360 Binney Street, Cambridge, MA 02142, USA

[‡]Department of Pharmacokinetics, Amgen Inc., 360 Binney Street, Cambridge, MA 02142, USA

[#]Department of Discovery Attribute Sciences, Amgen Inc., 360 Binney Street, Cambridge, MA 02142, USA

[§]Department of Neuroscience, Amgen Inc., 360 Binney Street, Cambridge, MA 02142, USA

Abstract

Glycine receptors (GlyRs) are pentameric glycine-gated chloride ion channels that are enriched in the brainstem and spinal cord where they have been demonstrated to play a role in central nervous system (CNS) inhibition. Herein we describe two novel classes of glycine receptor potentiators that have been developed using similarity- and property-guided scaffold hopping enabled by parallel synthesis, and pharmacophore-based virtual screening strategies. This effort resulted in the identification of novel, efficient and modular leads having favorable in vitro