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Dual antagonists of $\alpha 5\beta 1$ / $\alpha v\beta 1$ integrin for airway hyperresponsiveness

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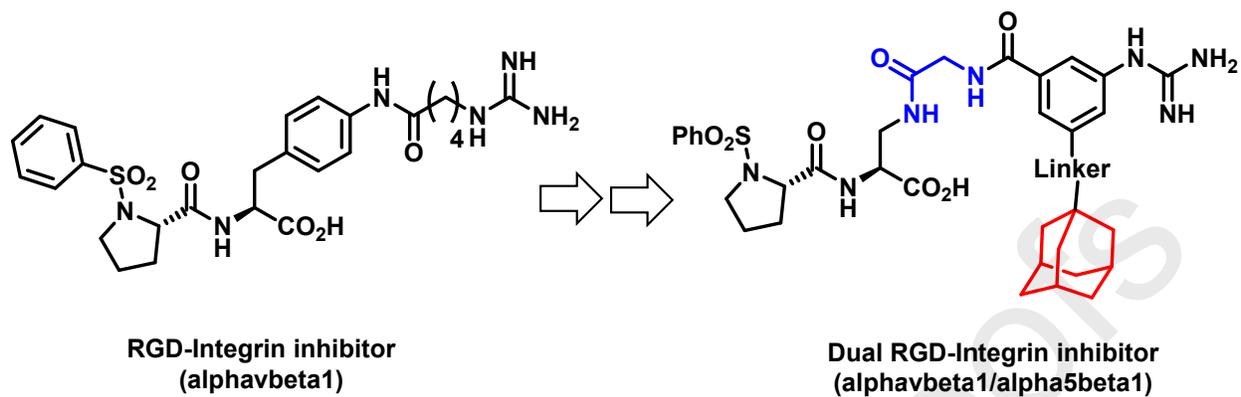
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Abstract

Inhibition of integrin $\alpha 5 \beta 1$ emerges as a novel therapeutic option to block transmission of contractile forces during asthma attack. We designed and synthesized novel inhibitors of integrin $\alpha 5 \beta 1$ by backbone replacement of known $\alpha \beta$ integrin inhibitors. These integrin $\alpha 5 \beta 1$ inhibitors also retain the nanomolar potency against $\alpha \beta$ integrin, which shows promise for developing dual integrin $\alpha 5 \beta 1 / \alpha \beta$ inhibitor. Introduction of hydrophobic adamantane group significantly boosted the potency as well as selectivity over integrin $\alpha \beta 3$. We also demonstrated one of the inhibitors (**11**) reduced airway hyperresponsiveness in Ex vivo mouse tracheal ring assay. Results from this study will help guide further development of integrin $\alpha 5 \beta 1$ inhibitors as potential novel asthma therapeutics.

Keywords: Integrin $\alpha 5 \beta 1$, Integrin $\alpha \beta 1$, Integrin inhibitor, RGD integrin, asthma

Graphical Abstract



Airway hyperresponsiveness (AHR) - excessive narrowing of airway in response to stimulus is the hallmark feature of asthma.¹ Most patients with asthma can benefit from anti-inflammatory agents and inhibitors of smooth muscle contraction to reduce AHR.² However, severe asthma still remains difficult to control and affects up to 10% of patients with asthma.³ Although biologics targeting disease-relevant cytokines in the inflammation process have recently emerged as add-on therapies, this approach is hindered by targeting only a limited subset of asthma patients (T₂-high) as well as imposing a significant economic burden on the individual, family, and society.⁴⁻⁵ Thus, there remains an urgent need to accelerate a novel therapeutic approaches to treat severe asthma.

