Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 3, pp. 275-280, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(96)00617-8

PYRIDAZINONES WITH A PENDANT ACYLSULFONAMIDE MOIETY AS ENDOTHELIN RECEPTOR ANTAGONISTS

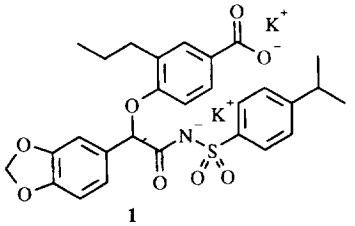
Dieter Dorsch,* Werner W. K. R. Mederski, Mathias Osswald, Ralf M. Devant, Claus-Jochen Schmitges, Maria Christadler and Claudia Wilm

Merck KGaA, Preclinical Pharmaceutical Research, 64271 Darmstadt, Germany

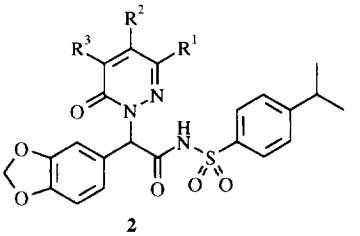
Abstract: Highly active endothelin receptor antagonists can be obtained by replacing the aryloxy group of L-749,329 by diversely substituted pyridazinone residues. The syntheses and structure-activity relationships of the new aryl-oxopyridazinyl-N-(4-arylsulfonyl)-acetamides **2** are reported. **2p** with a simple dimethyl-pyridazinone moiety was one of the most potent compounds *in vitro*.

Introduction:

The endothelins (ET-1, ET-2 and ET-3) are a family of 21-amino acid bicyclic peptides with ET-1 being the most potent endogenous vasoconstrictor reported to date.[1] The ETs exert their biological effects by interacting with at least two specific G-protein coupled receptors (ET_A and ET_B) which are distinguished by their relative affinities to these peptides.[2] The ET_A subtype, which has a tenfold higher affinity to ET-1 than to ET-3, is mainly found in vascular smooth muscle cells, where it mediates vasoconstriction, and in cardiac myocytes. The ET_B receptor, which has equal affinity to ET-1 and ET-3 is expressed predominantly on endothelial cells and to a lesser degree on vascular smooth muscle cells. The ET_B receptor on the endothelium mediates relaxation of the underlying smooth muscle cells via release of intercellular mediators such as nitric oxide and prostacyclin, whereas stimulation of ET_B receptors on smooth muscle cells causes contraction. Due to their potent physiological effects and because elevated levels of ET-1 have been found in a number of disease states, ET has been implicated in the pathogenesis of several diseases, such as myocardial infarction, hypertension, heart failure, atherosclerosis, cerebral and coronary vasospasm, renal failure and asthma.[3] Meanwhile, structurally diverse non-peptide endothelin receptor antagonists of differing subtype selectivity were discovered[2] and pharmacological studies have suggested the usefulness of such antagonists in the treatment of cardiovascular diseases.[3] One of the most potent ET antagonists is the acylsulfonamide L-749,329 (**1**).[4]



