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Discovery of novel heteroaryl-substituted chalcones as inhibitors of TNF-α-induced VCAM-1 expression

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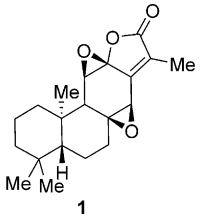
Abstract—Novel chalcone derivatives have been discovered as potent inhibitors of TNF-α-induced VCAM-1 expression. Thienyl or benzothienyl substitution at the *meta*-position of ring B helps boost potency while large substitution at the *para*-position on ring B is detrimental. Various substitutions are tolerated on ring A. A lipophilicity–potency relationship has been observed in several sub-series of compounds.

At sites of inflammation, the recruitment of leukocytes is mediated, at least in part, by the expression of vascular cell adhesion molecule-1 (VCAM-1) in response to various cytokines such as tumor necrosis factor-α (TNF-α).[1] Evidence from patients and animal models has indicated that upregulation of VCAM-1 occurs in plasma and tissues of numerous chronic inflammatory diseases such as asthma, rheumatoid arthritis and atherosclerosis.[2–6] A variety of agents have been reported as potent inhibitors of VCAM-1 expression.[7] Some have shown therapeutic efficacy in various animal models, establishing pharmacological proof-of-concept for VCAM-1 modulation as a therapeutic target.[8–10] Similarly, we have disclosed a multifunctional antioxidant with inhibiting effects on inducible VCAM-1 expression, which has shown efficacy in animal models of atherosclerosis and is currently in phase III clinical trials for the treatment of coronary artery disease.[11–13]

Some natural products, such as **1**[14] and **2**,[15] are known to inhibit the expression of VCAM-1. Since an α,β-unsaturated carbonyl is a common structural feature of



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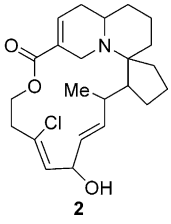

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these compounds, we set out to screen simple compounds containing this moiety. This led to the discovery of a series of chalcone derivatives as potent inhibitors of VCAM-1 expression. Naturally occurring and synthetic chalcones are known to have a wide range of potential pharmacologic activities[16] on cancer,[17] malaria,[18] leishmaniasis,[19] etc. Some chalcones have also been reported as anti-inflammatory agents.[20–23] Herein we report a novel series of heteroaryl-substituted chalcones exhibiting low micromolar IC_{50} values for inhibiting TNF-α-induced VCAM-1 expression.

As shown in Table 1, the two phenyl rings of the chalcone skeleton are designated 'ring A' and 'ring B', respectively, for convenience of discussion herein. While the parent chalcone, **3**, exhibits weak inhibition on inducible VCAM-1 expression (IC_{50} = 23 μM), when a

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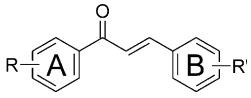
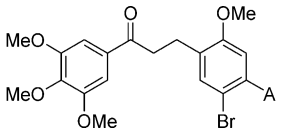
Table 1. Inhibiting profile of chalcones on inducible VCAM-1 expression[24]