Our groups have previously shown that reduction of AHR could be achieved by pharmacological inhibition of integrins.⁶ Integrins are heterodimeric transmembrane proteins consisting of alpha and beta subunits that are involved in several critical cell processes including anchorage, migration, remodeling, and signaling.⁷ They are the principal receptors used by cells to link the actin cytoskeleton with adjacent extracellular matrix (ECM) proteins, including fibronectin and collagens.⁸ In airway tissue, this integrin-ECM interaction plays a crucial role in force transmission and airway smooth muscle (ASM) cell proliferation ultimately leading to exaggerated airway narrowing. We demonstrated that inhibition of the $\alpha 5\beta 1$ integrin binding to fibronectin resulted in marked decrease of AHR in an ovalbumin-challenged mouse model of asthma. Our work also revealed that integrin inhibition has an additive effect when combined with currently available β -adrenergic agonists, which suggested the potential use of integrin inhibitors as adjuvant therapy to standard bronchodilators. However, the tool peptide

(ATN-161)⁹ used in our study suffered from low potency and exhibited low plasma stability. For this reason, we sought to identify novel small molecule inhibitors against the $\alpha 5\beta 1$ integrin.

The $\alpha 5\beta 1$ integrin has been previously proposed as an attractive therapeutic target in cancer therapy¹⁰ due to its effects on inhibiting angiogenesis, and there are several small molecule inhibitors against the $\alpha 5\beta 1$ integrin described in the literature.¹¹⁻¹⁴ In the initial activity profiling of these known inhibitors (**1-3**), we found they displayed poor selectivity against the $\alpha \nu\beta 3$ integrin and micromolar potency for $\alpha 5\beta 1$ integrin in our cell adhesion assay¹⁵. We next turned our attention to our $\alpha \nu\beta 1$ integrin inhibitor series¹⁶ and backbone replacement from phenylalanine with 2,3-diaminopropionic acid (DAP) was shown to influence the selectivity toward $\alpha 5\beta 1$ significantly (Figure 1). For example, **5** (DAP analogs of the selective $\alpha \nu\beta 1$ integrin inhibitor **4**) exhibited sub-micromolar IC_{50} against $\alpha 5\beta 1$ integrin while maintaining sub-nanomolar potency against $\alpha \nu\beta 1$ integrin in the cell adhesion assay. Moreover, **5** still displayed excellent selectivity against $\alpha \nu\beta 3$ integrin, which encouraged us to further investigate the DAP scaffold towards dual $\alpha 5\beta 1/\alpha \nu\beta 1$ integrin inhibitors. From dual mode of inhibition, it was anticipated that $\alpha \nu\beta 1$ integrin inhibition could add benefit to AHR by reducing cytokine release in ASM.¹⁷

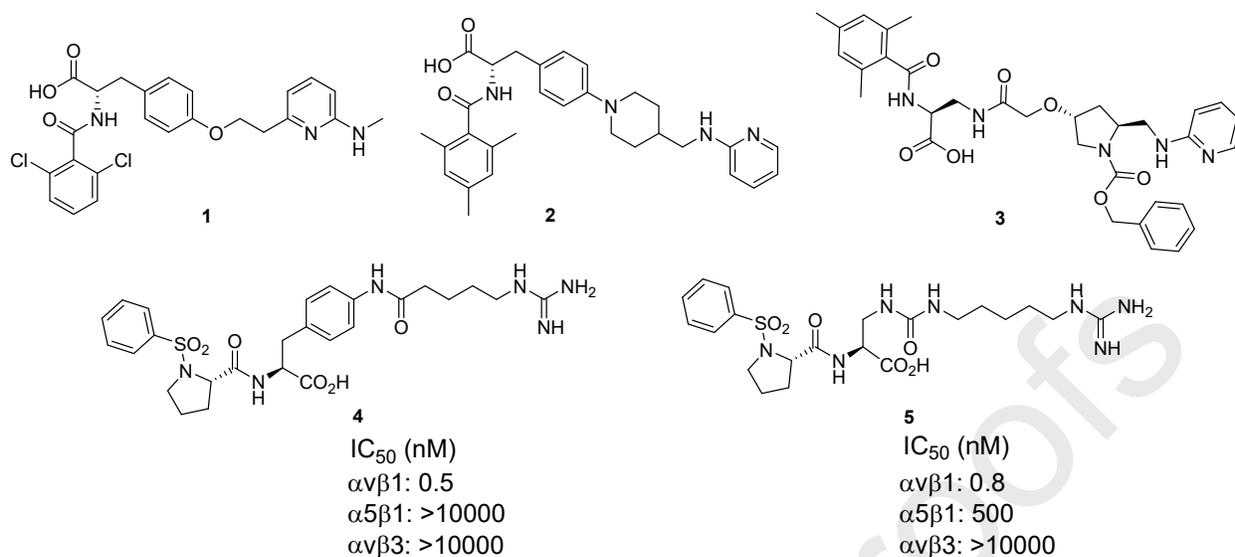
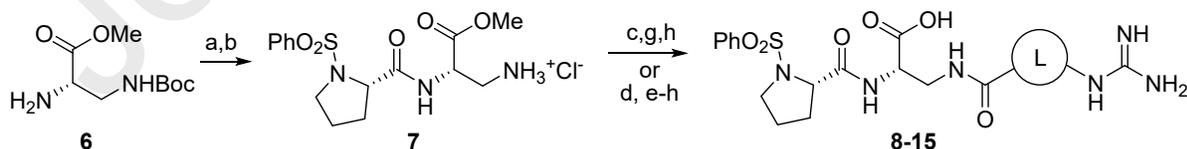


