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BENZOFURO[3,2-b]PYRIDINES AS MIXED ET_A/ET_B AND SELECTIVE ET_B ENDOTHELIN RECEPTOR ANTAGONISTS

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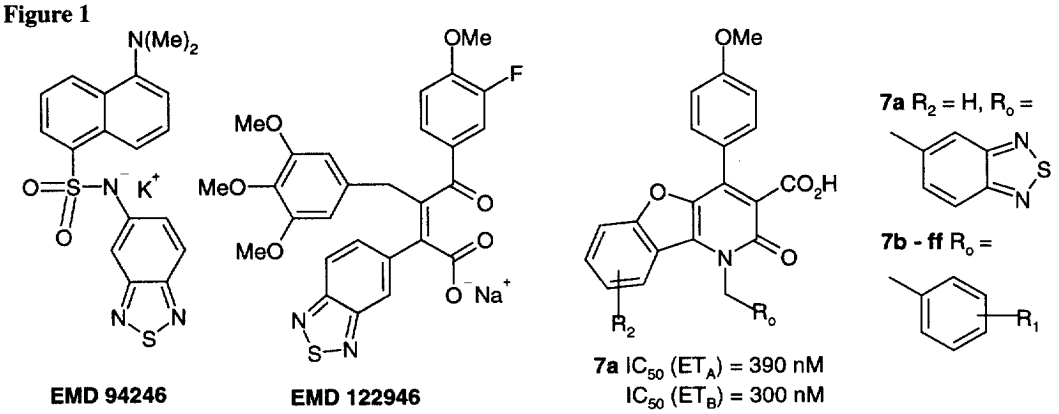
Abstract: The discovery, synthesis and structure-activity relationships of a series of novel benzofuro[3,2-b]pyridines as non-selective endothelin ET_A/ET_B as well as selective ET_B receptor antagonists are described. The most potent non-selective inhibitor **7s** displayed an IC_{50} of 21 nM and 41 nM for ET_A and ET_B receptors, respectively, whereas **7ee** merely showed affinity for the ET_B receptor (IC_{50} = 3.6 nM).

Keywords: antagonists, benzofuro[3,2-b]pyridines, endothelin, vasodilators

Introduction: In recent articles,[1-3] our group has described the identification and optimization of several classes of endothelin receptor antagonists. In particular[4,5] we have reported on a family of benzothiadiazole based compounds, exemplified by EMD 94246 and EMD 122946 (Figure 1), which are potent and highly selective for the ET_A receptor subtype. Previous studies[6] indicated that not only the ET_A but also the ET_B receptor contributed in mediating vasoconstriction. These observations and the fact that differing receptor profiles might be optimally effective for the treatment of particular disease states caused us to complement our ET_A candidates with mixed and ET_B selective compounds. Recently,[3] we described the non-selective antagonist **7a** (Figure 1). Variations at the benzofuro[3,2-b]pyridine core structure led to more potent non-selective and ET_B selective inhibitors, respectively. Herein, we report on their synthesis and structure-activity relationships.

