Vitronectin Receptor –$\alpha_V\beta_3$ Integrin– Antagonists: Chemical and Structural Requirements for Activity and Selectivity

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Abstract: $\alpha_V\beta_3$ integrin, a cell surface protein, has been targeted by a variety of natural and synthetic antagonists in the search for potential cancer and osteoporosis drug candidates. This review discusses chemical and structural requirements for activity and selectivity deduced from SAR studies and draws a tentative picture of the pharmacophore.

INTRODUCTION

Integrins are a large family of heterodimeric non-covalent proteins expressed on cell surface. They consist of two different chains, namely α and β chains, which can associate to provide a wide range of so called $\alpha_x\beta_y$ receptors. Among their biological functions, their role in cell adhesion led biologists and medicinal chemists to consider these receptors as therapeutic targets. For instance, $\alpha_v\beta_3$ integrin [1], also referred to as vitronectin receptor, is responsible for cell-extracellular matrix adhesion, an event involved in angiogenesis (the construction of new blood vessels) [2-4]. The blockade of this process resulting in preventing neovascularisation is therefore a promising way to promote tumour regression. This receptor is also implicated in cell migration and bone resorption and thus in prevention and treatment of tumour metastasis [5] and osteoporosis [6,7]. Since $\alpha_v\beta_3$ integrin was found to be a key component in many physiological processes, many groups focused on the isolation or preparation of proteinic, peptidic and ultimately non-peptidic antagonists [8-10]. Latter on, it was established that inhibiting the vitronectin binding to its receptor induced beneficial effects on a mouse tumour model and on osteoporosis [11,12]. Earlier studies shed light on the role of $\alpha_{IIb}\beta_3$ integrin (another closely related β_3 containing integrin) in the fibrinogen-mediated platelet aggregation process. Rapidly, this receptor was targeted for thrombotic disorder treatment [13,14].

Most of the integrin superfamily members, including $\alpha_{IIb}\beta_3$ and $\alpha_V\beta_3$, recognize the Asp-Gly-Arg (RGD in the one letter code) tripeptidic sequence, an epitope shared by a variety of extracellular ligands including vitronectin, fibronectin, osteopontin, bone sialoprotein and fibrinogen. Because of the structural similarities within the integrin family and between their respective ligands, the selectivity issue was a major concern in the design of potential therapeutic agents (e.g. $\alpha_v\beta_3$ vs. closely related $\alpha_{IIb}\beta_3$). Tackling this problem has faced the lack of structural data for both receptors. Hence, directed structure-activity relationship studies have been reported where biological assays on fibrinogen and vitronectin receptors were furnished. RGD, mediating the binding, has received special attention and was indeed a lead structure for developing potent and selective $\alpha_v\beta_3$ antagonists.

Identification of snake venom proteins [15-19] or monoclonal antibodies [4,20,21], preluded the preparation of cyclic peptides, pseudo peptides and non peptidic molecules. Peptidic antagonists featuring the RGD sequence first emerged, exhibiting nanomolar *in vitro* activities towards a series of integrins. The selectivity for $\alpha_v\beta_3$ versus $\alpha_{IIb}\beta_3$ was related to the β or γ-turn adopted and the length between crucial groups [22,23]. Latter on, the need for drug-like molecules has prompted medicinal chemists to devise non-peptidic antagonists. Indeed lower molecular weights and higher bioavailability would be more suited for drug development. These investigations culminated in the identification of numerous selective antagonists that entered clinical stages. Most of the RGD mimics disclosed so far as $\alpha_V\beta_3$ non-peptidic antagonists share a common pattern. They consist of a rigid, preferably achiral core unit, which links a guanidine type functionality and a carboxylic moiety. Additional surrogates of neighbouring residues were introduced to modulate the potency. These intensive investigations partly elucidated the structural and chemical requirements providing active and selective compounds.

This review will not only cover the literature but also will focus on achievements in the field and discuss the activities and selectivities in terms of 2D and 3D structures. A tentative picture of the pharmacophore will be drawn and illustrated with representative examples. Biological data will be given without details on the type of assays. It is noteworthy that comparing activities from different sources can be misleading. For that reason, most of the conclusions will be drawn using molecules tested in the same assays.