Compd	R	R′	VCAM-1 IC_{50} (μM)	ClogP
3	Hydrogen	Hydrogen	23	3.58
4	4-Methoxy	Hydrogen	14	3.59
5	3,4-Dimethoxy	Hydrogen	8	3.60
6	3,4,5-Trimethoxy	Hydrogen	6	3.61
7	3,4-Dimethoxy	4-Methoxy	6	3.61
8	4-Methoxy	3,4-Dimethoxy	15	3.61
9	2,4-Dimethoxy	4-Methoxy	7	3.61
10	4-Methoxy	2,4-Dimethoxy	29	3.61
11	3,5-Di-*tert*-butyl-4-hydroxy	Hydrogen	47	5.67
12	3,5-Di-*tert*-butyl-4-methoxy	Hydrogen	9	6.19
13	3,5-Di-*tert*-butyl-4-hydroxy	4-Methoxy	> 50	5.68
14	3,5-Di-*tert*-butyl-4-Methoxy	4-Methoxy	17	6.19
15	4-Fluoro	4-Fluoro	25	3.86
16	4-Fluoro	3-(Thien-2-yl)-4-fluoro	4	5.59
17	3,4,5-Trimethoxy	4-(Thien-2-yl)	6	5.34
18	3,4-Dimethoxy	4-(Thien-2-yl)	12	5.33
19	Hydrogen	2-Methoxy-5-(thien-2-yl)	5	5.30
20	3,4,5-Trimethoxy	2-Methoxy-5-(thien-2-yl)	3	5.35
21	4-Methoxy	2-Methoxy-5-(thien-2-yl)	3	5.33
22	2,5-Dimethoxy	2-Methoxy-5-(thien-2-yl)	2	5.34
23	3,5-Dimethoxy	2-Methoxy-5-(thien-2-yl)	2	5.34
24	3,4-Dimethoxy	2-Methoxy-5-(thien-2-yl)	3	5.34
25	2,6-Dimethoxy	2-Methoxy-5-(thien-2-yl)	3	5.34
26	2,4,6-Trimethoxy	2-Methoxy-5-(thien-2-yl)	3	5.35
27	4-Methoxy	2-Methoxy-5-(benzo[*b*]thien-2-yl)	3	6.48
28	3,4,5-Trimethoxy	2-Methoxy-5-(benzo[*b*]thien-2-yl)	2	6.50
29	3,4-Dimethoxy	2-Methoxy-5-(benzo[*b*]thien-2-yl)	2	6.49
30	3,4-Dimethoxy	2-Methoxy-5-(5-methylthien-2-yl)	2	5.65
31	3,4-Dimethoxy	2-Methoxy-5-(4-methylthien-2-yl)	2	5.65
32	3,4,5-Trimethoxy	2-Methoxy-5-(5-methylthien-2-yl)	2	5.65
33	3,4,5-Trimethoxy	2-Methoxy-5-(4-methylthien-2-yl)	2	5.65
34	3,4,5-Trimethoxy	3,4-Dimethoxy-5-(5-acetylthien-2-yl)	3	5.56
35	3,4-Dimethoxy	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	11	6.50
36	3,4,5-Trimethoxy	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)−	5	6.51
37	2,3,4-Trimethoxy	2,4-Dimethoxy-5-(thien-2-yl)	2	5.35
38	2,3,4-Trimethoxy	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	8	6.51
39	3,4,5-Trimethoxy	3-Bromo-4,5-dimethoxy	4	4.39
40	3,5-Dimethoxy-4-benzyloxy	3-Bromo-4,5-dimethoxy	> 50	5.96
41	2,4,5-Trimethoxy	3-Bromo-4,5-dimethoxy	2	4.39
42	2,4,5-Triethoxy	3-Bromo-4,5-dimethoxy	15	5.56
43	3,5-Dimethoxy-4-cyclopropylmethoxy	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)−	> 50	7.29
44	3,4-Methylenedioxy	2-Methoxy-5-(thien-2-yl)	4	5.05
45	3,4-Methylenedioxy	2-Methoxy-5-(5-methylthien-2-yl)	3	5.36
46	3,4-Methylenedioxy	2-Methoxy-5-(4-methylthien-2-yl)	4	5.36
47	3,5-Dimethoxy-4-(3,4,5-trimethoxybenzyloxy)	3,4,5-Trimethoxy	3	5.23
48	3-Methoxy-4-(1,4-benzodioxan-3-methoxy)	3,4,5-Trimethoxy	4	4.84
49	3,5-Dimethoxy-4-(2-methoxyethoxy)	3,4,5-Trimethoxy	5	3.63
50	3,5-Dimethoxy-4-(thien-2-ylmethoxy)	3,4,5-Trimethoxy	3	5.27
51	3,5-Dimethoxy-4-(4-methoxybenzyloxy)	3,4,5-Trimethoxy	1	5.21
52	3,5-Dimethoxy-4-(1,4-benzodioxan-3-methoxy)	3,4,5-Trimethoxy	2	4.84
53	3,5-Dimethoxy-4-furfuryloxy	3,4,5-Trimethoxy	3	4.80
54	3,5-Dimethoxy-4-(3,4-dimethoxybenzyloxy)	3,4,5-Trimethoxy	2	5.22
55	3,5-Dimethoxy-4-(3,4-methylenedioxybenzyloxy)	3,4,5-Trimethoxy	3	4.93
56	3-Methoxy-4-(3,4-dimethoxybenzyloxy)	3,4,5-Trimethoxy	2	5.21
57	3-Methoxy-4-(pyrid-2-ylmethoxy)	2-Methoxy-5-(thien-2-yl)	3	6.30
58	3-Methoxy-4-(pyrid-3-ylmethoxy)	2-Methoxy-5-(thien-2-yl)	3	6.30
59	3-Methoxy-4-(pyrid-4-ylmethoxy)	2-Methoxy-5-(thien-2-yl)	4	6.30
60	3-Methoxy-4-(4-ethoxycarbonylbenzyloxy)	2-Methoxy-5-(thien-2-yl)	4	7.08
61	3-Methoxy-4-(4-tert-butyloxycarbonylaminobenzyloxy)	2-Methoxy-5-(thien-2-yl)	> 50	8.25
62	3-Methoxy-4-(4-aminobenzyloxy)	2-Methoxy-5-(thien-2-yl)	7	6.49
63	2,4-Dimethoxy-5-(2,4-dimethoxyphenyl)	3,4,5-Trimethoxy	3	5.31
64	2-Methoxy-4-(thien-2-yl)	3,4-Difluoro	2	5.60
65	2-Methoxy-4-(3-acetylphenyl)	3,4,5-Trimethoxy	4	5.49
66	2-Methoxy-5-(thien-2-yl)	3-Fluoro-4-ethoxy	4	5.86
67	3-Methoxy-4-(4-carboxybenzyloxy)	2-Methoxy-5-(thien-2-yl)	5	6.61

