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Peptoids as Endothelin Receptor Antagonists

Falguni Dasgupta,* N. Gangadhar,† M. Bruhaspathy, Ashwani K. Verma, Simi Sarin and Ashish K. Mukherjee‡

New Drug Discovery Research, Ranbaxy Laboratories Limited, A-1 Phase-1 Okhla Industrial Area, New Delhi-110020, India

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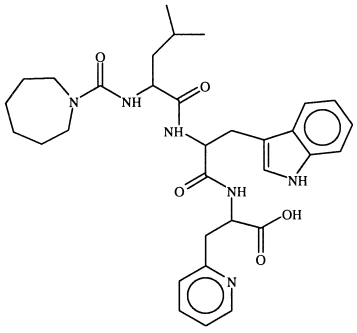
Abstract—A series of new peptoids as endothelin receptor antagonists has been synthesized. Screening them for their ability to bind with endothelin receptors (ET_A and ET_B) competitively in the presence of (^{125}I) endothelin led to the discovery of compounds as possible leads with IC_{50}s in the low micromolar concentrations.

Endothelin (ET-1), first isolated from the culture medium of porcine aortic endothelial cells, is a potent vasoconstrictor consisting of 21 amino acids.[1] This and two other structurally and functionally related vasoconstricting peptides termed endothelin-2 and endothelin-3 interact with two known G-protein coupled receptors ET_A and ET_B and induce vasoconstricting effects. ET_A, ET_B, and more recently identified ET_C, are tissue specific and are displayed preferentially in varying proportion on different cell types. ET_A is found in vascular smooth muscle tissue and is mainly responsible for vasoconstriction of smooth muscle cells while ET_B, which is found in nonvascular smooth muscle tissues, has been implicated in the release of endothelin derived relaxing factors.[2] Elevated levels of endothelin as compared to normal levels are found in patients suffering from a variety of diseases including hypertension,[3,4] pulmonary hypertension,[5] and cerebral vasospasm,[6,7] and evidence is accumulating that newer ET antagonists may not only provide a novel therapy for the treatment of such patients but also help in understanding the precise physiological roles of endothelins.

Early efforts undertaken by several laboratories to develop ET antagonists focused upon synthetic modification of the ET agonist peptides along with random



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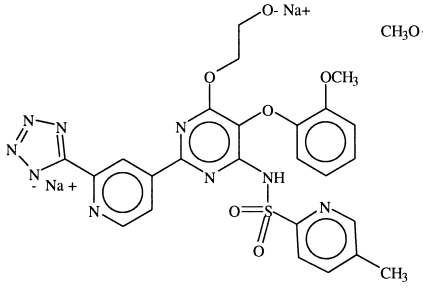
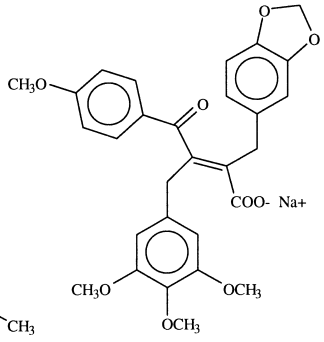


Ro-61-1790



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*Corresponding author at present address: BioMarin Pharm. Inc., 11 Pimentel Ct., Novato, CA 94949, USA. E-mail: fdcarbo@hotmail.com
†Present address: Molecumetics, 2023 120th Av. NE, Bellevue, WA 98005, USA.
‡Present address: Chembiotek Research International, Block GP, Plot G, Sector III, Salt Lake, Calcutta 700 091, India.

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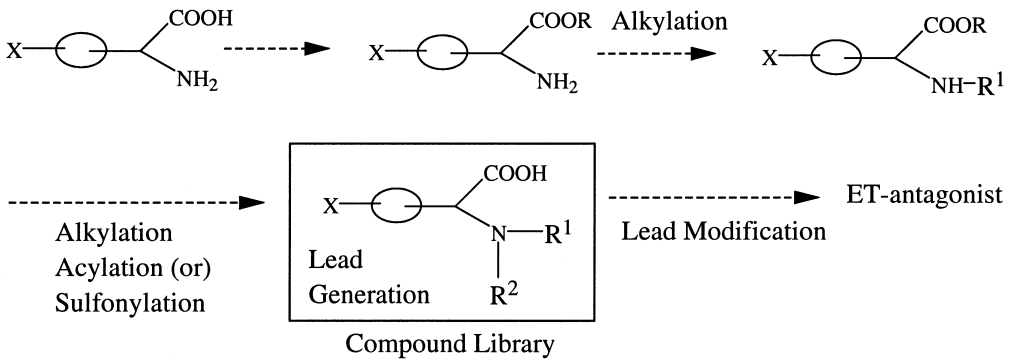

Scheme 1.

screening of available compound libraries. Thus, a number of highly potent peptidic as well as nonpeptidic antagonists were discovered, such as PD 156707, FR 139317, and Ro-61-1790 (shown above).[7a–c] These and some of the more recently identified small molecule antagonists not only suggest continuing interest in ETs but also exhibits the variety and the range of small molecules that can indeed be the lead compounds.[7d–o,8–13]

In an effort to quickly discover a new lead based on the available information, known compounds were classified into sulfonamides, nonsulfonamides (e.g., PD 156707), and peptides (e.g., BQ 123 and FR 139317). On scrutinizing the latter two classes, the minimum structural motif was perceived as one with a carboxylic residue suitably juxtaposed off a rigid bond across from three other groups selected from substituted/unsubstituted aryl residues. The simplest of these compounds was envisaged as *N*,*N*-disubstituted amino acids (i.e., peptoids). In this communication, success of this concept in identifying novel ET antagonists has been shown.

