Pergamon

Bioorganic & Medicinal Chemistry Letters 12 (2002) 125–128

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

The Design and Synthesis of a Novel Series of Indole Derived Selective ET_A Antagonists

David J. Rawson,* Kevin N. Dack, Roger P. Dickinson and Kim James

Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK

Received 30 April 2001; revised 3 October 2001; accepted 4 October 2001

Abstract—Conformational constraint has been used as the key design element in the identification of a series of potent and selective ET_A antagonists. The most potent antagonist, **32**, (ET_A $IC_{50} = 0.55$ nM) is 722-fold selective over the ET_B receptor, as measured by binding experiments.

Introduction

Since the discovery of the potent vasoconstrictor endothelin-1 (ET-1) in the laboratories of Yanagisawa over 10 years ago,[1] this 21 amino acid peptide has been the focus of intense scientific interest. Three distinct ET isoforms, ET-1, ET-2 and ET-3, have been discovered which exert their biological effect through at least two G-protein coupled receptors, ET_A and ET_B.[2] Elevated levels of endothelins have been associated with many disease states including congestive heart failure,[3] pulmonary hypertension,[4] chronic renal failure[5] and angina,[6] and antagonism of one or both of the ET receptors represents an attractive target for disease management. A large number of non-peptide ET antagonists of different subtype selectivity have been described in the literature and used as pharmacological tools to further increase our understanding of the physiological importance of ET.[7] Many have entered clinical development although, despite the immense potential of ET antagonists in the clinic, we still await the first marketed drug in the area. This paper discusses the design, synthesis and optimisation of a series of potent and selective ET_A antagonists.

Design and Synthesis

Many ET antagonists exhibit the common structural features[8] of three substituted aromatic (or heteroaromatic) rings and an acidic group (see Fig. 1 for representative examples). L-749,329[9] also exhibits these features and is a potent and moderately selective ET_A antagonist. In-house modelling studies indicated that conformational constraint could be used to 'lock' the relative positions of the presumed pharmacophoric groups of L-749,329 in the lowest energy conformation with the benzylic proton (H_B) adopting a position almost coplanar with the benzoate ring, minimising peri interactions with H_A (Fig. 2).

Several five- and six-membered rings were explored to provide a scaffold to put the key groups in the correct relative positions, and antagonist activity was measured

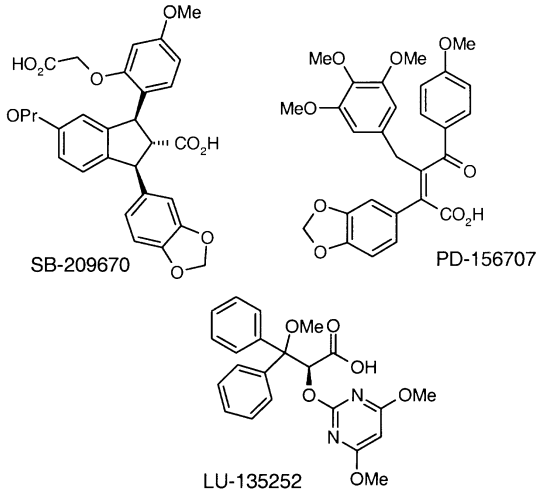


Figure 1.

*Corresponding author. Fax: +44-1304-651817; e-mail: david_rawson@sandwich.pfizer.com

0960-894X/02/$ - see front matter
PII: S0960-894X(01)00660-6

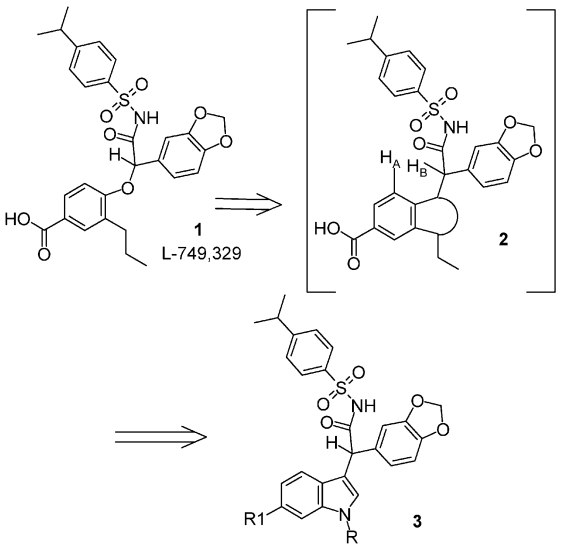


Figure 2.