(*continued on next page*)

Table 1 (*continued*)

Compd	R	R′	VCAM-1 IC_{50} (μM)	ClogP
68	3,5-Dimethoxy-4-carboxymethoxy	2-Methoxy-5-(thien-2-yl)	1	5.96
69	3,5-Dimethoxy-4-carboxymethoxy	3,4-Dimethoxy-5-(thien-2-yl)	1	4.81
70	4-(2-Carboxyisopropoxy)	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	6	6.72
71	4-Carboxymethylthio	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	1	6.66
72	Hydrogen	2-Carboxymethoxy-4-methoxy-5-(benzo[*b*]thien-2-yl)	1	5.94
73	4-Trifluoromethyl	2-(Carboxyisopropoxy)-4-methoxy-5-(thien-2-yl)	4	6.58
74	3,5-Dimethoxy-4-hydroxy	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	1	6.20
75	3-Methoxy-4-hydroxy	2-Methoxy-5-(thien-2-yl)	7	5.03
76	3,4-(Dihydroxymethylmethylenedioxy)	3,4-Dimethoxy-5-(thien-2-yl)	1	3.78
77	4-(D-Glucopyranosylamino)	2,4-Dimethoxy-5-(benzo[*b*]thien-2-yl)	17	3.69
78	3,4,5-Trimethoxy	2-Methoxy-5-bromo	1	4.38
79	3,4,5-Trimethoxy	2,4-Dimethoxy-5-bromo	2	4.39
80	 A = H (**80**) or MeO (**81**)		>50	4.31
81			>50	4.30

methoxy group is introduced to ring A the potency increases (compound **4**, $IC_{50} = 14$ μM). A second methoxy group on ring A brings the IC_{50} value to 8 μM (compound **5**) and a third one improves the potency slightly further (compound **6**, $IC_{50} = 6$ μM). This methoxy effect was observed in the beginning of our foray into the chalcone series.