Several natural and unnatural amino acids were identified for the synthesis of target peptoids. The first series of compounds was prepared using L-tyrosine and L-tryptophan as shown in Scheme 1. Several compounds were synthesized[14] and screened for their antagonistic activities.

Screening of these compounds revealed their affinity for endothelin receptors in terms of their ability to competitively inhibit ET. Chart 1 (ref 16) represents the results of a study using a number of our newly synthesized peptoids and radiolabelled (^{125}I) endothelin in a receptor binding assay.[15] It was clear that the carboxylic function was necessary for activity. The tryptophan series exhibited improved activity and selectivity for ET_B while the tyrosine series of compounds were generally more specific for the ET_A receptor. In summary, we have described the SAR of a novel set of peptoids that have a wide range of ET_A and ET_B receptor affinities. It is hoped that biophore mapping of our new series and comparing with the energy minimized 3-D model of the well-known active compounds will help us to design molecules with improved activity. Preparation of a series of analogues with other *N*-substitutents as well as synthesis of several dipeptoids has been planned with a view to improve efficacy as well as selectivity of these initial lead molecules.

Acknowledgements

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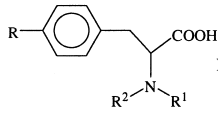
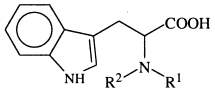
14. **General method**: Amino acid ethyl ester was dissolved in DMF containing pyridine and alkylated, for example, with *p*-methoxybenzyl chloride (1.2 equiv), to give the *N*-alkylated compound in 70% yield. The reaction mixture was poured into ice-water and the product extracted using dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), filtered and evaporated to give the crude product. This was usually treated with the second alkylating or acylating reagent in the presence of excess pyridine at room temperature to afford the *N*,*N*-disubstituted compound in 80% yield. Finally, methanolic solution of the ester was treated with 1 N aq LiOH (0.23 N final) at room temperature to give the final peptoid in quantitative yield. All products were purified by silica gel column chromatography and analyzed by ^1H NMR ($CDCl_3$–TMS); e.g., **2**/**7** substituted tyrosine showed chemical shifts (δ ppm) at 7.5 (d, 1H, CH= of cinnamoyl), 7.08–6.66 (m, ArH), 6.6 (d, 1H, CH= of cinnamoyl), 5.93 (s, 2H, CH_2 of di-*O*-methylidene), 4.55 (d, 1H, β-CH_2 of Tyr), 4.36 (m, 1H, α-H of Tyr), 4.06 (d, 1H, β-CH_2 of Tyr), 3.73 (s, 3H, OCH_3), 3.3–3.2 (m, 2H, *N*-CH_2Ar). In those instances where the cinnamoyl residue needed to be introduced, the acylation step had to be carried out prior to alkylation (for improved yield).
15. Receptor binding assay was developed *in house* by A. Chugh, A. K. Ray and J. B. Gupta, of Pharmacology Group, Ranbaxy Laboratories Limited following a protocol similar to the one described by Stavros, F. D.; Hasel, K. W.; Okun, I.; Baldwin, J.; Feriks, K. J. *Cardiovasc. Pharmacol.* **1993**, *22*, S34.
16. The asterisks (**) indicate 'not determined' in Chart 1.

AMINO ACID	R^1/R^2 =	IC_{50} (μM)								
		2/1	**2/4**	**2/5**	**1/9**	**1/7**	**2/7**	**3/7**	**8/7**	**2/7**
		R = OH	R = OH	R = OCH_3	R = OH	R = OH	R = OH	R = OH	R = OH	R = H
		ET_A > 100	ET_A 36	ET_A 5	ET_A 21.3	ET_A 38	ET_A 6	ET_A 31	ET_A 8	ET_A 27
		ET_B 5.5	ET_B **	ET_B 19	ET_B 55	ET_B 66	ET_B 12.6	ET_B **	ET_B 8	ET_B 6.4
		2/6	**1/6**	**2/5**	**1/1**	**1/7**	**2/7**			
		ET_A; ET_B >100	ET_A 30 ET_B 49	ET_A 42 ET_B 35	ET_A 16.3 ET_B 6.7	ET_A 8.9 ET_B 0.66	ET_A 10 ET_B 0.47			

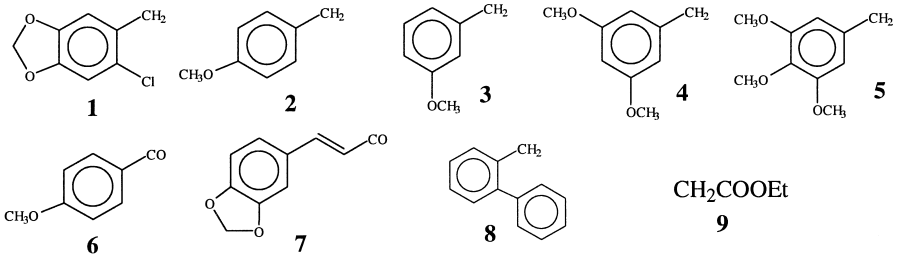


Chart 1.