

Poster presentation

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Synthesis and characterization of NS-2028 analogues

Anastasia Pyriochou*¹, Athanasios Giannis² and Andreas Papapetropoulos¹

Address: ¹Lab for Molecular Pharmacology, Dept of Pharmacy, University of Patras, Greece and ²Institute for Organic Chemistry, University of Leipzig, Leipzig, Germany

Email: Anastasia Pyriochou* - apyriochou@upatras.gr

* Corresponding author

from 4th International Conference of cGMP Generators, Effectors and Therapeutic Implications Regensburg, Germany. 19–21 June 2009

Published: 11 August 2009

BMC Pharmacology 2009, 9(Suppl 1):P55 doi:10.1186/1471-2210-9-S1-P55

This abstract is available from: <http://www.biomedcentral.com/1471-2210/9/S1/P55>

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Background

Soluble guanylyl cyclase (sGC) is a ubiquitously expressed enzyme that synthesizes the second messenger cGMP. sGC has low basal activity which can be stimulated several hundred-fold by nitric oxide. Although, many NO activators and stimulators have been described only two chemically related sGC inhibitors exist: ODQ and NS-2028. The use of the above mentioned sGC inhibitors has helped researchers unravel many of the actions of the NO/sGC/cGMP pathway. The mechanism of action of NS-2028 and ODQ is believed to involve oxidation of the heme iron, making sGC unresponsive to NO. The aim of the present work was to synthesize and characterize a number of NS-2028 analogues for their ability to inhibit sGC. To this end 5 such analogues were generated and are shown below in Figure 1.

Results

Compound C was as effective and potent as NS-2028, suggesting that substituting the Br atom in position 8 with a bulkier m-trifluoromethylphenyl group does not alter the activity of NS-2028. Compound B that carries a p-methoxyphenyl group in position 8 was as effective as NS-2028 and ODQ, but was less potent, as it only inhibited SNP-induced cGMP formation by 43% at 0.1 μ M, compared to >80% observed with ODQ or NS-2028 when used at the same concentration. Compound A that has an expanded oxadiazolo ring was both less potent and less effective in blocking SNP-induced cGMP production. Expanding the oxazin ring to a benzodiazepinone ring resulted in a compound (compound D) with markedly

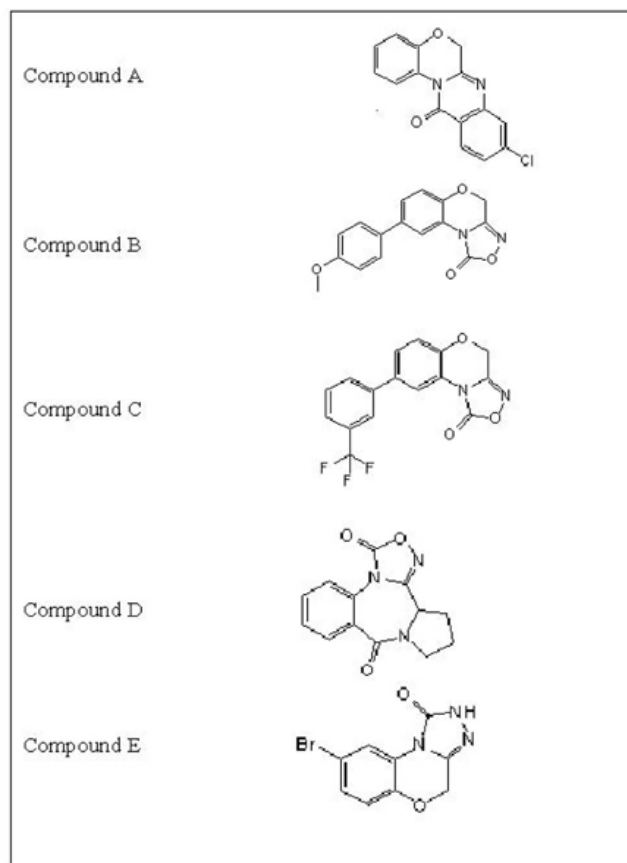


Figure 1

reduced inhibitory activity. Finally, compound E in which the oxadiazolo ring has been converted to a triazolo ring was devoid of any sGC inhibitory activity.

Conclusion

We conclude that the oxadiazolo ring of NS-2028/ODQ is of major importance for the action of this class of inhibitors.

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