Compounds **7** and **8** show different inhibitory effects on VCAM-1 expression, although both have the same number of methoxy groups in the molecule; compound **7**, with two methoxy groups on ring A, is more potent than **8**, with one methoxy group on ring A ($IC_{50} = 6$ and 15 μM, respectively). Comparison of another pair, **9** ($IC_{50} = 7$ μM) and **10** ($IC_{50} = 29$ μM), further shows that methoxy substitution on ring A is more important than on ring B for the inhibitory effect on VCAM-1 expression. As shown above, however, when there are already two methoxy groups on ring A, the contribution of a third one on ring A in boosting potency of the compound is limited (compare **5**, $IC_{50} = 8$ μM, with **6**, $IC_{50} = 6$ μM). Therefore, it makes almost no difference on potency whether an additional methoxy group is introduced to ring A or B when there are already two methoxy groups on ring A. For example, introduction of a methoxy group to ring A of **5** generates compound **6** and to ring B generates **7**; compounds **6** and **7** are equipotent ($IC_{50} = 6$ μM).

Phenol **11** shows poor potency on the inhibition of VCAM-1 expression ($IC_{50} = 47$ μM). However, when the phenol group of **11** is methylated, the corresponding methyl ether (**12**) exhibits better potency ($IC_{50} = 9$ μM). This outcome is presumably due to an increase in lipophilicity in **12**. Comparison of another pair, **13** ($IC_{50} > 50$ μM) and **14** ($IC_{50} = 17$ μM), shows a similar trend.

Compound **15** exhibits weak inhibition for VCAM-1 expression with an IC_{50} value of 25 μM. When a thienyl group is introduced to the *meta*-position of ring B of this compound the potency is increased dramatically (**16**, $IC_{50} = 4$ μM). On the other hand, however, compound **6** has an IC_{50} value of 6 μM; the introduction of a thienyl group to the *para*-position of ring B does not change the potency (**17**, $IC_{50} = 6$ μM). The introduction of a thienyl group to the *para*-position of ring B of **5** even brings the IC_{50} value from 8 to 12 μM (compound **18**). As further discussed below, these findings directed the design of novel, more potent compounds in this project. We decided, from this point on to put a heteroaryl group on the *meta*-position and avoid large substitution on the *para*-position of ring B.

Due to the *dramatic meta*-thienyl effect on ring B, compound **19**, without any substitution on ring A, is already a relatively potent inhibitor of VCAM-1 expression ($IC_{50} = 5$ μM). Therefore, introduction of methoxy group(s) to ring A of **19** does not increase the potency by much (**20** through **26**, $IC_{50} = 2$-3 μM). This is also true when the thienyl group is replaced by a benzothienyl group (compare **27**, $IC_{50} = 3$ μM, with **28**, $IC_{50} = 2$ μM, and **29**, $IC_{50} = 2$ μM).

The substitution patterns on ring A of **7** and **9** are different, but yet the two compounds show similar potencies on VCAM-1 expression. Compounds **22**–**25** are regioisomers each with two methoxy groups on ring A and all have roughly the same potency on inhibition of VCAM-1 expression. Compounds **20** and **26** are regioisomers each with three methoxy groups on ring A and show the same potency. These data suggest that, in contrast to ring B, substitution patterns on ring A do not affect the efficacy of compounds as dramatically.

Substitutions on the accompanying thienyl ring are also accommodated. Comparison of **30** or **31** with **24** reveals that the introduction of a methyl group to the thienyl group does not affect potency. This can also be confirmed by comparison of **32** or **33** with **20**. An acetyl group on the thienyl group is also tolerated (**34**).