1



2

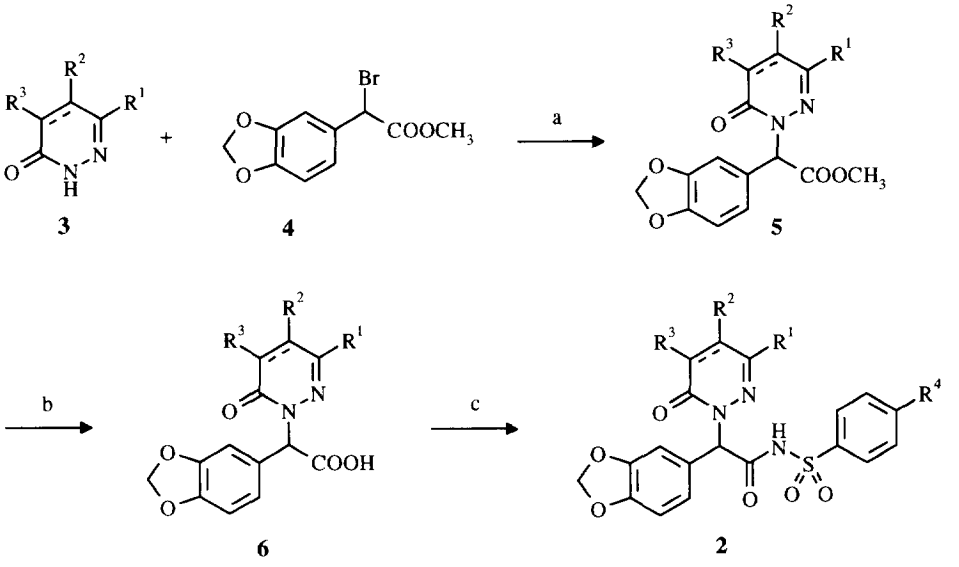
* E-mail: dorsch@merck.de
Fax: ++49-6151-723129

We determined the minimum energy conformations of several derivatives of **1** where the aryloxy residue was replaced by different heterocycles using the molecular modelling program HyperChem™. The best overlap with **1** was achieved by a 4-arylpyridazinone derivative and therefore such derivatives were synthesized first. We report here on the synthesis and ET antagonistic properties of compounds related to L-749,329 with one aromatic ring replaced by a heterocyclic pyridazinone moiety (**2**).

Synthesis:

The synthesis of the pyridazinone derivatives **2** (Scheme 1) was performed in analogy to the synthesis of **1**[4]. Dihydropyridazinones or pyridazinones **3**, synthesized according to procedures described in the literature,[5] were alkylated with methyl (1,3-benzodioxol-5-yl)-(bromo)-acetate (**4**)[4,6] in the presence of caesium carbonate in dimethylformamide. The esters **5** were hydrolyzed to the acids **6**, which were coupled with substituted aryl sulfonamides in the presence of carbonyl diimidazole and 1,8-diazabicyclo[5.4.0]undecene[7] to give the target acyl sulfonamides **2**.

Scheme 1



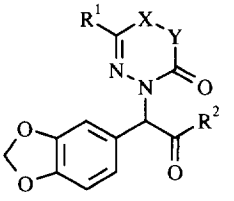
a: 1.1 equivalents caesium carbonate, DMF; b: 1.1 equivalents NaOH, methanol; c: 1.1 equivalents CDI, THF, 60°C, 2 h, then 1.1 equivalents *p*-$R^4PhSO_2NH_2$, 1.1 equivalents DBU, 60°C, 3 h.

Results and discussion:

The compounds were screened for their ability to inhibit specific [^{125}I]-ET-1 binding to rat aorta membranes (ET_A) and porcine kidney (inner medulla) membranes (ET_B).[8] The biological data are summarized in Tables 1 and 2. First we reasoned that in analogy to known endothelin antagonists a second aromatic group in addition to the benzodioxole group was necessary for good binding. We, therefore, began our studies with the

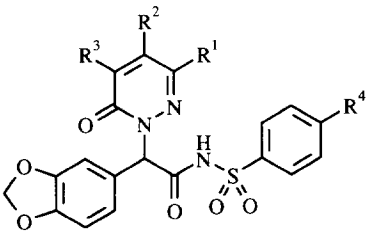
phenyldihydropyridazinone **6a** with a carboxylic group; this compound was, however, inactive. The introduction of an acylsulfonamide moiety as in L-749,329 gave compound **2a** with IC_{50} values for ET_A binding in the micromolar range. While the introduction of substituents on the phenyl group did not increase the affinity to the ET_A receptor, some of the compounds obtained in this way also showed affinity to the ET_B receptor (**2b**, **2f**). No significant difference in binding was observed between the dihydropyridazinone **2b** and the corresponding pyridazinone **2h**. Also, the introduction of a methyl group at the pyridazinone nucleus (**2i**) did not affect the binding properties. But much to our surprise, the replacement of the aromatic residue by a methyl group (**2j**) resulted in a 100fold increase in ET_A binding, which was comparable with L-749,329 (**1**). We took this as a starting point to further investigate alkylpyridazinone derivatives.