Figure 1. Structures of $\alpha 5\beta 1$ integrin inhibitors **1-3** and $\alpha v\beta 1$ integrin inhibitors **4-5**

For design of a dual inhibitor, we synthesized a handful of analogs of **5** using conventional chemistry to explore the linker effect in DAP scaffold (**Scheme 1**). Thus, commercially available Boc-protected L-2,3-diaminopropionic acid methyl ester **6** was coupled with benzenesulfonyl-L-proline to provide amine **7** after deprotection of Boc protecting group under acidic condition. Reaction of the common intermediate amine **7** with Boc-protected ω -guanidino *p*-nitrophenylchloro carbamate yielded the urea series (**8-10**) after deprotection and hydrolysis. Similarly, coupling of amine **7** with N-Boc-protected carboxylic acids provided amides (**11-15**) after TFA removal of Boc group followed by mild hydrolysis with LiOH and HPLC purification.

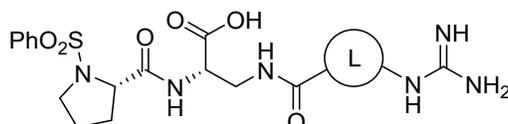


Scheme 1 Synthesis of **8-15** *Reagents and Conditions*: a) N-benzenesulfonyl-L-proline, HCTU, DIPEA, b) 4M HCl in dioxane (70% for the two steps) c) RNHCO₂PhNO₂, DIPEA or R'CO₂H, HCTU, DIPEA, d) Boc-

Gly, HCTU, DIPEA e) 4M HCl in dioxane f) R''CO₂H, HCTU, DIPEA g) TFA, DCM h) LiOH, THF-H₂O. See the Supplementary data for details of syntheses.

8-15 were then tested against three integrins - $\alpha 5\beta 1$, $\alpha \nu\beta 1$, and $\alpha \nu\beta 3$ for their potency and selectivity (Table 1). Among the compounds with simple alkyl linkers between DAP and the terminal phenylguanidine moiety, higher potency was observed for 6-atom linker (compound **5**). Increase of linker rigidity by introduction of phenyl ring further boosted the potency (compound **11-15**) toward $\alpha 5\beta 1$ integrin. While amide linker for DAP (compound **10**) is preferred for $\alpha 5\beta 1$ integrin inhibition, urea linker (compound **8**) showed much higher potency against $\alpha \nu\beta 1$ integrin. Thus, presence of additional hydrogen bond donor in urea linker could fine tune the selectivity between $\alpha 5\beta 1$ and $\alpha \nu\beta 1$ integrin. On the other hand, a huge increase of potency against $\alpha 5\beta 1$ integrin was observed in rigid *m*-phenyl guanidine compound **11** and **12**. Glycine-linked compound **11** is particularly promising for development of a dual inhibitor as it exhibits comparable potency for both $\alpha 5\beta 1$ and $\alpha \nu\beta 1$ integrin. It is also worth mentioning aza-glycine linker compound **12** favors $\alpha 5\beta 1$ integrin as suggested by previous works.¹¹⁻¹² While the potency was improved more than 10-fold in compound **11** or **12**, selectivity over $\alpha \nu\beta 3$ integrin was not still satisfactory in either **11** or **12**. Surprisingly, a dramatic increase of selectivity over $\alpha \nu\beta 3$ integrin was achieved by substituted *m*-phenylguanidine series (compound **13-15**). We chose an amide linker for phenyl ring substitution due to its facile synthesis and introduced additional alkyl chain to increase lipophilicity. Either hydrophobic alkyl amide substitution (**13**) or positively charged alkyl amide substitution (**14**) boosts the selectivity but did not increase the potency against $\alpha 5\beta 1$ integrin. The best compound was **15** containing 1-adamantyl group to mask the amine. Compound **15** not only showed great selectivity over $\alpha \nu\beta 3$ integrin but also exhibited excellent