Furthermore, when the thienyl group is replaced by a benzothienyl group the potency remains or increases slightly (compare **27** with **21**, **29** with **24**, or **28** with **20**). These results further suggest that there might be a large pocket for the *meta*-position of ring B at the binding site of a yet unknown biological target. And, as discussed above (**15** and **16**), occupation of this pocket by the ligand helps increase its potency.

Compound **29** has an $IC_{50} = 2$ μM. When a methoxy group is introduced to the *para*-position of ring B (compound **35**), the potency is reduced 5-fold to $IC_{50} = 11$ μM. Comparison of **28** with **36** also indicates that a methoxy group at the *para*-position of ring B lowers potency when there is a benzothienyl at the *meta*-position. The same trend does not exist with the smaller thienyl in the *meta*-position (compare **37** with **38**). This could mean that the binding site of ring B is sterically constrained. When there is a (smaller) thienyl substitution at the *meta*-position, a methoxy group at the *para*-position can be tolerated; however, when there is already a (larger) benzothienyl at the *meta*-position occupying the site, there is no room for a methoxy group at the *para*-position.

When a methoxy group on ring A of **39** is replaced by a benzyloxy group (**40**) the potency is completely lost. Replacement of the methoxy groups on ring A of **41** with ethoxy groups (**42**) also dramatically decreases the potency. Even when the *para*-methoxy on ring A of **36** is replaced with a small cyclopropylmethoxy group (**43**) the potency is completely lost. On the other hand, when the two methoxy groups on ring A of **24**, **30**, or **31** are replaced with a methylene dioxy group, respectively, the potency is not affected by much (**44**, **45**, or **46**). Taken together, it would seem that only small substitutions can be tolerated on ring A. However, further investigation revealed that many other compounds with an ether linkage longer than a methoxy group (**47**–**56**) are potent inhibitors of VCAM-1 expression. From **41** to **42**, there is significant increase in calculated logP value (from 5.96 to 4.39), while there is not much change from, e.g., **24** ($IC_{50} = 3$ μM) to **44** ($IC_{50} = 4$ μM). In fact, all the calculated logP values of compounds **47**–**56** are lower than that of compound **40** (Table 1). These data suggest that large substituents can be tolerated on ring A, but the lipophilicity needs to be in the right range for the compounds to be potent for the inhibition of VCAM-1 expression.

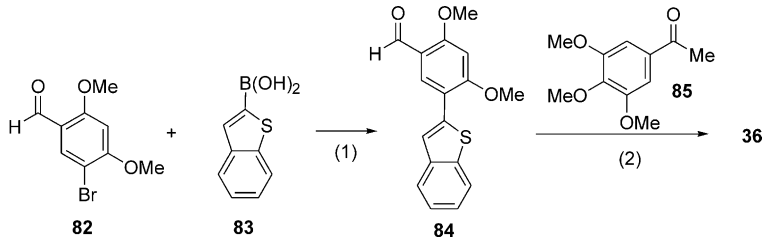
Compounds **57**, **58**, and **59** all have a pyridylmethoxy substitution on ring A. Although they all have higher ClogP values than compound **40** (Table 1), these are potent inhibitors of VCAM-1 expression. Therefore, different sub-series of compounds have different lipophilicity requirements for the compounds to be potent. Similarly, when a carbonyl is introduced to the molecule, the requirement for ClogP is changed. Compound **60** has a high ClogP value (7.08) but still is relatively potent. However, compound **61**, with a ClogP of 8.25, is too lipophilic to be potent. When the Boc group is removed from **61**, the ClogP drops to 6.49 and the compound (**62**) shows moderate potency. An aryl group directly attached or fused to ring A can also be tolerated (**63**–**66**).