against cloned human ET_A receptor. The 3-substituted indole (**3**) proved to be the best template to develop SAR further. The synthetic strategy adopted, using an appropriately *N*-alkylated 6-bromoindole as starting material, allowed us to rapidly explore SAR on the indole A-ring. The bromine atom of **5** could be transformed into a methyl ester by halogen–metal exchange followed by quenching of the resulting lithio intermediate into a THF solution of methylchloroformate. Coupling with methyl 2-(1,3-benzodioxol-5-yl)-2-bromoacetate proceeded smoothly and selective ester hydrolysis of the alkyl ester in the presence of the benzoate ester gave **6**. Activation of the acid and coupling with 4-isopropylphenylsulphonamide in the presence of a strong base furnished the acylsulphonamide **7**. This was converted to **8** and **9** through hydrolysis and amine coupling, respectively (Scheme 1).

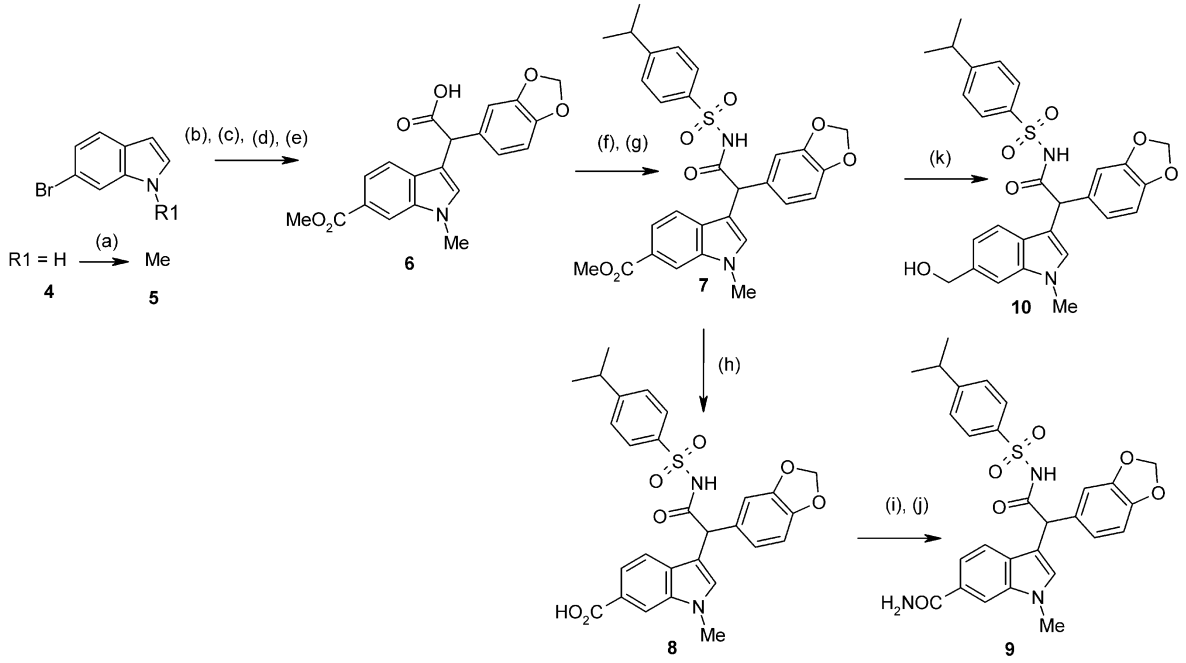
A more versatile route, avoiding the capricious selective ester hydrolysis, was subsequently developed where the 6-bromoindole **5** was coupled directly with 2-(1,3-benzodioxol-5-yl)-2-bromoacetate (**11**) to yield **12** (Scheme 2). Following acylsulphonamide formation (using the conditions already described) the bromide could be functionalised using standard coupling methodologies (e.g., palladium mediated carbonylation, Stille, Heck and Suzuki couplings).