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PROTEINS, PEPTIDES AND PSEUDO-PEPTIDES AS $\alpha_V\beta_3$ ANTAGONISTS

Proteins

Initial efforts led to the identification of naturally occurring molecules as $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ antagonists. Potent proteins were isolated from snake venom (namely disintegrins) or found in leeches including echistatin [15,16], kistrin [17,18], barbourin [19] or decorsin [24] featuring RGD or KGD located at the end of an hairpin. In spite of its high activity, echistatin, presenting the RGD sequence, lacked selectivity for either integrin. In contrast, the KGD tripeptide occurring on barbourin induced a unique selectivity for $\alpha_{IIb}\beta_3$. Maigret and co-workers investigated the behaviour of echistatin and barbourin in water by molecular modelling and concluded for an unexpected binding of barbourin on the secondary binding site for fibrinogen [25]. Indeed, the *C*-terminal dodecapeptide of the fibrinogen binds on a second subsite, which is independent from RGD binding site. This binding is partly responsible for selectivity towards $\alpha_{IIb}\beta_3$ [13,14]. Meanwhile, monoclonal antibodies such as LM609 and vitaxin blocked angiogenesis [4,26] and 23C6 inhibited osteoclast cells spreading responsible for bone resorption [27]. Although these molecules exhibited high activities, their proteinic nature was an obstacle for further development. Lower molecular weight would provide more bioavailable compounds. Thus, small peptides and non-peptidic molecules were designed and prepared with promising pharmacokinetic profiles.

Peptidic and Pseudo-Peptidic Antagonists

More recently, the vitronectin receptor, the $\alpha_V\beta_3$ integrin, was found to play a key role in many biological functions. The RGD sequence, mediating its binding, was widely studied and included into cyclic peptidic structures to provide highly active $\alpha_V\beta_3$ antagonists. For instance, *c*(RGDfV) **1**, disclosed by Kessler group [28,29] (Fig. (**1**)) and related molecules (e.g. *c*(RGDfK) [30,31], *c*(RGDf-N(Me)V) [32], *c*(RGDfβLeu) **2** [33] and *c*(VfDGR) [34]) exhibited increased activities compared to their acyclic counterparts. A cyclic dimer of this sequence *c*(RGDRGD) **3**, has also been reported that exhibited high affinity and selectivity for $\alpha_V\beta_3$ integrin versus $\alpha_{IIb}\beta_3$ [35]. Since *c*(RGDRGD) was still active in the nanomolar range and almost as selective as *c*(RGDfV), Burgess and Lim suggested that the fourth aminoacid was not a prerequisite for activity though it may improve it [35]. Kessler and co-workers have shown that the nature of this fourth aminoacid modulated the potency, while the reversal of alpha carbon stereochemistry resulted in a loss of activity owing to a large change in conformation [30]. Similarly, cyclic cores have been introduced that induced the correct conformation to the tripeptidic sequence. For example, 4 [36], 5 [37], and 6 [38] adopted the postulated bioactive conformation (Fig. (**2**)),

