

# SAR around small molecules as LFA-1 antagonists

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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 diseases<sup>1</sup>. Efalizumab (Raptiva®) was approved in 2003 in US for moderate-to-severe psoriasis. Because of the therapeutic potential of the inhibition of LFA-1-mediated immune response, there has been an intense effort to identify orally available, small molecule inhibitors of this interaction<sup>2</sup> (Fig. 1).

Last-Barney et al.<sup>3</sup> have postulated a binding model of BIRT-377 bound to LFA-1 wherein the inhibitor adopts a conformation orienting the 3,5-dichlorophenyl and the p-bromophenyl aromatic rings in a favorable edge-to-face interaction. The two compounds (I) and (II)<sup>4</sup> are constrained analogues of BIRT-377.

To study the influence of this conformation on the potency of the compounds, other conformationally constrained analogues were synthesized, employing rigid bicyclic systems (Fig. 2).

Fig-1: Analogs from several recently disclosed, structurally diverse chemical series

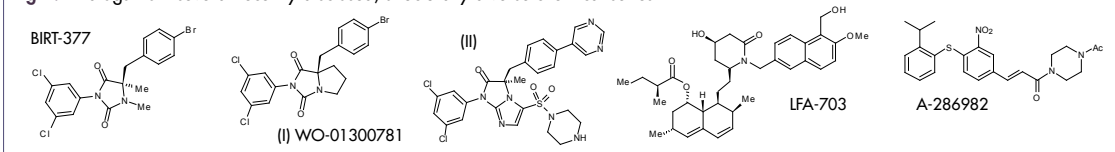
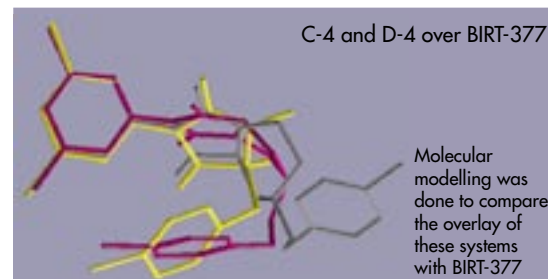
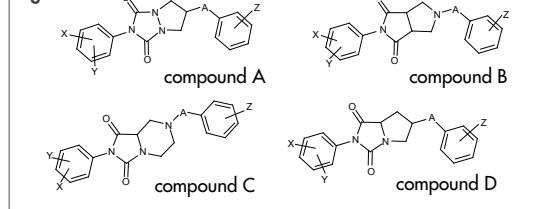
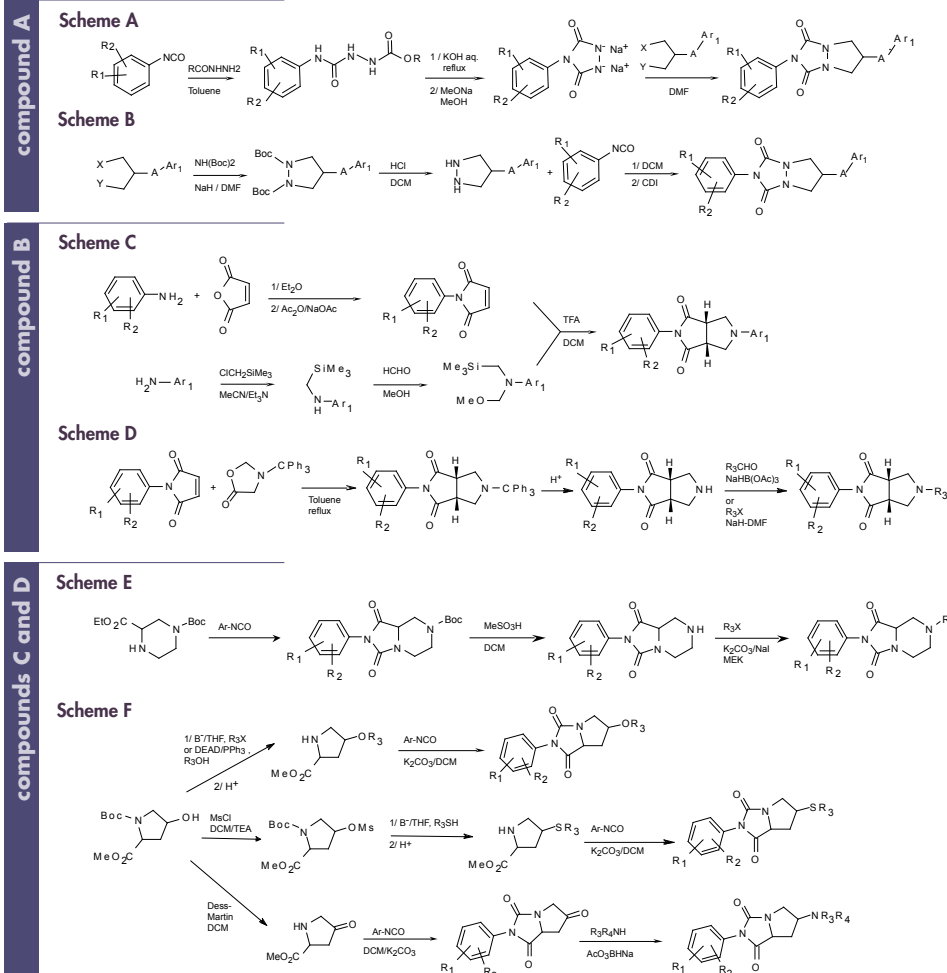


