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AMIDE BOND SURROGATES: A STUDY IN THIOPHENESULFONAMIDE BASED ENDOTHELIN RECEPTOR ANTAGONISTS[1]

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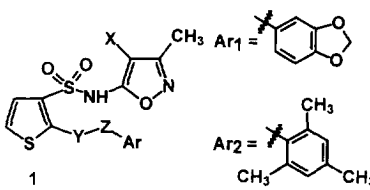
Abstract: The potential proteolytic instability of the amide bond present in some ET_A selective thiophenesulfonamide endothelin antagonists exemplified by TBC-10708 led us to investigate the replacement of this moiety with stable amide bond surrogates such as a *trans* double bond and an ethylene spacer. The effect of these replacements on the binding affinity is described. © 1997 Elsevier Science Ltd.

The family of bicyclic polypeptides, which includes the endothelins[2] (ETs) and sarafotoxins,[3] has been implicated in a variety of diseases such as congestive heart failure, hypertension, angina, acute renal failure, myocardial ischaemia, cyclosporin induced renal toxicity, pulmonary diseases, and other endothelin mediated disorders.[4] The pharmacological actions of ETs and sarafotoxins are mediated by two distinct subtype endothelin receptors, namely ET_A and ET_B.[5] Hence, an aggressive research effort has been focused by various research groups to develop endothelin receptor antagonists,[6] which are useful tools in elucidating the pharmacological roles of the endothelins and their clinical utility will become clear as these antagonists progress through clinical evaluations.



No.	X	Y	Z	Ar	IC_{50} (nM, ET_A)
1a	Br	CO	O	Ar_1	8.9
1b	Cl	CO	NH	Ar_2	0.63
1c	Br	CH_2	O	Ar_2	62

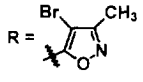
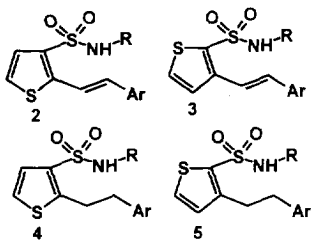
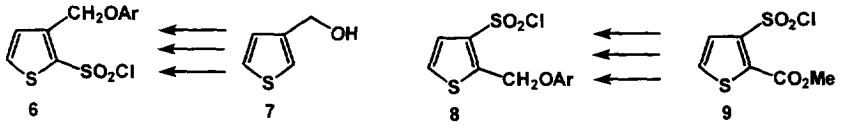


Figure 1



The high affinity ET_A selective endothelin antagonists **1a** and **1b** discovered in this laboratory[6b,c] showed negligible in vivo efficacy. This was attributed to the proteolytic susceptibility of the ester or amide bonds present in **1a** and **1b**, which led us to investigate the replacement of these moieties with stable surrogates. One such replacement of the amide or ester functionality with an aryloxymethyl group resulted in substantial loss of ET_A potency (**1c** vs. **1a** and **1c** vs. **1b**).[6d] Based on these results, we proposed that the carbonyl group in **1a** and **1b** may impose a conformational preference for the spatial display of the phenyl ring for optimum binding and/or the carbonyl group may have favorable interaction with receptor elements. In order to address the conformational issues, the amide or ester bond was replaced with a constrained *trans* double bond and a

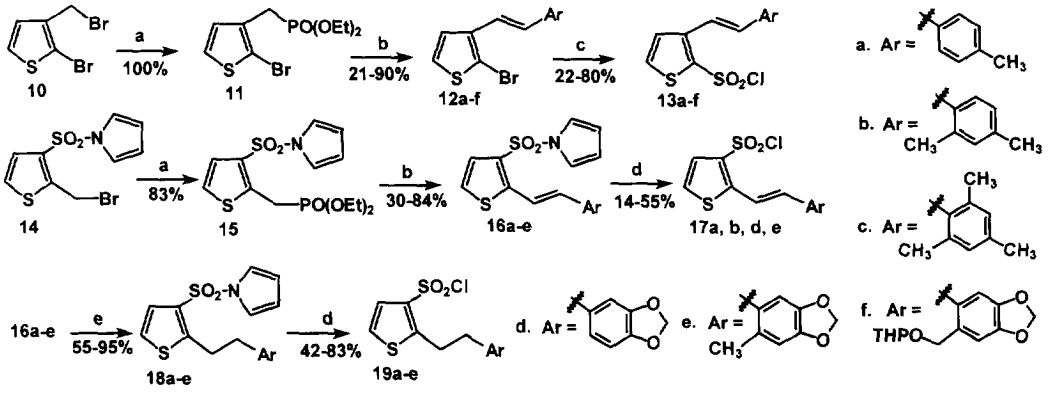
flexible single bond, for comparative studies. This communication describes the effect of such replacements on the binding affinity of the resultant ligands.