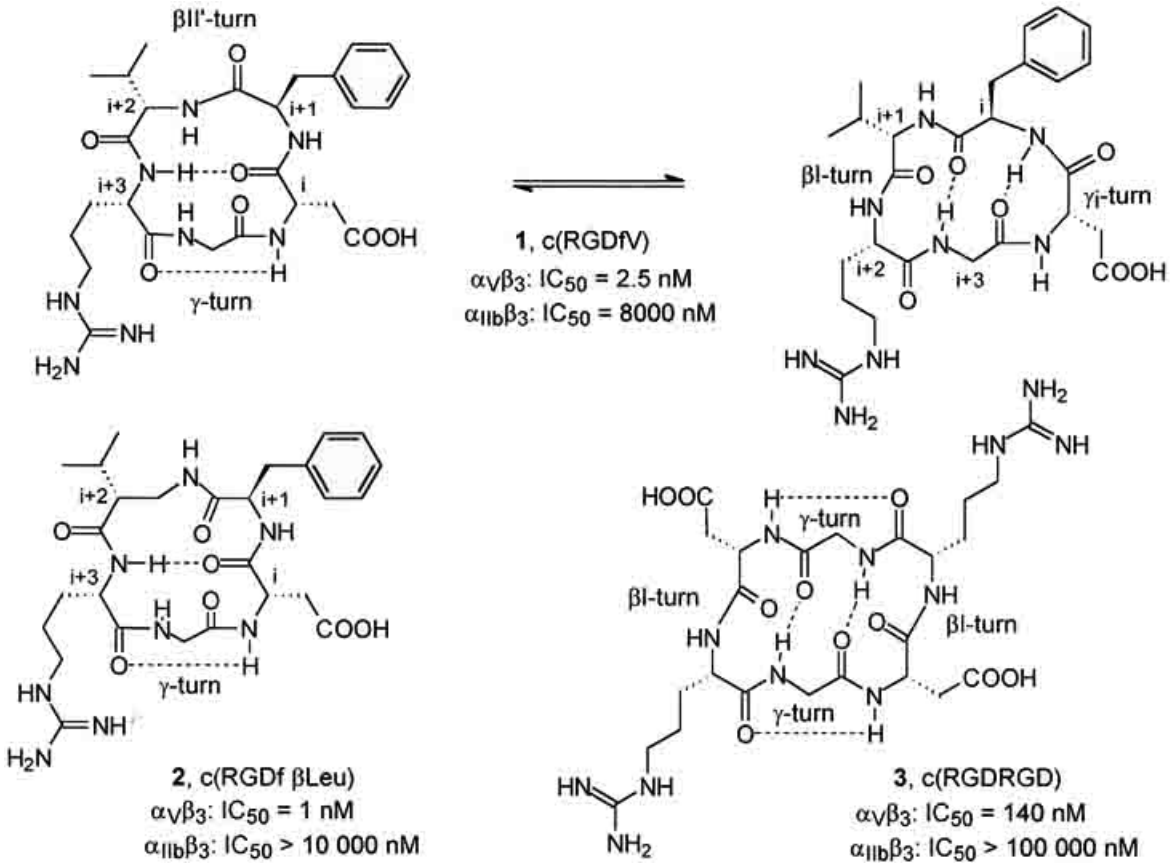

Fig. (1). Selected cyclic peptides and their solution structures as determined by NMR (**1**, **2** and **3**) and molecular dynamics (**1**).

