

New conformationally constrained LFA-1 antagonists

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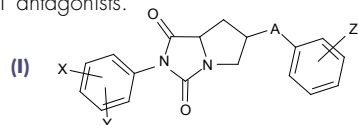
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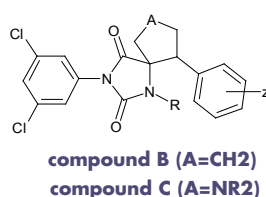
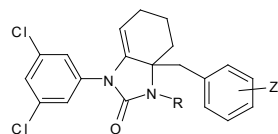
LFA-1 (Leukocyte Function Associated Antigen-1), is a member of the $\beta 2$ -integrin family and is expressed on all leukocytes. The LFA-1/ICAM interaction promotes tight adhesion between activated leukocytes and the endothelium, as well as between T cells and antigen-presenting cells.

Evidence from both animal models and clinical trials provides support for LFA-1 as a target in several different immune or inflammatory diseases¹. Efalizumab (Raptiva[®]) a fully humanized LFA-1 antibody was approved by the FDA in 2003 in use for moderate-to-severe psoriasis.

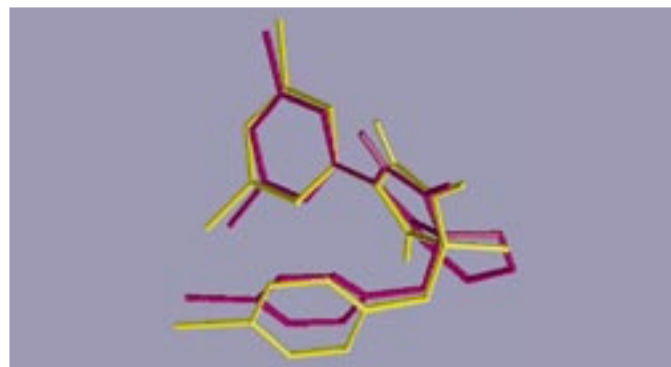
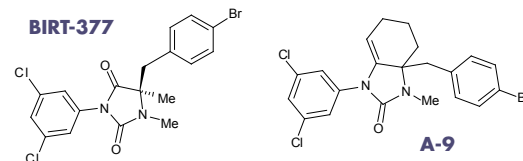
As discussed in the preceding poster, a series of conformationally constrained bicyclic analogs were prepared as LFA-1 antagonists. Of these, the bicyclic[5.5]hydantoin scaffold (I) that adapts a "half-open book" conformation led to a series of potent LFA-1 antagonists.



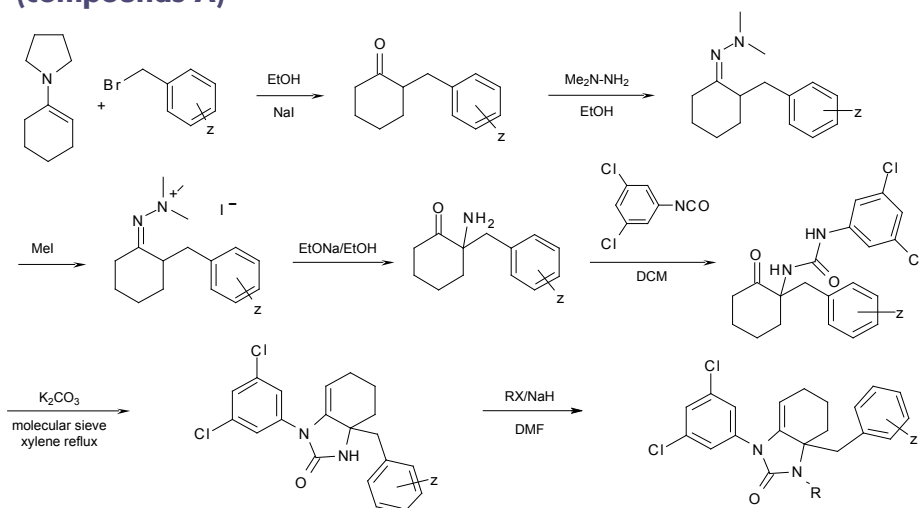
In order to further explore the effect of conformational rigidity on the generation of potent LFA-1 antagonists, tetra-hydrobenzimidazolones of the type (A) and spirocyclic hydantoin of the type (B and C) were designed and synthesized. This poster will focus on the synthesis and SAR of compounds of type A.



Overlay of this core with BIRT-377 showed that the desired conformation could be attained employing bicyclic systems of type A.



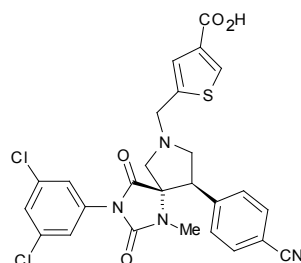
Synthetic sequence to prepare tetrahydrobenzimidazolones (compounds A)



Spirohydantoin (compounds B and C)

Extensive work on the spirocyclic hydantoin series (compounds of type B, C) led us to the identification of BMS-587101. The synthesis and SAR of spirocyclic hydantoin will be presented elsewhere.

(Presented in part at the 231st National meeting of the American Chemical Society; Atlanta, GA, March 26-30, 2006; Abstracts of papers, T.G. M. Dhar et al.).



SAR of tetrahydrobenzimidazolones

Cpd.	Z	R	H1Hela/ HSB IC ₅₀ (nM)	logD n-octanol (pH 7.4)	Solubility (μ M) (pH 7.4)
A-1	4-CN	H	17,5	4,48	8,87
A-2	4-CN	Me	6,5	4,54	2,65
A-3	4-CN	Et	25,5	5,09	1,95
A-4	4-CN	Ac	45,5	>4,8	0,17
A-5	4-CN	CH ₂ COOEt	74	4,3	<1
A-6	4-CN	CH ₂ COOH	110	0,96	183,9
A-7	4-CN	(CH ₂) ₅ COOH	16,5	2,53	186,1
A-8	4-Br	H	56	>4,8	<1
A-9	4-Br	Me	34	>5	<1
A-10	4-Br	Ac	134	>5,1	0,40
A-11	4-Br	CH ₂ COOEt	140	>4,6	0,25
A-12	4-{2-pyrimidinyl}	Me	5,9	4,17	<1

Modulation of the substitution on the benzyl ring showed that large group with heterocycles (pyrimidine) are tolerated, and that the physicochemical properties can be optimized by modifying the substituent on the N-1 nitrogen.

The *in vitro* potency of compounds of Type A in the adhesion assay (HeLa/HSB or HUVEC/T cell) is comparable to BMS-587101

Compound	H1Hela/HSB IC ₅₀ (nM)	HUVEC/TCells IC ₅₀ (nM)
A-8	56	82
A-9	34	21
A-2	6.5	Not determined
BMS-587101	25 ± 1	20 ± 1

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References

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- Anderson ME and Siahhan TJ, *Peptides* 2003;24(3):487-501
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CONCLUSIONS

- Compounds of type A are potent LFA-1 antagonists. As was seen in other series, the 3,5-dichlorophenyl moiety and the N-methyl group on the hydantoin ring is optimum. Replacement of the amide carbonyl of BIRT-377 with a exocyclic alkene did not significantly alter the *in vitro* potency of this series of LFA-1 antagonists.
- Extensive work on the spirocyclic hydantoin series (compounds of type B, C) led us to the identification of the clinical compound BMS-587101.