Having achieved satisfactory inhibitory potency on VCAM-1 expression with some of the compounds discussed above, we turned our attention then to the introduction of solubility to them. Since many of the compounds contained methyl ether substitution(s), various carboxylic residues were attached to the chalcone skeleton through an ether linkage. Compound **67** with a benzoic acid-containing side chain on ring A shows modest potency ($IC_{50} = 5$ μM). A glycolic acid residue on ring A gives better potency (**68**, **69**, $IC_{50} = 1$ μM, respectively). Compound **70** ($IC_{50} = 6$ μM) with an isobutyric acid-containing side chain is less potent, likely due to the *para*-methoxy on ring B, as discussed above. Thioether linkage is also tolerated (**71**, $IC_{50} = 1$ μM). A glycolic group can also be introduced to the *ortho*-position of ring B (**72** and **73**, $IC_{50} = 1$, and 4 μM, respectively). Hydroxy groups were also considered for improving solubility (**74**–**77**).

Although it has been observed with many compounds reported herein and elsewhere,[11] dependence of potency on lipophilicity is secondary to structural requirements. For example, **7** and **8** are regioisomers and have the same calculated log P value, but have different effects on VCAM-1 expression (Table 1). In other words, the lipophilicity-potency relationship is only meaningful within structurally similar sub-series of compounds. Any further extrapolation would only generate confusion. When the methyl group of the *para*-methoxy on ring A of **36** ($IC_{50} = 5$ μM) is removed, the potency increases (**74**, $IC_{50} = 1$ μM) presumably due to the decrease in lipophilicity. However, the same exercise on **24** ($IC_{50} = 3$ μM) results in a decrease in potency (**75**, $IC_{50} = 7$ μM). Here, **24** already has the right lipophilicity and the removal of the methyl group moves the lipophilicity of the compound out of the optimal range. Diol **76** ($IC_{50} = 1$ μM) is more potent than tetraol **77** ($IC_{50} = 17$ μM). Although both have similar ClogP values (Table 1), the former is in the optimal range and the latter is not in their respective series.

When the C–C double bond of **78** ($IC_{50} = 1$ μM) or **79** ($IC_{50} = 2$ μM) is reduced, the potency is completely lost (**80**, **81**, $IC_{50} > 50$ μM, respectively). This indicates that the α,β-unsaturated carbonyl in the compounds reported herein is probably (part of) the pharmacophore.

Except for a few commercially available ones, all the compounds reported herein have been prepared through an aldol condensation of a ring A-containing ketone and a ring B-containing aldehyde. Heteroaryl substitutions on either ring are introduced through a cross-coupling reaction such as the Suzuki reaction. As shown in Scheme 1, 5-bromo-2,4-dimethoxybenzaldehyde (**82**) was coupled with benzo[*b*]thiophene-2-boronic acid (**83**) in the presence of tetrakis(triphenylphosphine)palladium(0) to give 5-(benzo[*b*]thien-2-yl)-2,4-dimethoxybenzaldehyde (**84**) in 93% yield, which was in turn condensed with 3′,4′,5′-trimethoxyacetophenone (**85**) under a basic condition to give compound **36** in 88% yield.



Scheme 1. Reagents and conditions: (1) Tetrakis(triphenylphosphine)palladium(0), sodium carbonate solution (2 M), ethylene glycol dimethyl ether (DME), reflux; (2) Sodium hydroxide solution (50%), ethanol.

In summary, a series of novel, heteroaryl-substituted chalcone derivatives has been discovered as potent inhibitors of inducible VCAM-1 expression. Thienyl or benzothienyl substitution at the *meta*-position of ring B helps boost potency while large substitution at the *para*-position on ring B is detrimental. Various substitutions are tolerated on ring A. A lipophilicity–potency relationship has been observed in several sub-series of compounds. Current SAR efforts are focused on bringing favorable pharmacologic and pharmacokinetic properties to some of the lead compounds reported herein for asthma and rheumatoid arthritis drug discovery, and the results will be reported in due course.

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