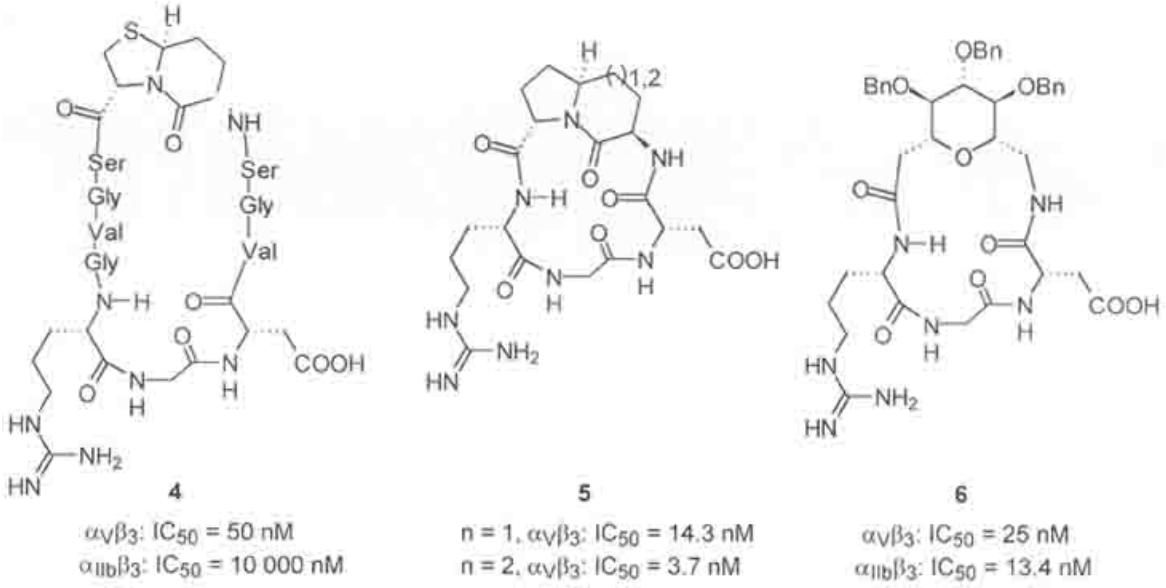

Fig. (2). Selected cyclic pseudopeptides.

though the last two showed poor selectivities. Concurrent structural studies gave more insights into differences between $\alpha_{IIb}\beta_3$ and $\alpha_V\beta_3$ antagonists and consequently into the corresponding integrin binding sites whose three-dimensional structures have not yet been solved. It is worth to note that incorporating backbones into cyclic structures allowed fairly easy conformational studies compared to the native proteins. The structural data discussed below were subsequently exploited in the design of non-peptidic compounds.

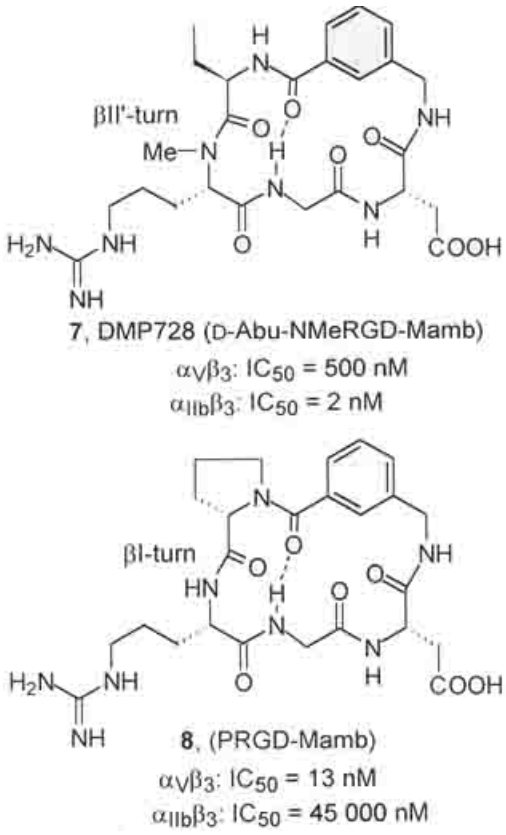

Fig. (3). DuPont Merck cyclic peptides.

Role of the Turn Type Incorporating the RGD Sequence

Examination of secondary structures led DuPont Merck group to reverse the specificity of the cyclic peptide DMP728 (D-Abu-NMeArg-Gly-Asp-Mamb, **7**), a strong and highly selective $\alpha_{IIb}\beta_3$ antagonist, which adopted a type II' β-turn (roughly planar) (Fig. (**3**)). Substitution of a D-aminoacid inducing the β-II' turn for a L-aminoacid afforded a type I β-turn (C_α of the Arg raised above the plane) molecule (Pro-Arg-Gly-Asp-Mamb, **8**) specific for $\alpha_V\beta_3$ integrin (Fig. (**3**)) [39]. As presented on Fig. (**1**), NMR and modelling studies invoked a γ-turn centred on G for either Kessler cyclic pentapeptide **1** [29], structurally related **2** [33] and *c*(RGDRGD) **3** [35], specific for $\alpha_V\beta_3$ integrin. These turns are complemented by β turns centred on different positions [35]. Investigations from SmithKline Beecham group on cyclic peptides indicated that an extended conformation about Gly was optimal for RGD binding to $\alpha_{IIb}\beta_3$ while a turn in the Gly region, resulting in a shorter overall length, favoured selectivity for $\alpha_V\beta_3$ [32,23].