Scheme I

The sulfonyl chlorides required for the synthesis of thiophenesulfonamides **2-5** (Figure 1) were derived from the commercially available thiophene derivatives **7** and **9**, as briefly summarized in Scheme I. The phosphonates **11** and **15** (Scheme II), obtained by reacting their respective bromothiophenes[6d] **10** and **14** with triethylphosphite, were condensed with substituted benzaldehydes to afford thiophenes **12a-f** and **16a-e**, respectively. Treatment of the thiophenes **12a-f** with *n*-BuLi, to effect the lithium-bromine exchange, followed by quenching of the anions with sulfur dioxide and oxidation of the resultant sulphinates with NCS gave the desired sulfonyl chlorides **13a-f**. Catalytic hydrogenation of the double bond in derivatives **16a-e** gave the saturated analogs **18a-e**. Removal of the pyrrole protecting group[7] in **16a**, **b**, **d**, **e**, and **18a-e** by basic hydrolysis followed by reacting the resultant sulfonates with $POCl_3$ and PCl_5 mixture gave the desired sulfonyl chlorides **17a**, **b**, **d**, **e**, and **19a-e**, respectively.

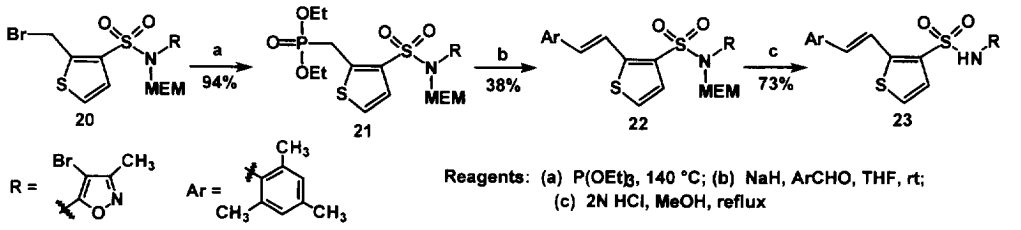
Scheme II



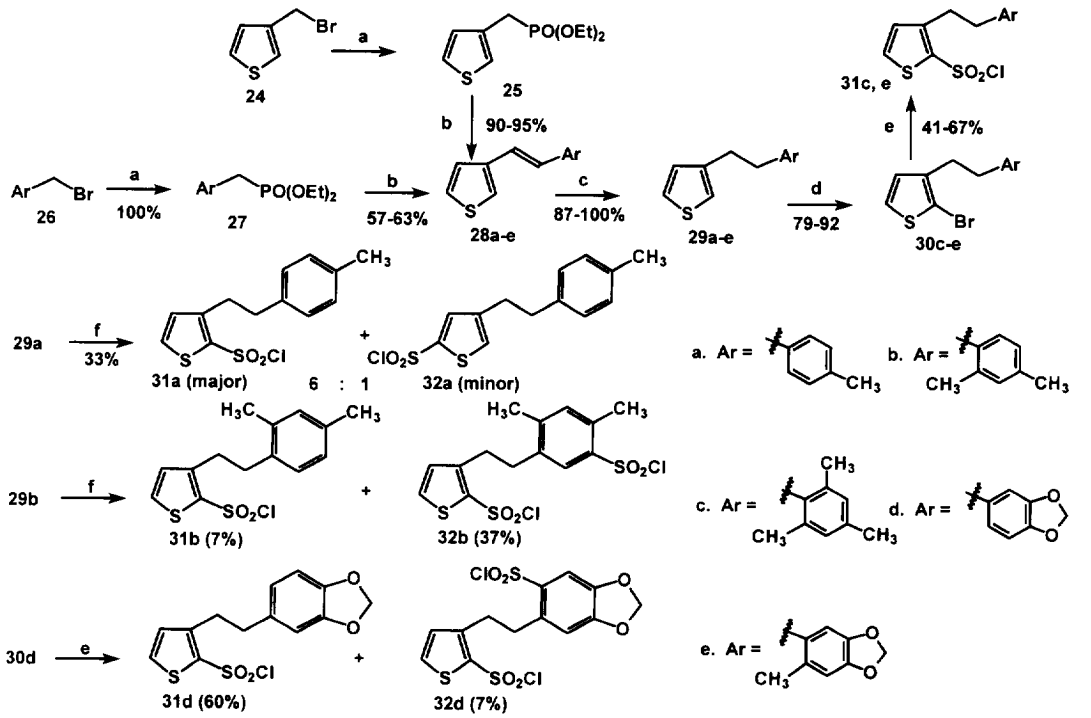
Reagents: (a) $P(OEt)_3$, 140 °C; (b) NaH, ArCHO, THF, rt; (c) *n*-BuLi, THF, -78 °C; then SO_2; then NCS; (d) KOH or NaOH, EtOH, H_2O, reflux; $POCl_3$, PCl_5, rt; (e) 10 % Pd-C, EtOAc, 60 psi H_2, 2 days.