Examples from Table 1 with $R_2 = Et$ or H were synthesised using the strategy outlined in Scheme 1 using the appropriate indole *N*-substituent. Examples **17**, **18**, **20**, **21** and **22** were prepared from 6-bromo-1-ethylindole using the method used to prepare **7**, **8** and **9**. Examples **14** and **16** were derived from 6-cyano1-methylindole using the methodology described in Scheme 1 (Scheme 3) and examples **10** and **15** were prepared by lithium aluminium hydride reduction of examples **7** and **14,** respectively.

Results

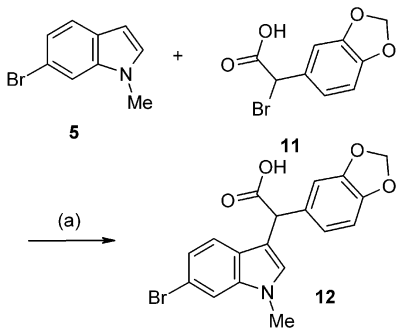
Binding affinities were determined by competition binding with ^{125}I-labelled ET-1 for both human cloned ET_A ($hcET_A$) and ET_B ($hcET_B$) receptors.[10]

Once we had discovered the utility of the indole template, our initial work focused on optimisation of the

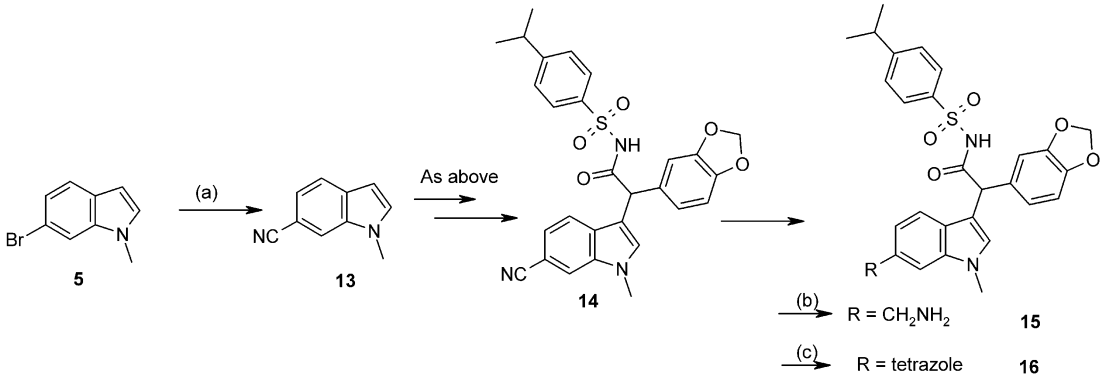


Scheme 1. Reagents and conditions: (a) NaH, MeI, DMF, 25 °C; (b) ^{s}BuLi, Et_2O, −78 °C; (c) methyl chloroformate, Et_2O, −78 °C–20 °C; (d) methyl 2-(1,3-benzodioxol-5-yl)-2-bromoacetate, 2,6-dimethylpyridine, DMF, 80 °C, 8 h; (e) NaOH, 3:1 MeOH/1,4-dioxan, reflux, 1 h; (f) *N,N′*-carbonyldiimidazole, CH_2Cl_2, reflux, 12 h; (g) 1,8-Diazabicyclo[5.4.0.]undec-7-ene, isopropylbenzenesulphonamide, CH_2Cl_2, reflux, 12 h; (h) NaOH, THF/MeOH, 6 h, reflux; (i) *N,N′*-carbonyldiimidazole, THF, reflux, 12 h; (j) NH_3; (k) $LiAlH_4$, THF.