Role of the Distance

As mentioned above, shorter distance between both crucial groups was found to be favourable for selective binding to $\alpha_V\beta_3$ over $\alpha_{IIb}\beta_3$ [23]. This was in good agreement with the NMR work from Kessler and co-workers in which inhibitory activity was related to the distance between the C_β atoms of Arg and Asp residues incorporated in cyclic peptides. This study indicated that the optimum distance was in the range of 7.5-8.5 Å for binding to $\alpha_{IIb}\beta_3$ and at or below 6.7 Å for binding to $\alpha_V\beta_3$. This also showed that $\alpha_{IIb}\beta_3$ receptor was less sensitive to structural variations in the RGD backbone and could accommodate a larger distance than the $\alpha_V\beta_3$ integrin [40].

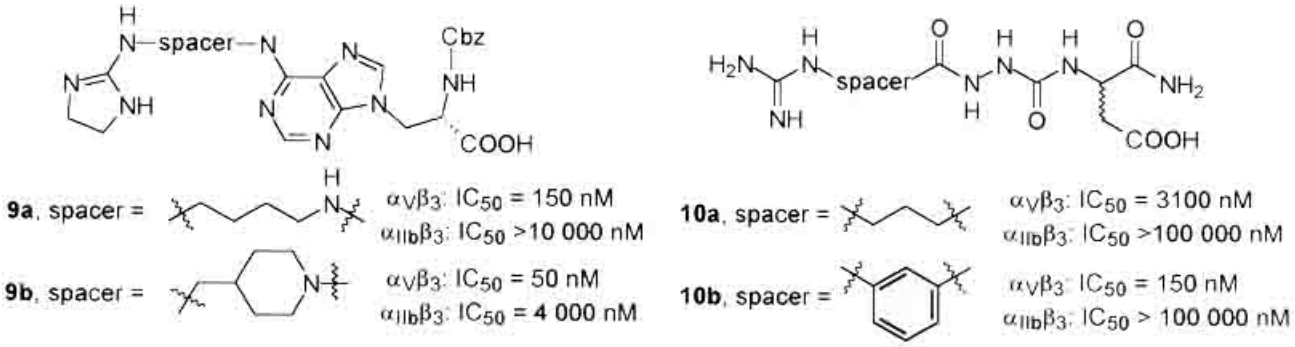

Fig. (4). Purine and urea-based peptidomimetics.

NON-PEPTIDIC ANTAGONISTS

The promising results from biology led to the opening of large programs aiming at the discovery of $\alpha_V\beta_3$ antagonists in both pharmaceutical and academic groups [7,8]. They described compounds different from cyclic peptides or $\alpha_{IIb}\beta_3$ antagonists disclosed earlier, which were prepared by library screening, lead optimisation, or rational design. During the lead generation or optimisation stages, combinatorial [41], parallel [42] and classical chemistries, solid [43-46] or liquid phase technologies were exploited.

In spite of their apparent dissimilarity, most of these molecules were constructed using the same pattern including a rigid core bearing appendages. These latter carried carboxylates and basic groups as arginine and aspartic acid side chain mimetics. In the following paragraphs, we will successively point out to these features with an emphasis on the means to address the selectivity issue.

