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Lead Discovery of α,β-Unsaturated Sulfones from a Combinatorial Library as Inhibitors of Inducible VCAM-1 Expression

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Abstract—α,β-Unsaturated sulfones have been discovered from a combinatorial library as leads for a new series of inhibitors of inducible VCAM-1 expression. Although not essential, further conjugation of the sulfonyl group to another vinyl group or a phenyl group increases the potency dramatically.

Although leukocyte recruitment into inflamed tissue is an essential physiologic process to remove the inflammatory stimulus, this beneficial response can lead to a chronic and detrimental inflammatory process if the stimulus is not properly eliminated and therefore, leukocyte recruitment is also a key factor in the pathogenic process of inflammation. At sites of inflammation, the recruitment of leukocytes is mediated, at least in part, by the expression on endothelial cells of adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin, that are induced in response to various cytokines such as TNF-α.[1]

Steroids and other anti-inflammatory drugs with broad-spectrum activities are certainly effective in treating numerous diseases and inflammatory conditions. However, long-term usage of these drugs often leads to unacceptable side effects. Some leukocytes, including T cells, monocytes, and eosinophils, constitutively express very late antigen-4 (VLA-4), the receptor of VCAM-1, and are key effector cells in various inflammatory disorders.[2–4] Tissue samples from patients have also indicated that VCAM-1 is highly expressed in many diseases.[5] Adhesion of monocytes and lymphocytes to the arterial endothelial lining is one of the earliest detectable events in human atherosclerosis and these are the principal leukocyte subsets populating atherosclerotic lesions.[6] A recent study showed that VCAM-1, but not ICAM-1, plays a dominant role in the initiation of atherosclerosis although both VCAM-1 and ICAM-1 are upregulated in atherosclerotic lesions.[7] Moreover, since circulating neutrophils do not express VLA-4, selective inhibitors of the expression of VCAM-1 are likely to have potential as therapeutic agents.[8]

A variety of agents have been reported as potent inhibitors of VCAM-1 expression.[9] Establishing pharmacological proof-of-concept for VCAM-1 modulation as a therapeutic target, a cyclic depsipeptide effectively inhibited VCAM-1 expression and reduced inflammation in a dermal model of inflammation,[10] a monoclonal antibody against VCAM-1 inhibited neointimal formation in a mouse model of arterial wall injury,[11] and a disubstituted 1,4-diazepine diminished the increase in paw thickness in a mouse model of collagen-induced arthritis.[12]

In this Letter, we report on the lead discovery of a series of compounds as inhibitors of inducible VCAM-1 expression from a commercial combinatorial library. Two initial hits with designated structures **1** and **2** (Fig. 1) from the library exhibited modest inhibitory potencies in vitro on VCAM-1 expression with IC_{50} of 20 and 23 μM, respectively. A synthesis of pure compounds **1** and **2** was then undertaken to confirm their structures

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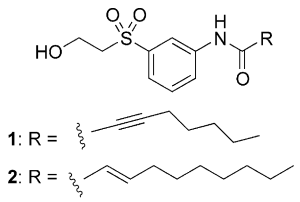
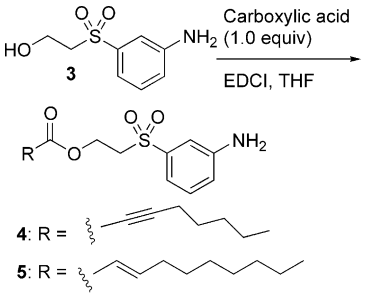


Figure 1.

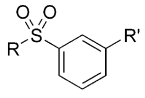


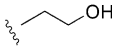
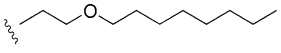
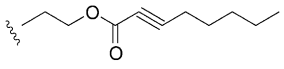
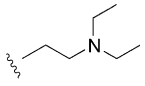
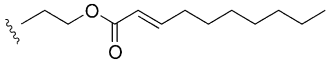
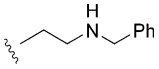
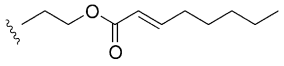
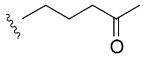
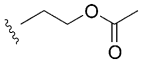
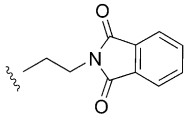
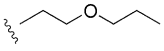
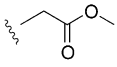
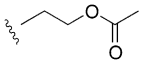
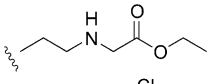
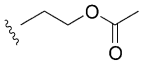
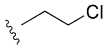
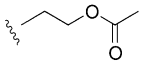
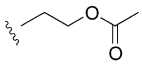
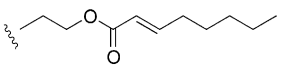
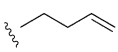
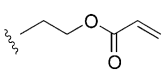
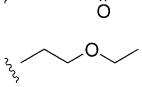
Scheme 1.

and activities. As shown in Scheme 1, however, when compound **3** was acylated using the same condition as for the original library, carboxylic esters **4** and **5** instead of amides **1** and **2** were obtained. Compounds **4** and **5** showed IC_{50} of 6 and 28 μM (see Table 1), respectively, and hence the structures of the two initial hits were revised as **4** and **5**. The methylene group attached to the hydroxyl group in **3** shows up at about 3.6 ppm in ^1H NMR while the corresponding methylene group in **4** or **5** at >4 ppm. All other ester analogues described in this Letter showed the same pattern as **4** and **5**. Next we set out to decipher the minimal pharmacophore of compounds **4** and **5** as a starting point in the search for a new series of inhibitors of inducible VCAM-1 expression.