indole substitution. We quickly discovered that 6-substitution was favoured over 5- and 7-substitution (results not shown), and a carboxyl group as in **8** was favoured over methyl ester (**7**) or cyano (**14**), although the compound was significantly less potent than **1**. *N*-Alkylation had little effect on potency (compare **8**, **18** and **19**), and no benefit was achieved by relacement of the carboxyl at the indole 6-position with tetrazole (**16**), hydroxymethyl (**10**) or aminomethyl (**15**). However, potency equivalent to that of **1** was obtained by replacement with a carboxamide group as in **9** and **20**. Successive alkylation of the amide in **20** to give **21** and **22** was detrimental. Although compounds were ET_A selective, ET_A/ET_B selectivity was generally modest (Table 1) and this prompted the second phase of study.

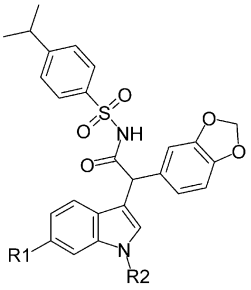


Scheme 2. Reagents and conditions: (a) 2,6-dimethylpyridine, DMF, 80 °C, 8 h.



Scheme 3. Reagents and conditions: (a) CuCN, *N*-methylpyrrolidine, 150 °C, 48 h; (b) $LiAlH_4$, THF; (c) $TMSN_3$, Bu_2SnO, toluene, reflux, 14 h.

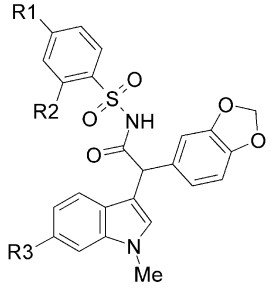
Table 1. In vitro endothelin receptor binding affinity (IC_{50} (nM))



Compd	R_1	R_2	hcET_A IC_{50} (nM)	hcET_B IC_{50} (nM)	Ratio ET_A/ET_B
1 (L-749,329)	—	—	0.8[a]	16[a]	—
7	CO_2Me	Me	100	ND[b]	—
8	CO_2H	Me	22	1500	68.2
9	$CONH_2$	Me	2.3	34	14.8
10	CH_2OH	Me	19	450	23.7
14	CN	Me	61	ND	—
15	CH_2NH_2	Me	38	204	5.4
16		Me	35	ND	—
17	CO_2Me	Et	210	ND	—
18	CO_2H	Et	32	2200	68.8
19	CO_2H	H	31	ND	—
20	$CONH_2$	Et	3.5	68	19.7
21	CONHMe	Et	30	210	7
22	$CONMe_2$	Et	72	474	6.6

[a]Merck binding data.
[b]Not determined.

Table 2. In vitro endothelin receptor binding affinity (IC_{50} (nM))



Compd	R_1	R_2	R_3	$hcET_A$ IC_{50} (nM)	$hcET_B$ IC_{50} (nM)	Selectivity ET_A/ET_B
9	^{i}Pr	H	$C(O)NH_2$	2.3	34	15
23	H	H	$C(O)NH_2$	12	2,570	184
24	Me	H	$C(O)NH_2$	1.8	774	430
25	Cl	H	$C(O)NH_2$	7.5	1,100	146
26	CF_3	H	$C(O)NH_2$	6.5	228	35
27	OMe	H	$C(O)NH_2$	2.8	94	34
28	H	Me	$C(O)NH_2$	5.2	1,056	203
29	H	OMe	$C(O)NH_2$	5.0	310	62
30	H	CO_2H	$C(O)NH_2$	3.1	846	272
31	Me	OMe	$C(O)NH_2$	1.1	302	275
32	Me	OEt	$C(O)NH_2$	0.55	397	722