Arginine Side Chain Mimics

Of prime interest, the *N*-terminus of the RGD mimetics was found to play a central role in modulating receptor specificity. Chemists investigated alterations that furnished potent and selective $\alpha_V\beta_3$ antagonists regardless of the rest of the molecule. For instance, flexibility, basicity and length of this appendage were examined. In drug design, rigidifying the backbone in a conformation close to the bioactive one usually led to enhanced potency because of a smaller loss of entropy upon binding. As exemplified in Fig. (**4**), this concept was nicely applied to purine-based RGD mimetics [47]. Thus, introducing the five-atom side chain of **9a** into a piperidine ring led to **9b**, three times as active as **9a**. Similarly, a benzene ring was successfully introduced onto **10a** to provide **10b** with a concomitant gain in activity [48]. From these works, one could conclude in the need of rigid spacers. However, this approach was not universally applicable. In the benzodiazepine series, Keenan, Miller *et al.* constrained **11a** into **11b**, without increase in potency (Fig. (**5**)) [49]. This can result from an inadequate locked conformation of **11b**, which did not match the binding site requirements. In addition, other highly active compounds featured flexible spacers as illustrated on Fig. (**6**). For instance, the high activities and/or selectivities exhibited by **12a** from Hoechst Marion Roussel [50], **13a** from DuPont [43,51], **14a** from SmithKline Beecham [52-54], or **15a** from Searle [55] revealed that rigid spacers were not prerequisites (Fig. (**6**)).

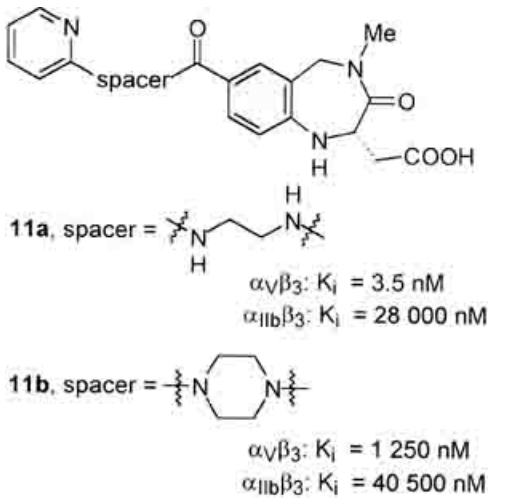

Fig. (5). Benzodiazepine-based non-peptidic antagonists.

The length of this spacer was a common characteristic of most of the disclosed compounds. Three or four carbon atoms or carbon and heteroatoms from the central core were required for optimal activity. A closer look revealed that spacers tended to be rather hydrophobic. As a general rule, optimal distance between the *C*-terminal carboxylic acid and the *N*-terminal guanidino group seems to be roughly twelve C-C bonds for an $\alpha_V\beta_3$ antagonist (as in RGD sequence) while $\alpha_{IIb}\beta_3$ would prefer a substrate where the two groups are further apart with a distance of thirteen bonds [50]. In spite of the two dimensional nature of this rule, it was a useful indication for primary design. Indeed, as depicted on Fig. (**7**), exceptions were described where thirteen (**16b**) [56] or eleven bonds (**17a**, SB 223245) [23,52,57,58] afforded active $\alpha_V\beta_3$ antagonists.

The nature of the guanidine mimetic, including pK_a, geometry and H-bonding characteristics, has been carefully investigated by most of the pharmaceutical groups. Based on the hypothesis that a negatively charged moiety was not a prerequisite for potency against $\alpha_V\beta_3$, medicinal chemists introduced less basic guanidine mimetics with a gain in selectivity (Fig. (**8**), (**9**)). Interestingly, charge delocalisation that often leads to pKa decrease favoured selectivity for