An alternative approach to prepare the 2-cinnamylthiophene-3-sulfonamide **23** is described in the Scheme III in which isoxazoleamine moiety is introduced before the cinnamyl group. The bromomethyl derivative[6d] **20** was reacted with triethylphosphite to provide the phosphonate **21**, which was condensed with mesitaldehyde to afford the 2-cinnamylthiophenesulfonamide **22**. Removal of the MEM protecting group by acidic hydrolysis gave the desired sulfonamide **23**.

Scheme III



Scheme IV



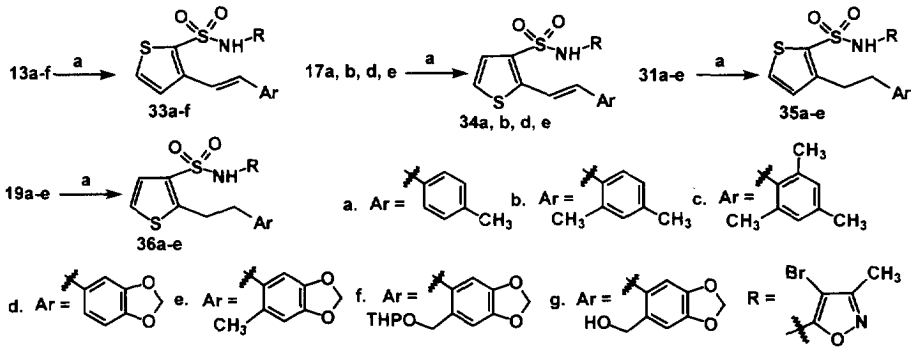
Reagents: (a) $P(OEt)_3$, 140 °C; (b) NaH, ArCHO, THF, rt; (c) 10 % Pd-C, EtOAc, 60 psi H_2, 2 days; (d) 1.1 equiv. NBS, AcOH:$CHCl_3$, rt; (e) *n*-BuLi, THF, -78 °C; then SO_2; then NCS; (f) 1 equiv. $ClSO_3H$, CH_2Cl_2, -5 °C; then $POCl_3$, PCl_5, rt.

The synthesis of the 3-arylethylthiophene-2-sulfonyl chlorides are outlined in the Scheme IV. Benzyl bromides **26a** and **26d** were reacted with triethylphosphite to provide phosphonates **27a** and **27d**. These phosphonates were condensed with thiophene-3-carboxaldehyde to get unsaturated analogs **28a** and **28d**. Alternatively, 3-bromomethylthiophene[6d] **24** was converted to the corresponding phosphonate **25**, which was condensed with substituted benzaldehydes to get unsaturated derivatives **28b**, **28c**, and **28e**. Catalytic hydrogenation of the double bond in **28a-e** gave the respective saturated analogs **29a-e**. These intermediates **29a-e** were transformed to the desired sulfonyl chlorides by a regioselective introduction of the sulfonyl group

at the 2-position.[8] Thus, the analog **29a** was treated with 1.1 equivalent of chlorosulfonic acid at -5 °C followed by treatment of sulfonic acid with $POCl_3$ and PCl_5 mixture gave the sulfonyl chloride **31a** as a major product and the regioisomer **32a** as a minor product (6:1 ratio). On the other hand, under similar reaction conditions the 3-(2,4-diemthylphenethyl)thiophene **29b** gave the desired sulfonyl chloride **31b** as a minor product and bis-sulfonyl chloride **32b** as a major product. A slightly different methodology was adopted to circumvent this problem in the synthesis of the sulfonyl chlorides **32c-e**. Thiophenes **29c-e** were brominated at the 2-position using NBS under acidic conditions.[8] The bromides **30c-e** were transformed to the sulfonyl chlorides as described earlier (Scheme II, step c). The formation of the bis-sulfonyl chloride **32d** was presumed to be due to the bromination of the electron rich aromatic ring, which was converted to the sulfonyl chloride functionality in the next step. The sulfonyl chlorides were purified by column chromatography to get individual isomers, except **31a** and **32a**, which were used as a mixture in the next step.