Table 1



Compound	R^1	X-Y	R^2	$IC_{50}(ET_A)$ [M]	$IC_{50}(ET_A)$ [M]
6a	Ph	CH_2-CH_2	OH	$> 10^{-5}$	$> 10^{-5}$
2a	Ph	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$2.6 \cdot 10^{-6}$	$> 10^{-5}$
2b	4-methoxy-phenyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$2.9 \cdot 10^{-6}$	$4.2 \cdot 10^{-6}$
2c	3,4-dimethoxy-phenyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$4.1 \cdot 10^{-6}$	$> 10^{-5}$
2d	2,4-dimethoxy-phenyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$> 10^{-5}$	$> 10^{-5}$
2e	2,5-dimethoxy-phenyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$> 10^{-5}$	$> 10^{-5}$
2f	4-chlorophenyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$2.7 \cdot 10^{-6}$	$6.4 \cdot 10^{-6}$
2g	2-thienyl	CH_2-CH_2	$NHSO_2C_6H_4$-*p*-*i*Pr	$3.2 \cdot 10^{-6}$	$> 10^{-5}$
2h	4-methoxy-phenyl	CH=CH	$NHSO_2C_6H_4$-*p*-*i*Pr	$3.2 \cdot 10^{-6}$	$5.7 \cdot 10^{-6}$
2i	4-methoxy-phenyl	$CH=CCH_3$	$NHSO_2C_6H_4$-*p*-*i*Pr	$4.0 \cdot 10^{-6}$	$7.7 \cdot 10^{-6}$
2j	CH_3	CH=CH	$NHSO_2C_6H_4$-*p*-*i*Pr	$3.4 \cdot 10^{-8}$	$2.9 \cdot 10^{-6}$
1	-	-	-	$4.1 \cdot 10^{-8}$	$9.0 \cdot 10^{-7}$

Table 2



Compound	R^1	R^2	R^3	R^4	$IC_{50}(ET_A)$ [M]	$IC_{50}(ET_A)$ [M]
2j	CH_3	H	H	*i*Pr	$3.4 \cdot 10^{-8}$	$2.9 \cdot 10^{-6}$
2k	CH_3	H	H	H	$2.3 \cdot 10^{-7}$	$> 10^{-5}$
2l	CH_3	H	H	OCH_3	$1.6 \cdot 10^{-7}$	$> 10^{-5}$
2m	CH_3	H	H	Br	$2.3 \cdot 10^{-7}$	$> 10^{-5}$
2n	CH_3	H	H	Ph	$2.4 \cdot 10^{-7}$	$2.4 \cdot 10^{-6}$
2o	CH_3	H	H	*tert.*-butyl	$3.2 \cdot 10^{-8}$	$2.0 \cdot 10^{-6}$
2p	CH_3	H	CH_3	*i*Pr	$2.9 \cdot 10^{-8}$	$3.5 \cdot 10^{-6}$
2q	CH_3	H	CH_3	*tert.*-butyl	$2.0 \cdot 10^{-8}$	$1.2 \cdot 10^{-6}$
2qa[a)]	CH_3	H	CH_3	*tert.*-butyl	$1.8 \cdot 10^{-8}$	$5.5 \cdot 10^{-7}$
2qb[b)]	CH_3	H	CH_3	*tert.*-butyl	$2.6 \cdot 10^{-6}$	$> 10^{-5}$
2r	*tert.*-butyl	H	H	*i*Pr	$4.0 \cdot 10^{-6}$	$> 10^{-5}$
2s	cyclopropyl	H	H	*i*Pr	$2.6 \cdot 10^{-7}$	$2.6 \cdot 10^{-6}$
2t	*n*-propyl	H	H	*i*Pr	$6.4 \cdot 10^{-7}$	$8.4 \cdot 10^{-6}$
2u	*n*-propyl	H	CH_3	*i*Pr	$2.9 \cdot 10^{-7}$	$4.5 \cdot 10^{-6}$
2v	CH_3	H	ethyl	*i*Pr	$3.2 \cdot 10^{-8}$	$2.6 \cdot 10^{-6}$
2w	CH_3	CH_3	H	*i*Pr	$3.4 \cdot 10^{-7}$	$5.2 \cdot 10^{-6}$
2x	$-(CH_2)_3-$		H	*i*Pr	$2.5 \cdot 10^{-6}$	$1.7 \cdot 10^{-6}$