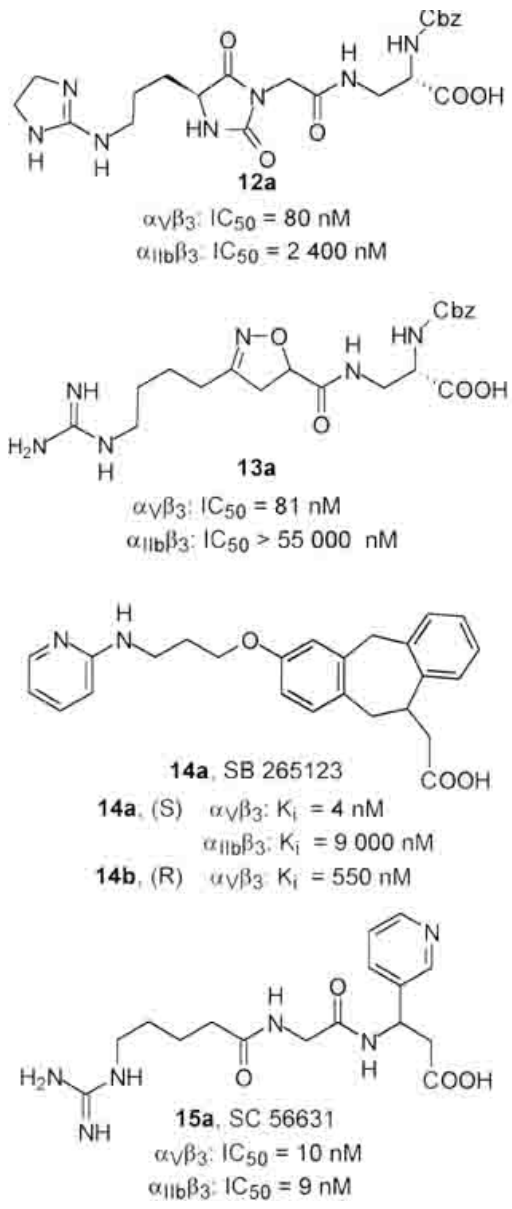

Fig. (6). Selected flexible antagonists.

$\alpha_V\beta_3$ (pyridinium **17c** versus amidinium **17b**, Fig. (**8**) [23]. Noticeable increases in activity and in selectivity were observed while shifting pKa from twelve to four (**13b** to **13d**, Fig. (**8**)) [51]. However, the concurrent change in lipophilicity might play a synergic role. As also illustrated by work from DuPont group, reducing the basicity (from **16d** to **16e** or **16f**) profoundly influenced the selectivity (Fig. (**9**)). Batt and co-workers concluded that moderate basicity induced higher potency for $\alpha_V\beta_3$ along with better selectivity over $\alpha_{IIb}\beta_3$ [56]. Merck research group remarkably prepared compounds with selectivity for either $\alpha_v\beta_3$ or $\alpha_{IIb}\beta_3$ simply by altering the arginine side chain mimetic (Fig. (**10**)), identifying optimal features for either integrin [59]. Thus, this type of compounds, initially designed as $\alpha_{IIb}\beta_3$ antagonists (**18a**), was rapidly and efficiently converted into $\alpha_V\beta_3$ antagonists (such as **18d**), the reversal in selectivity being attributed to the guanidine mimetics only. Embedding the guanidinium group into an imidazole ring also led to an increase in activity and selectivity [47]. A part of Aventis Pharma group program on purine-based vitronectin receptor antagonists focused on cyclic and acyclic guanidines. They observed a substantial increase in activity when cyclic guanidines such as imidazole or 2-aminobenzymidazole were used (**9a** or **9c** compared to **9d**, Fig. (**11**)) [47]. The same trick also led to an increase in selectivity in Hoechst Marion Roussel hydantoin-based series (**12b** vs. **12a**, Fig. (**11**)) [50]. It was postulated that this would result from an orientation of the guanidine mimetic that discouraged certain bidentate binding arrangements. As hypothesized by many groups, selectivity for either $\alpha_{IIb}\beta_3$ or $\alpha_V\beta_3$ can be tuned using end-on/side-on interaction within the active site [47,50,51]. The interactions with $\alpha_{IIb}\beta_3$ shown on Fig. (**12**), normally achieved by both ω nitrogens of the guanidine, are no longer retained when these nitrogens are included in rings. This property was successfully exploited to design selective $\alpha_V\beta_3$ antagonists [47,50,51]. Thus, either ω/δ or ω/ω' guanidinium nitrogens have been included into rings (Fig. (**9**)) resulting in modulation of the selectivity (**13c** vs. **13e**) [51]. As can be seen in all the aforementioned examples, the aromatic character of the amine was not essential for either activity or selectivity. However, it could affect the pK_a and play a role in the side-on/end-on interaction. For instance, **17c** or **18d** showed opposite selectivities.