Fig-2



## Various schemes of synthesis of compounds A, B, C and D



## In vitro activity of bicyclic compounds

Cpd. type	R1, R2	A	Ar1	R3	H1Hela/HSB IC <sub>50</sub> or % inhib@1 $\mu$ m
A-1	3,5-Cl	O-CH <sub>2</sub>	4-Br Phenyl		193 nM
A-2	3,5-Cl	O-CO	4-Br Phenyl		798 nM
A-3	3,5-Cl	CH <sub>2</sub> -CH <sub>2</sub>	4-Br Phenyl		25%
B-1	3,5-Cl	-	-	Benzyl	inactive
B-2	3,5-Cl	-	-	4-Cl Phenethyl	947 nM
B-3	3,5-Cl	-	-	4-MeO-Benzyl	16%
B-4	3,5-Cl	-	-	4-Br Benzyl	635 nM
B-5	3,5-Cl	-	-		1500 nM
B-6	3,5-Cl	-	4-CN Phenyl		inactive
C-1	3,5-Cl	-	-	H	12%
C-2	3,5-Cl	-	-	4-Br-Benzyl	5%
C-3	3,5-Cl	-	-		5%
C-4	3,5-Cl	-	-	4-Br Phenethyl	41%

Cpd. type	R1, R2	A	R3	Stereo	H1Hela/HSB IC <sub>50</sub> or % inhib@1 $\mu$ m
D-1	3,5-Cl	O		7aS,5S	28%
D-2	3,5-Cl	O	4-Br-Phenyl	7aS,5S	480 nM
D-3	3,5-Cl	O	4-Br-Benzyl	7aS,5R	935 nM
D-4	3,5-Cl	O	4-Br-Benzyl	7aS,5S	85 nM
D-5	3,5-Cl	O	4-Br-Benzyl	7aR,5R	275 nM
D-6	3,5-Cl	O	3-Br-Benzyl	7aS,5S	755 nM
D-7	3,5-Cl	O	4-CN-Benzyl	7aS,5S	270 nM
D-8	3,5-Cl	O	4-Cl-Benzyl	7aS,5R	620 nM
D-9	3,5-Cl	O	4-[2-CNPh]-Benzyl	7aS,5S	28%
D-10	3,5-Cl	S	4-Br-Benzyl	7aS,5S	290 nM
D-11	3,5-Cl	NH	4-CN-Benzyl	7aS,5S	175 nM
D-12	3,5-Cl	NH	4-CN-Benzyl	7aS,5R	11%
D-13	3,5-Cl	NH	4-Br Phenethyl	7aS,5S	20%
D-14	3,5-Cl	NH	4-Br Phenethyl	7aS,5R	5%
D-15	3,5-Cl	NMe	4-Br-Benzyl	7aS,5S	175 nM
D-16	3,5-Cl	NEt	4-CN-Benzyl	7aS,5S	730 nM

## CONCLUSIONS

A series of conformationally constrained bicyclic analogs were prepared as LFA-1 antagonists. Of these, the bicyclic[5.5]hydantoin scaffold that adapts a "half-open" book conformation led to a series potent LFA-1 antagonists. Optimization of the length and nature of the linker, stereochemistry at the 5 and 7a positions of the hydantoin scaffold, led to (D-4) as a potent inhibitor of the LFA-1/ICAM interaction.

## References

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