a) enantiomer 1 (>99.5% ee). b) enantiomer 2 (99.4% ee).

We continued our studies with variation of R^4 at the benzenesulfonyl moiety. As listed in Table 2, nearly all substituents we introduced gave lower activities (**2k -2n**). Only the *tert.*-butyl compound **2o** was comparable with **2j**. The introduction of a second methyl group as in **2p** and **2q** had no influence on binding.

All compounds described so far were prepared as racemates. Therefore, it was important to determine the ET_A and ET_B binding properties of the different enantiomers. As an example, **2q** was separated by chromatography on a chiral β-cyclodextrin column[9] into the two enantiomers **2qa** and **2qb**. **2qa** clearly is the active enantiomer with respect to both receptors (Table 2).

Increasing the size of the alkyl group R^1 as in compounds **2r - 2u** diminished activity, whereas a slightly bulkier substituent R^3 (**2v**) had no influence on binding. The introduction of a methyl group in position 4 gave a compound (**2w**) with lower activity, also the annellation of a cyclopentene ring (**2x**).

For two of the compounds (**2j, 2p**), functional ET antagonism was determined by generating ET-1 concentration-response curves in isolated rat aortic rings without endothelium (ET_A) and, for **2p**, IRL-1620 concentration-response curves[10] in isolated rabbit jugularis vein (ET_B) in the absence or presence of the antagonist.[11] Both compounds are functional antagonists of the ET_A-receptor with pA_2 values of 6.2 (**2j**) and 5.9 (**2p**). The latter compound is also a functional antagonist at the ET_B-receptor with a pA_2 value of 5.8. The concentrations for ET_A functional antagonism are about fifty times larger than expected from the IC_{50} value for the receptor binding. This is different from findings for L-749,329, where both parameters for the ET_A receptor ($IC_{50} = 4.1 \cdot 10^{-8}$ M, $pA_2 = 8.5$) correlate well. Therefore, for full functional antagonism structural requirements may exist that are not realized with the compounds described in this paper.

Acknowledgement:

We would like to thank Gabriele Czmok, Herbert Glas, Annette Herberz, Angela Rittersberger and Helmut Reubold for preparing the compounds mentioned in this paper and Christina Heiner, Patric Kriesch, Gabriele Mahr, Rolf Löffler and Lydia Schulze for measuring the biological data.

References and notes:

1. Yanagisawa, M.; Kurihara, H.; Kimura, S.; Tomobe, Y.; Kobayashi, M.; Mitsui, Y.; Yazaki, Y.; Goto, K.; Masaki, T. *Nature* **1988**, *332*, 411.
2. Cheng, X.-M.; Nikam, S. S.; Doherty, A. M. *Current Medicinal Chemistry* **1994**, *1*, 271 and references cited therein.
3. Rubanyi, G. M.; Polokoff, M. *Pharmacol. Rev.* **1994**, *46*, 325.
4. (a)Walsh, T. F.; Fitch, K. J.; Chakravarti, P. K.; Williams, D. L.; Murphy, K. A.; Nolan, N. A.; O'Brien, J. A.; Lis, E. V.; Pettibone, D. J.; Kivlighn, S. D.; Gabel, R. A.; Zingaro, G. J.; Krause, S. M.; Siegl, P. K. S.; Clineschmidt, B. V.; Greenlee, W. J. *Abstract of Papers,* 208th Am. Chem. Soc. Natl. Mtg., August 21 - 25, **1994**, MEDI 145. (b) Greenlee, W. J.; Walsh, T. F.; Pettibone, D. J.; Tata, J. R.; Rivero, R. A.; Williams, D. L., Bagley, S. W.; Dhanoa, D. S.; Chakravarty, P. K.; Fitch, K. J.; Broten, T. P.; Kevin, N. J. *Europ. Pat. Appl.* 0,617,001 (*Chem. Abstr.* **1995**, *122*, 31129). (c) see also: 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.; Veber, D. F.; Greenlee, W. J. *BioMed. Chem. Lett.* **1995**, *5*, 1155.

