

**SULFONAMIDES AND DERIVATIVES THEREOF THAT MODULATE
THE ACTIVITY OF ENDOTHELIN**

ABSTRACT

Sulfonamides and methods using these sulfonamides for inhibiting the binding of an endothelin peptide to an endothelin receptor by contacting the receptor with the sulfonamide are provided. Methods for treating endothelin-mediated disorders by administering effective amounts of one or more of these sulfonamides or prodrugs thereof that inhibit or increase the activity of endothelin are also provided. The sulfonamides have formula (I) in which Ar^1 is a 3- or 5-isoxazolyl and Ar^2 is selected from among alkyl, including straight and branched chains, aromatic rings, fused aromatic rings and heterocyclic rings, including 5-membered heterocycles with one, two or more heteroatoms and fused ring analogs thereof and 6-membered rings with one, two or more heteroatoms and fused ring analogs thereof. Ar^2 is preferably thiophenyl, furyl, pyrrolyl, naphthyl, and phenyl. Compounds in which Ar^1 is a 4-halo-substituted isoxazole are more active than the corresponding alkyl-substituted compound and compounds in which Ar^1 is substituted at this position with a higher alkyl tend to exhibit greater affinity for ET_B receptors than the corresponding lower alkyl-substituted compound.



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