The greater potency of compound **4** compared with **5** could be due to either the triple bond on the side chain or the shorter side chain of compound **4**. Compound **6**, with the same length of side chain as **4** but a double bond instead of a triple bond, was not as potent as **4** in the in vitro assay (see Table 1). This might mean that a

Table 1. Inhibiting profile of type-1 compounds on inducible VCAM-1 expression[13]



Compd	R	R′	IC_{50} (μM)	Compd	R	R′	IC_{50} (μM)
3		Amino	NE	**16**		H	NE
4		Amino	6	**17**		H	NE
5		Amino	28	**18**		H	NE
6		Amino	17	**19**		H	NE
7		Amino	10	**20**		H	NE
8		Amino	NE	**21**		H	NE
9		*N*-Acetylamino	4	**22**		H	NE
10		*N*-Propylamino	NE	**23**		H	2
11		*N*-Octylamino	NE	**24**		H	2
12		H	12	**25**		H	NE
13		H	17	**26**		H	NE
14		H	7	**27**		*N*-Octylamino	29
15		H	NE				

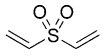
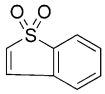
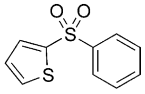
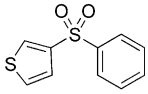
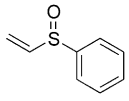
propioloyl residue was more important than an acryloyl residue on the side chain for the inhibition of VCAM-1 expression. However, compound **7** with a simple acetyl residue on the side chain exhibited an IC_{50} of 10 μM. When there was no carboxylic ester group on the side chain the activity was completely lost (**3** and **8**). Therefore, it was reasonable to conclude at this point that a carboxylic ester group on the side chain was essential for the inhibitory activity.

When an acetyl group was introduced to the amino group on the phenyl ring of **7** using excess amount of acetic anhydride and triethylamine, the product (**9**) was even more potent. When an alkyl group was introduced to the amino group (**10** and **11**), however, the activity was eliminated. This might mean that the biological target of this series of compounds cannot tolerate a large substitution at the amino group and the good potency of **9** could be due to an electronic effect of the acetyl group. Interestingly, when the amino group was removed, the resulting compounds (**12**, **13**, and **14**) exhibited similar potencies as their parent compounds (compare **12** with **7**, and **13** with **6**). Therefore, an amino group was not essential for the activity of this series of compounds and did not help increase the potency. Among the compounds that lack an amino group on the phenyl ring, it was shown again that a carboxylic ester group on the side chain was essential. When the carboxylic ester was replaced by an ether residue (**15** and **16**) or an amino group (**17** and **18**) on the side chain the activity was completely lost.

When the carboxylic ester oxygen on the side chain of **12** was replaced with a methylene unit, the product (**19**) was inactive. Although one of the imide carbonyl groups in compound **20** resembles the carbonyl group of **12** with a nitrogen replacing the oxygen, the compound was inactive. In the structures of **21** and **22**, there is a carboxylic ester group but neither showed any activity. It was concluded at this point that a carboxylic ester group in the pattern of **12** was essential for activity. However, compound **23** defied this conclusion. It does not have a carboxylic ester group on the side chain but showed an IC_{50} of 2 μM on the inhibition of inducible VCAM-1 expression. It was suspected at this point that both compounds **12** and **23** eliminated to the common α,β-unsaturated sulfone **24** during the in vitro biological assay.

Indeed α,β-unsaturated sulfone **24** turned out to be an active compound (Table 1). When there was no α,β-unsaturated double bond (**25**) or the double bond was not conjugated with the sulfonyl group (**26**) the activity was completely lost. Once again, an *N*-alkyl amino group at the meta position on the phenyl ring dramatically decreased the potency (**27**). All the compounds that can undergo an elimination reaction leading to compound **24** showed inhibitory activity on inducible VCAM-1 expression. However, since the compounds may not eliminate completely during the biological assay their potencies vary. Compound **23** may eliminate completely because it showed the same potency as **24**.

Table 2. Inhibiting profile of type-2 compounds on inducible VCAM-1 expression[13]

Compd	Structure	IC_{50} (μM)
28		14
29		5
30		4
31		NE
32		NE
33		NE

When the phenyl group of compound **24** was replaced by a methyl group (**28**) the potency dropped dramatically (Table 2). However, when the phenyl group was replaced with a vinyl group the product (**29**) was still potent ($IC_{50} = 5$ μM) though not as much as **24**. When the vinyl group of **24** was conjugated to the phenyl ring in the same molecule potency was more or less maintained in the product (**30**). When the vinyl group is replaced with a thienyl group the activity was completely eliminated (**31** and **32**). When the sulfonyl group of **24** was replaced with a sulfinyl group (**33**, racemic) the potency was eliminated. Therefore a sulfonyl group is essential for the inhibitory activity.

Special attention was paid to potential cell toxicities caused by testing compounds. We could visually distinguish between toxicity and inhibitory efficacy on VCAM-1 expression in our in vitro assay. None of the potent compounds reported in this Letter showed toxicity at the concentrations used although at higher concentrations some might do.

In summary, α,β-unsaturated sulfones have been discovered from a combinatorial library as leads for a new series of inhibitors of inducible VCAM-1 expression. Although not essential, further conjugation of the sulfonyl group to another vinyl group or a phenyl group increases the potency dramatically.

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13. 'NE' stands for 'no effect.' For a general protocol used to test compounds for inhibition of inducible VCAM-1 expression, see ref 9.