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Poster presentation

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Synthesis and characterization of NS-2028 analogues

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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 sythesize 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

Compounds 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 NS2028 and ODQ, but was less potent, as it only inhibited SNP-induced cGMP formation by 43% at 0.1 μÌ, 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

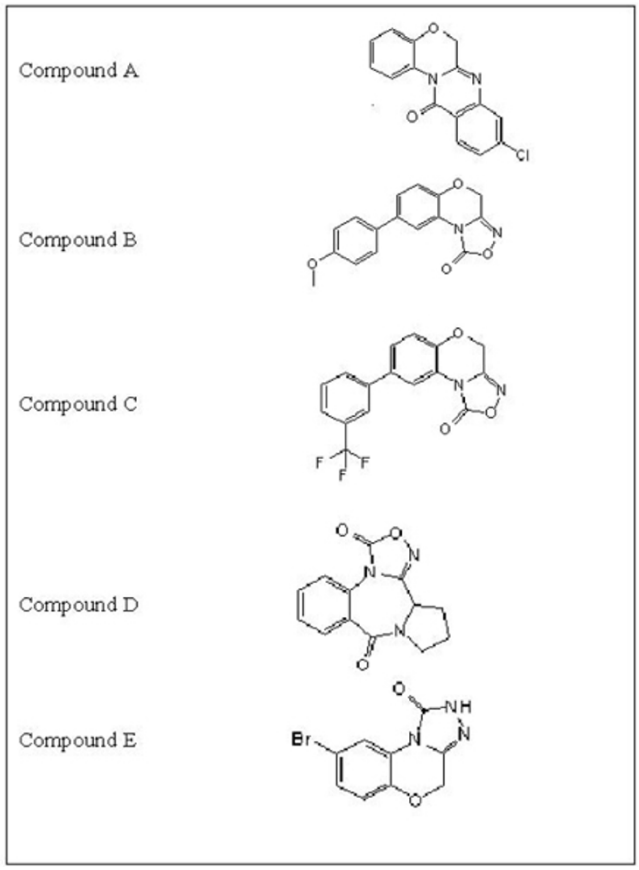

Figure 1

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.