nanomolar potency for $\alpha 5\beta 1$ and sub-nanomolar potency for $\alpha v\beta 1$ integrin. Since all the amide compounds **13-15** shared the same feature in amide linker on the phenyl ring, we speculated that adamantane at the terminal position played a key role in improvement of potency.

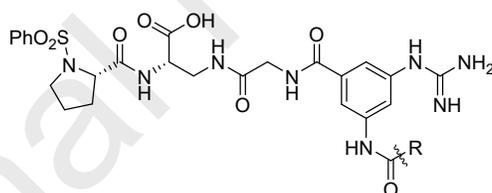


ID	L	IC ₅₀ (nM) ± SD		
		$\alpha 5\beta 1$	$\alpha v\beta 1$	$\alpha v\beta 3$
5		501±90	0.8±0.2	6,800±500
8		9,700±900	4±0.8	>100,000
9		900±150	0.9±0.2	15,000±930
10		830±20	316±80	10,000±790
11		40±18	32±8	1,100±200
12		50±20	158±20	6,500±900
13		110±24	Not tested	16,800±400
14		32±6	Not tested	56,000±2,000
15		2.6±0.9	0.8±0.1	8,800±15

Table 1. Cell adhesion assay for $\alpha 5\beta 1$ integrin inhibitors The measurement of cell adhesion was performed according to the published procedure.¹⁵ SW480 plated on fibronectin (0.3 $\mu\text{g/ml}$) was used for $\alpha 5\beta 1$ assay and CHO αv adhering to fibronectin (0.3 $\mu\text{g/ml}$) was used for $\alpha v\beta 1$. For

$\alpha\beta 3$, SW480 transfected with human $\beta 3$ adhering to fibrinogen (1 $\mu\text{g/ml}$) was used. Data represent means \pm S.D.; $n = 3$ or higher

In order to test if there is a specific binding site for adamantane in $\alpha 5\beta 1$ integrin, we synthesized a series of adamantane analogs with varied length of alkyl chain and tested them in solid-phase binding assay (**Table 2**). A solid-phase binding assay was used to compare the binding affinity to different integrins without the influence of cellular factors affecting the cell adhesion assay. All the synthesized adamantane compounds **15-19** showed single-digit nanomolar IC_{50} s against both $\alpha 5\beta 1$ and $\alpha \nu \beta 1$ integrin. The linker length did not influence the potency and it was speculated that adamantane moiety induce non-specific binding. Furthermore, we also ruled out any specific hydrogen bonding patterns since reverse amide **18** or amide **15** showed comparable potency. Interestingly, the selectivity appears to decrease among $\alpha \nu$ integrins as the linker length increased.