Figure 1



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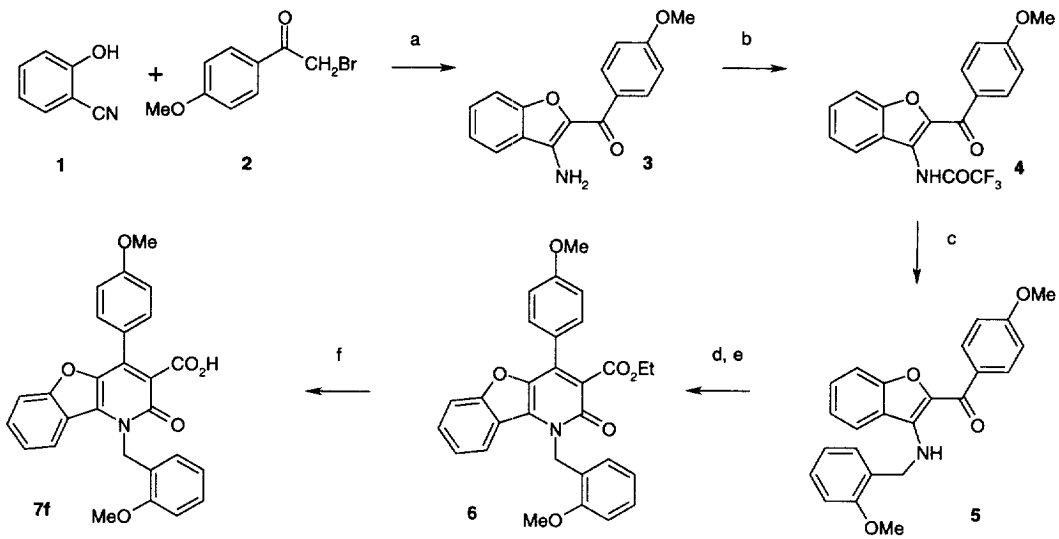
Chemistry: The general synthesis of the benzofuro[3,2-b]pyridines bearing an aryl group in 1 and 4 position is exemplified for the preparation of **7f** in Scheme 1.

2-Cyanophenol **1** was reacted with 2-bromo-4'-methoxyacetophenone **2** and potassium carbonate in acetone to give the cyclized aminobenzofuran derivative **3** in excellent yield.[7] Acetylation of **3** with trifluoroacetic anhydride and alkylation of the acetamido intermediate **4** with 2-methoxybenzyl chloride under phase transfer conditions afforded the monobenzylated aminobenzofuran **5** in excellent overall yield. The benzofuro[3,2-b]pyridine nucleus was formed *via* an intramolecular Knoevenagel condensation. Therefore, aminobenzofuran **5** was acylated with ethyl malonyl chloride and the resulting intermediate was then cyclized with silica gel to give the benzofuropyridine ester **6** in good yield. Through this procedure we could avoid the formation of a mixture of *N*- and *O*-alkylated products which is usually the result of a direct alkylation of the benzofuropyridine structure. Alkaline hydrolysis of the ester **6** provided the targeted acid **7f** in excellent yield.

Scheme 1

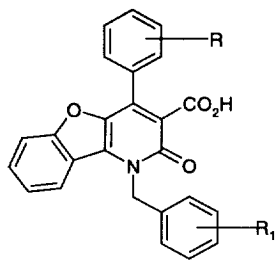


a. K_2CO_3, acetone, reflux, 12h, 95%; b. $(CF_3CO)_2O$, 100%; c. 2-MeO-Ph-CH_2Cl, $BnNEt_3Cl$, toluene, NaOH, 97%; d. EtO_2CCH_2COCl, 85%; e. silica gel, CH_2Cl_2, reflux, 69%; f. KOH, 98%.

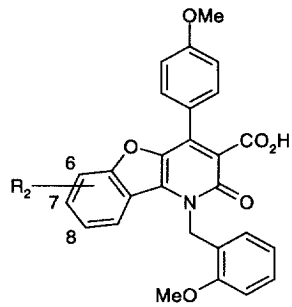
Results and discussion: Structure-activity relationships were investigated using IC_{50} values obtained for the competition of ^{125}I-Endothelin-1 binding to rat aorta membranes (ET_A) and porcine kidney (inner medulla) membranes (ET_B)[8] (Table 1). The *in vitro* functional assay was performed by obtaining ET-1 concentration-response curves [$pA_2(ET_A)$] in isolated rat aortic rings without endothelium and sarafotoxin 6c concentration-response curves [$pA_2(ET_B)$] in isolated rabbit jugularis vein in the absence or presence of the antagonist.[9] Sarafotoxin 6c mediates vasoconstriction in jugularis vein *via* the ET_B receptor.