5. The syntheses of pyridazinones **3** that served as starting materials for pyridazinone derivatives **6** and **2** were performed according to the following references: **6a**, **2a** - **2f**: Kane, J. M.; Huber, E. W.; Miller, F. P.; Kehne, J. H. *Pharmazie* **1992**, *47*, 249; **2g**: Steiner, G.; Gries, J.; Lenke, D. *J. Med. Chem.* **1981**, *24*, 59. **2h**: Steck, E. A.; Brundage, R. P., Fletcher, L. T. *J. Heterocycl. Chem.* **1974**, *11*, 755; **2i**: Dixon, S.; Gregory, H.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2139; **2j** - **2o** :Poppenberg, O. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3257; **2p**, **2q**, **2u**: Baraldi, P. G.; Bigoni, A.; Cacciari, B.; Caldari, C.; Manfredini, S.; Spalluto, G. *Synthesis* **1994**, 1158; **2r**, **2s**, **2v**: Coates, W. J.; McKillop, A. *Synthesis* **1993**, 334; **2t**: Grundmann, C. *Chem. Ber.* **1948**, *81*, 1; **2w**, **2x** : Horning, R. H., Amstutz, E. D. *J. Org. Chem.* **1955**, *20*, 707.
6. Methyl (1,3-benzodioxol-5-yl)-(bromo)-acetate (**4**) was prepared by treatment of methyl (1,3-benzodioxol-5-yl)-(hydroxy)-acetate (obtained from 1,3-benzodioxol-5-carbaldehyde according to Slotta, K. H.; Haberland, G. *J. prakt. Chem.* **1934**, *139*, 211) with phosphorus tribromide in toluene. The overall yield of **4** from 1,3-benzodioxol-5-carbaldehyde was 54%.
7. Drummond, J. T.; Johnson, G. *Tetrahedron Lett.* **1988**, *29*, 1653.
8. Sogabe, K.; Nirei, H.; Shoubo, M.; Nomoto, A.; Ao, S.; Notsu, Y.; Ono, T. *J. Pharmacol. Exp. Therap.* **1993**, *264*, 1040.
9. Chiradex (Merck), eluent: 50 : 50 methanol, 0.1 M sodium phosphate buffer (pH 6.4).
10. The ET_B receptor mediated NO and prostacyclin release was inhibited with the NO-synthase inhibitor L-NAME and indomethacin, respectively, in the rabbit jugularis vein. Therefore, IRL-1620 mediates contraction of the jugularis vein via the ET_B receptor on smooth muscle cells.
11. (a) Clozel, M.; Breu, V.; Burri, K.; Cassal, J.-M.; Fischli, W.; Gray, G. A.; Hirth, G.; Löffler, B.-M.; Müller, M.; Neidhart, W.; Ramuz, H. *Nature* **1993**, *365*, 759. (b) White, D. G.; Cannon, T. R.; Garatt, H.; Mundin, J. W.; Sumner, M. J.; Watts, I. S. *J. Cardiovasc. Pharmacol.* **1993**, *22 (Part 8, Supplement)*, S 144.

(*Received in Belgium* 30 *October* 1996; *accepted* 18 *December* 1996)