ID	R	IC_{50} (nM) \pm SD						
		$\alpha 5\beta 1$	$\alpha \nu \beta 1$	$\alpha \nu \beta 3$	$\alpha \nu \beta 5$	$\alpha \nu \beta 6$	$\alpha \nu \beta 8$	$\alpha 4\beta 1$
15		0.8 \pm 0.2	0.14 \pm 0.01	>10000	3002 \pm 1240	2762 \pm 84	>10000	105 \pm 12
16		1.6 \pm 0.1	< 0.1	>10000	>10000	>10000	>10000	136 \pm 47
17		1.4 \pm 0.1	< 0.1	>10000	>10000	>10000	>10000	100 \pm 30
18		1.0 \pm 0.1	0.3 \pm 0.2	>10000	980 \pm 320	>10000	>10000	161 \pm 32
19		0.7 \pm 0.3	< 0.1	>10000	320 \pm 1.8	1867 \pm 56	6832 \pm 470	182 \pm 44

Table 2. Solid phase binding assay of adamantane analogs 15-19. See the Supplementary data for details. Data represent means \pm S.D.; $n = 3$

Though we cannot exclude the possibility of integrin internalization pathway / degradation by hydrophobic adamantane for the increased potency,¹⁸⁻¹⁹ it appears that combination of alkyl chain and adamantane moiety might increase integrin binding affinity through hydrophobic interaction. Hydrophobic interaction may also explain the superior selectivity over $\alpha\beta3$ integrin. Computational docking study that showed hydrophobic moiety is not favored in $\alpha\beta3$ integrin due to the presence of multiple polar residues (Tyr, Asp) in $\alpha\beta3$ integrin (Figure 2). Further studies on the selectivity among different RGD integrins and different hydrophobic groups are currently underway in our laboratory. It is also remarkable that these adamantane-containing compounds **15-19** showed much improved selectivity (>100 fold) against $\alpha4\beta1$ integrin while our previous potent $\alpha\beta1$ inhibitor **4** demonstrated marginal selectivity.²⁰

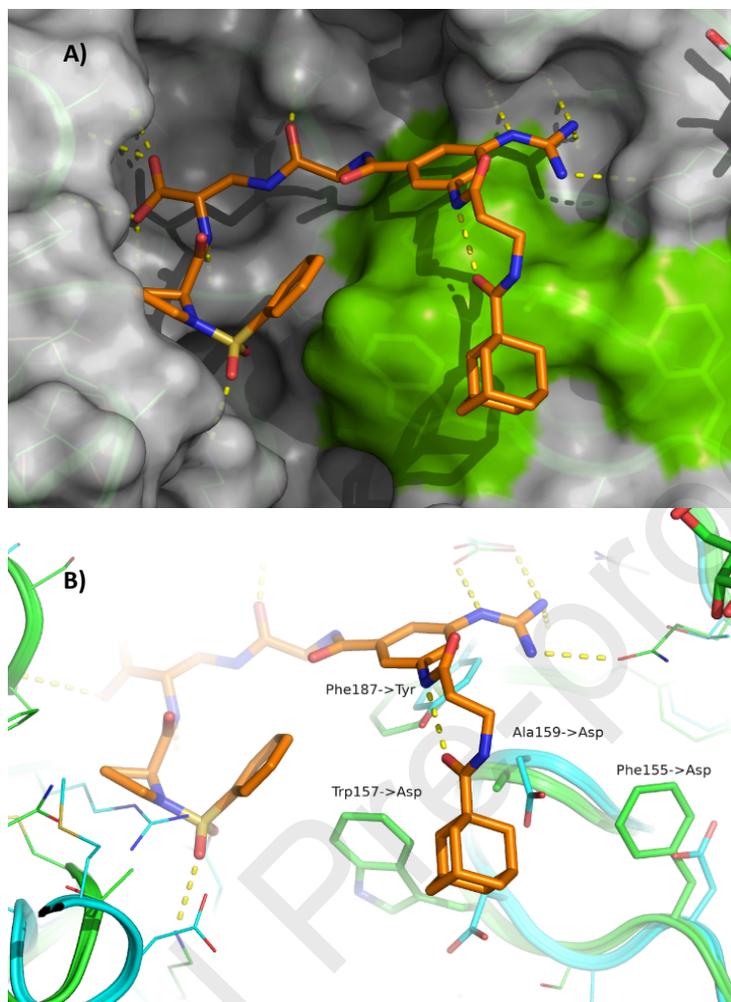


Figure 2. A model of 17 (orange) bound to $\alpha 5\beta 1$. The model is based on the published $\alpha 5\beta 1$ structure 4wk0.pdb and has been minimized using MOE/CCG. A) Connolly surface of the model. The green patch shows selected hydrophobic side chains of $\alpha 5$: Phe155, Trp157, Ala159, & Phe187. B) Same $\alpha 5\beta 1$ model (green) shown as above w/o surface. The cyan atoms represent the crystal structure of $\alpha v\beta 3$, 3ije.pdb. Four hydrophilic substitutions are highlighted in the αv chain that attenuate the affinity for the adamantine group in **17**.

