Abstract #55 | Poster

New potential soluble guanylyl cyclase (sGC) activators: Design, synthesis and NMR-driven interaction studies with the *Nostoc sp.* HNOX domain

Aggeliki Roumana[1], Aikaterini I. Argyriou[1], Garyfallia I. Makrynitsa[1], Styliani A. Chasapi[1], Minos-Timotheos Matsoukas[1], Stavros Topouzis[1]

[1] *University of Patras, Dept. of Pharmacy, Rio-Patras, Greece*

Introduction

Soluble guanylyl cyclase (sGC) plays a crucial role in mediating the biological effects of nitric oxide (NO). It is a heterodimer consisting of one alpha (α_1 or α_2) and one beta (β_1 or β_2) subunit, with a prosthetic heme group located in the *β1* H-NOX regulatory domain. sGC catalyzes the conversion of guanosine triphosphate (GTP) to the second messenger cyclic guanosine monophosphate (cGMP), upon binding of nitric oxide (NO) to the heme group[1]. A number of pathological states, in particular cardiovascular and pulmonary diseases[2] have been at least partly attributed to impairment of the NO-sGC-cGMP pathway, due for example to low NO bioavailability and/or heme oxidation and subsequent sGC dysfunction. Besides NO donors, two functional classes of sGC agonists have been identified: the heme-dependent sGC stimulators such as the recently approved drug riociguat (BAY 63-2521) and the clinically evaluated vericiguat (BAY 1021189)[2] as well as the heme-independent sGC activators, such as the amino dicarboxylic acid derivative cinagiguat (BAY 58-2667)[2]. Notably, the enzymatic activity of sGC by sGC activators is enhanced after oxidation or removal of the heme moiety due for example to oxidation of the heme iron and loss of the heme group from sGC, a change elicited by synthetic tricyclic oxadiazolone derivatives such as the closely related analogues ODQ and NS2028[3,4].

Methods

In the present study, following a rational drug design approach, we designed new potential sGC activators with structural features which may enable both the oxidation of the heme moiety (e.g. a fused oxadiazolidinone ring) and sGC activation (e.g. appropriate carboxylic substituents).

Results

Our presentation will describe a) the progress of our efforts towards the synthesis of the target molecules and b) the characterization by NMR-based analysis of the binding mode of a sGC activator, cinaciguat (BAY 58-2667), with recombinant *Nostoc sp.* HNOX domain.

Conclusions

Our study aims to help elucidate the requisite features of rationally-designed compounds as well as the precise molecular events critical for NO/heme-independent activation of the sGC.

References

1. Childers, KC & Garcin, ED, *Nitric Oxide* **2018**, *77*, 53–64.
2. Sandner, P et al., Handbook of Experimental Pharmacology. Springer, Berlin, Heidelberg, **2018**.
3. Zhao, Y et al., *Biochemistry* **2000**, *39*,10848–10854.

4. Olesen, SP et al., *Br. J. Pharmacol*. **1998**, *123*, 299–309.

Acknowledgement

The research/project “Novel functional activators of the soluble Guanylate Cyclase (sGC)” *ΕΔΒΜ-34, #* 80436 is implemented through/has been co-financed by the Operational Program "Human Resources Development, Education and Lifelong Learning" and is co-financed by the European Union (European Social Fund) and Greek national funds.