Using the most potent analogue (**9**) from Table 1 as a starting point, the effect of modification of substitution in the sulphonamide ring on ET_A/ET_B selectivity was explored using the methodology described in Scheme 1, steps (f) and (g). The ET_A/ET_B selectivity proved very sensitive to aryl sulphonamide substitution (Table 2) with 4-methyl favoured for both potency and selectivity (**24**). Larger substituents, such as OMe and ^{i}Pr, were less selective (**9** and **27**). 2-Substitution with either Me or OMe (**28** and **29**) resulted in small increases in ET_A affinity compared to the unsubstituted phenyl group (**23**). The combination of 4-methyl and 2-alkoxy, especially ethoxy, gave excellent levels of both potency and selectivity (**31** and **32**). The SAR generated at the sulphonamide and indole rings proved to be additive and we were able to tune the absorption and in vivo profile of our antagonists by combining the 2 SARs (a paper describing these studies will be published separately).

In summary, we have used conformational constraint to design a novel series of endothelin antagonists. By appropriate substitution at the indole 6-position and on the benzenesulphonamide ring, compounds with excellent potency and selectivity have been identified.

Acknowledgements

The authors wish to thank D. Ellis, M. Sproates, V. Sethi, K. Mills, S. Planken, K. Malloy, P. Bradley and M. Closier for their assistance in preparing the compounds and C. Long, K. Holmes and J. Wakerell for the in vitro screening of these compounds.

References and Notes

1. Yanagisawa, M.; Kurihra, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature (London)* **1988**, *332*, 411.
2. (a) Arai, H.; Hori, S.; Aramori, I.; Ohkubo, H.; Nakanishi, S. *Nature (London,)* **1990**, *348*, 730. (b) Sakurai, T.; Yanagisawa, M.; Takuwa, Y.; Miyazaki, H.; Kimura, S.; Goto, K.; Masaki, T. *Nature (London)* **1990**, *348*, 732. (c) Karne, S.; Jayawickreme, C. K.; Lerner, M. R. *J. Biol. Chem.* **1993**, *268*, 19126.
3. Rodeheffer, R. J.; Lerman, A.; Heublein, D. M.; Burnett, J. C., Jr. *Am. J. Hypertension* **1991**, *4*, 9A.
4. Stewart, D. J.; Levy, R. D.; Cernacek, P.; Langleben, D. *Ann. Intern. Med.* **1991**, *114*, 464.
5. Stockenhuber, F.; Gottsauner-Wolf, M.; Marosi, L.; Liebisch, B.; Kurz, R. W.; Balcke, P. *Clin. Sci. (London)* **1992**, *82*, 255.
6. Stewart, J. T.; Nisbet, J. A.; Davies, M. J. *Br. Heart. J.* **1991**, *66*, 7.
7. For a recent review on Endothelin Antagonists see: Benigni, A.; Remuzzi, G. *Lancet* **1999**, 133.
8. For further examples of antagonists sharing these pharmacophoric features, see: Bunker, A. M.; Edmunds, J. J.; Berryman, K. A.; Walker, D. M.; Flynn, M. A.; Welch, K. M.; Doherty, A. M. *Biorg. Med. Chem. Lett.* **1996**, *6*, 1061. Elliot, J. D.; Lago, M. A.; Cousins, R. D.; Gao, A.; Leber, J. D.; Erhard, K. F.; Nambi, P.; Elshourbagy, N. A.; Kumar, C. *J. Med. Chem.* **1996**, *37*, 1553.
9. Walsh, T. F.; Fitch, K. J.; Williams, D. L., Jr.; Murphy, K. L.; Nolan, N. A.; Pettibone, D. J.; Chang, R. S. L.; O'Malley, S. S.; Clineschmidt, B. V.; Verber, D. F.; Greenlee, W. J. *Biorg. Med. Chem. Lett.* **1995**, *5*, 1155.
10. Initial work was carried out in the racemic series and the data presented is from this series. Several antagonists were separated by chiral HPLC using a Chiralpak™ column. Details of the synthesis of optically pure indole antagonists of this class will be published elsewhere.