With potent dual inhibitors in hands, we also tested activity of compound **11** in an ex vivo ring contraction assay (Figure **3**). This assay measures the force generated by mouse tracheal rings in response to increasing doses of the contractile agonist methacholine. The advantage to this functional assay is the ability to see the effect of integrin inhibition on a tissue level. We observed that treatment with the inhibitor caused

a dose-dependent decrease in cytokine-enhanced contraction. It is also worth noting that inhibition of contraction was observed even in the concentration lower than IC_{50} in cell adhesion assay.

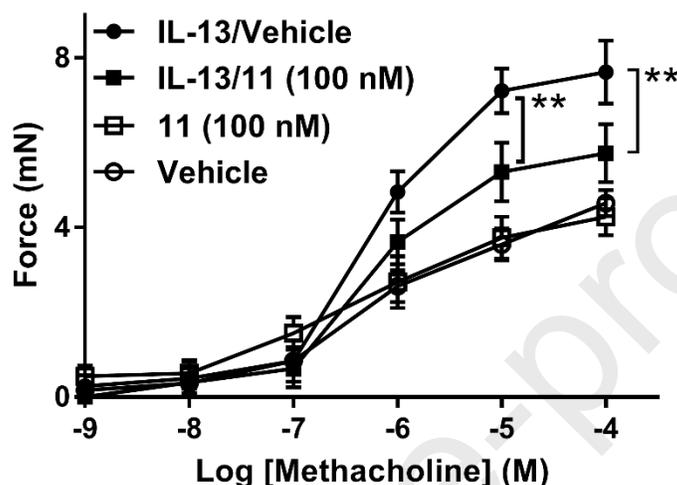


Figure 2. Mouse trachea ring contraction assay Force exerted on WT mouse tracheal rings measured after incubation for 12 h with IL-13 (100 ng/mL), then 1 h with compound 11 or vehicle with a range of concentrations of methacholine. Negative controls without IL-13 treatment are also shown. $n=3$ rings per group. $**P<0.01$, repeated measures of variance.

Unfortunately, our inhibitors showed suboptimal pharmacokinetic properties. For example, one of our promising compounds **15** showed limited solubility and poor permeability in Caco-2 cell assay (P_{app} (A-B/B-A, $\times 10^{-6}$ cm/s) = 0.37/0.27). Since airway smooth muscle resides under epithelial layer of the lung, compounds with low cell permeability are not favored for *in vivo* assessment in mouse mode. Further optimization to improve physicochemical and pharmacokinetic properties is in progress. In summary, highly potent dual inhibitors for $\alpha 5\beta 1/\alpha v\beta 1$ integrin based on DAP were identified. Excellent selectivity over $\alpha v\beta 3$ integrin by boosting $\alpha 5\beta 1$ potency was achieved using an adamantane moiety and we hope this study could provide additional insight to design better inhibitors against $\alpha 5\beta 1$ and $\alpha v\beta 1$ integrin.

Declaration of Competing Interest

W.F.D. and D. S. have an equity interest in Pliant Therapeutics which conducts work in a similar area of research. W.F.D. and D.S. are founders and scientific advisory board members and C.C. is an employee of Pliant Therapeutics.

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Supplementary data

Supplementary data to this article can be found online at xx.xxxxx.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

W.F.D. and D. S. have an equity interest in Pliant Therapeutics which conducts work in a similar area of research. W.F.D. and D.S. are founders and scientific advisory board members and C.C. is an employee of Pliant Therapeutics.