The sulfonyl chlorides **13a-f**, **17a**, **b**, **d**, **e**, **19a-e**, and **31a-e** were treated with 5-amino-4-bromo-3-methylisoxazole[6e] under basic conditions to afford the desired sulfonamides[9] **33a-f**, **34a**, **b**, **d**, **e**, **35a-e**, and **36a-e** (Scheme V). Purifiction of the crude sulfonamide **33f** by preparative HPLC using a C18 cloumn and water/acetonitrile solvent gave **33f** and **33g** (1:1 ratio), in which the THP protecting group was removed.

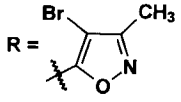
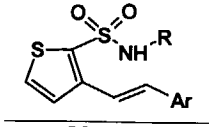
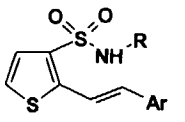
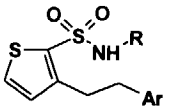
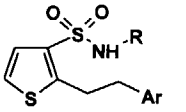
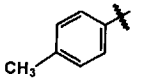
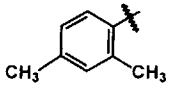
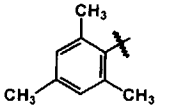
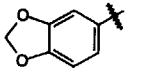
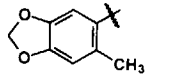
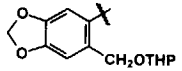
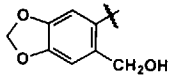
Scheme IV



Reagents: (a) NaH, THF, 5-amino-4-bromo-3-methylisoxazole, 0 °C - rt

The IC_{50} values obtained for this series of thiophenesulfonamides using ^{125}I-ET-1 in a competitive radioligand assay for both the cloned human ET_A and ET_B receptors are summarized in Table 1.[10] As observed in the amide series, the binding affinity was increased by the substitution of the benzene ring at the appropriate position with the methyl substitutent as seen in analogs **33a**, **33b**, and **33c**. This observation was further supported by the similar trend in the regioisomeric analogs **34a**, **34b**, and **23** and also in the phenethyl analogs **35a-c**, and **36a-c**. Similarly, *ortho* substitution of the phenyl ring in the methylenedioxy derivative **33d** gave **33e**, which resulted in reasonable improvement in the ET_A receptor affinity. Similar improvement was displayed by the regioisomeric thiophenesulfonamides **34d** vs. **34e** and phenethyl analogs **35d** vs. **35e** and **36d** vs. **36e**.

Table 1. IC_{50} Values for the thiophenesulfonamides

R = 												
		IC_{50} (μM)			IC_{50} (μM)			IC_{50} (μM)			IC_{50} (μM)	
No	Ar	ET_A	ET_B	**No**	ET_A	ET_B	**No**	ET_A	ET_B	**No**	ET_A	ET_B
33a		0.936	6.635	**34a**	0.231	4.13	**35a**	0.347	9.355	**36a**	0.106	11.7
33b		0.18	2.97	**34b**	0.166	2.97	**35b**	0.102	4.295	**36b**	0.055	3.48
33c		0.053	1.72	**23**	0.044	2.00	**35c**	0.058	1.395	**36c**	0.046	2.09
33d		0.218	9.955	**34d**	0.141	5.245	**35d**	0.237	17.85	**36d**	0.205	9.24
33e		0.072	5.37	**34e**	0.081	3.28	**35e**	0.091	12.45	**36e**	0.062	8.895
33f		0.073	4.135		**			**			**	
33g		0.079	3.24		**			**			**	

** this isomer was not synthesized

There was no change in binding affinity in analogs **33f** and **33g** compared to **33e**. The ET_B binding affinity of the thiophenesulfonamides described in this series ranges from 2 to 12 μM. In general, the binding affinities of cinnamylthiophenesulfonamides and phenethylthiophenesulfonamides are very similar.

In summary, thiophenesulfonamides **33c**, **23**, **35c** and **36c** are the best ET_A selective inhibitor (IC_{50} = ~50 nM) in this series. There was no significant difference in the ET_A binding affinity of arylethyl- and aryloxymethylthiophenesulfonamides (**35c** or **36c** vs. **1c**), which suggests that the oxygen atom in aryloxymethylthiophenesulfonamides is not a necessary element for highly potent inhibitory activity. Also, there was no significant difference in the ET_A binding affinity of arylethyl- and cinnamylthiophenesulfonamides, which suggests that the conformation alone could not significantly influence the binding affinity. The thiophenesulfonamides described in this series are about 100-fold less potent in their ET_A binding affinity compared to 2-aryloxycarbonylthiophene-3-sulfonamides or 2-arylaminocarbonylthiophene-3-sulfonamides. These observations indicate the relevance of the carbonyl group in **1a** and **1b** (Figure 1) with respect to both conformational bias and possible interactions with key receptor elements.

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References and Notes

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