The receptor binding affinities of compounds **7b** - **7ff** are summarized in table 1. The initial benzofuro[3,2-b]pyridine-3-carboxylic acid core structure **7b** had no effect for the ET_A or ET_B receptor. In analogy to the known endothelin antagonists we reasoned that electron-donating substituents at the aromatic rings could improve binding affinities. The introduction of a 4-methoxy substituent at the 3-phenyl ring gave compound **7c** with IC_{50} values for both subtypes in the micromolar range. To optimize the R_1 position (type I; compounds **7d**-

Table I. Endothelin Receptor Affinity [IC_{50}]



I



II

Cpd	type	R	R_1	R_2	ET_A (μM)	ET_B (μM)
7b	I	H	H		> 10.0	> 10.0
7c	I	4-OMe	H		2.7	3.0
7d	I	4-OMe	4-OMe		> 10.0	> 10.0
7e	I	4-OMe	3-OMe		2.7	1.6
7f	I	4-OMe	2-OMe		0.38	0.12
7g	I	4-OMe	2-OEt		0.90	1.3
7h	I	4-OMe	2-Me		0.42	0.30
7i	I	4-OMe	2-*i*Pr		0.71	0.66
7k	I	4-OMe	2-SMe		2.7	6.4
7l	I	4-OMe	2-Cl		1.3	2.7
7m	I	3-OMe	2-OMe		1.5	3.5
7p	I	2-OMe	2-OMe		> 10.0	> 10.0
7n	I	2,5-diOMe	2-OMe		0.49	6.8
7o	I	2,4-diOMe	2-OMe		1.2	0.43
7q	I	3,4,5-triOMe	2-OMe		> 10.0	0.17
7r	I	3,4-OCH_2O-	2-OMe		1.2	1.9
7s	I	4-OMe	2,5-diOMe		0.021	0.041
7t	I	4-OMe	2,3-diOMe		3.5	5.2
7u	I	4-OMe	2,6-diOMe		> 10.0	> 10.0
7v	I	4-OMe	2,4,5-triOMe		> 10.0	> 10.0
7aa	II			7-NO_2	2.1	0.2
7bb	II			7-NH_2	2.3	0.027
7cc	II			7-$NHSO_2Me$	> 10.0	0.12
7dd	II			7-$NMeSO_2Me$	> 10.0	0.0086
7ee	II			7-$NEtSO_2Me$	> 10.0	0.0036
7ff	II			7-N*n*PrSO_2Me	> 10.0	0.013

7l) the *para* methoxy group at the R position was kept constant. Of these compounds the *ortho* methoxy derivative **7f** showed the best affinities for both ET_A and ET_B receptor in the submicromolar range. The attempt to optimize further the activity at the R position keeping the *ortho* methoxy substituent as R_1 (compounds **7m** - **7r**) led to a loss in both binding affinities compared to compound **7f**. To improve binding affinity , molecules with additional substituents relative to **7f** in R_1 position (compounds **7s** - **7v**) were synthesized. Introducing a second methoxy group in 5-position of the benzyl ring led to analogue **7s** with nearly balanced affinity for both receptors. This compound was an order of magnitude more potent in comparison with **7f** [IC_{50} (ET_A) = 21 nM; IC_{50} (ET_B) = 41 nM]. When Abbott scientists discovered that introduction of an alkyl sulfonamide group in their core structure improved ET_B affinity[10], we combined this substitution at R_2 (type II) with compound **7f**. To our surprise (compounds **7aa** - **7ff**), the substitution at the 7-position of the benzofuropyridine ring led to selective ET_B receptor antagonists. The *N*-ethyl sulfonamide **7ee** displayed an IC_{50} for the ET_B receptor of 3.6 nM without having an effect at the ET_A receptor. For benzopyridines **7s** and **7ee** the functional ET_A and ET_B antagonism was determined, respectively. Compound **7s** is a functional antagonist for the ET_A receptor with a pA_2 value of 6.3 and **7ee** a functional antagonist for ET_B with a pA_2 value of 6.9. Unfortunately, these derivatives are less active than expected from the IC_{50} values for receptor binding.

In conclusion, we discovered a non-selective (**7s**) and a selective ET_B (**7ee**) endothelin receptor antagonist with nanomolar binding affinities, respectively. However, both compounds displayed diminished functional antagonistic activities.

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