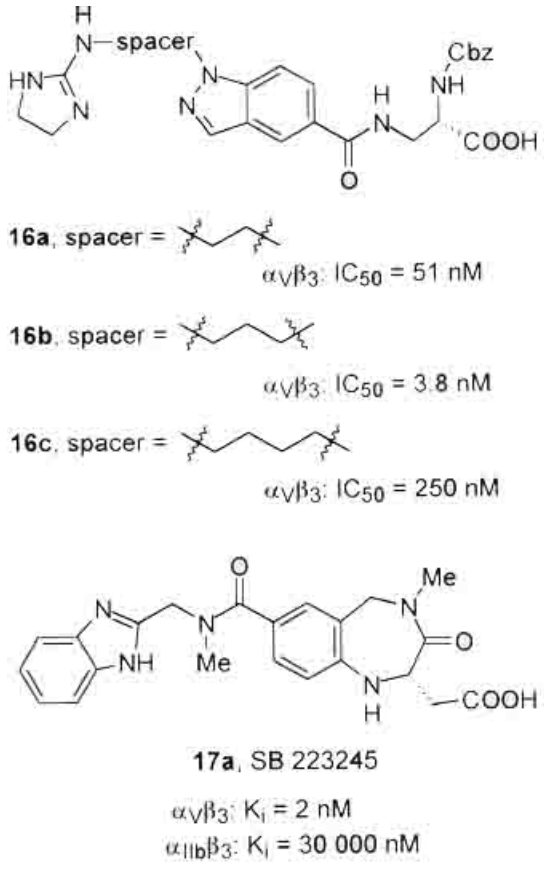

Fig. (7). Unusual number of bonds between pharmacophoric moieties.

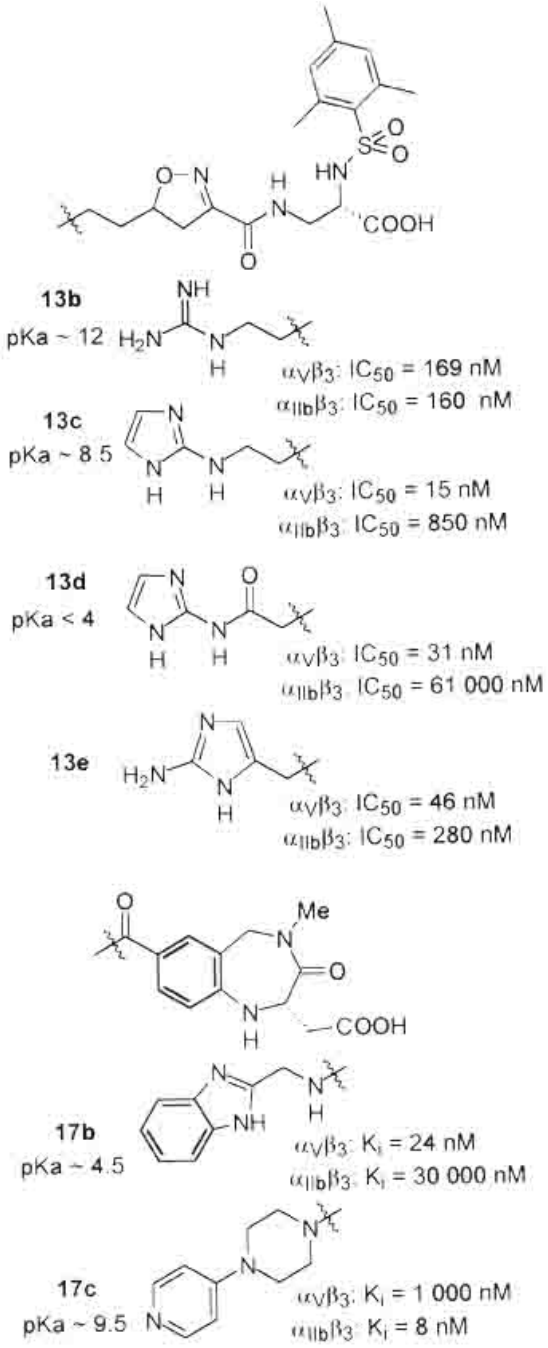

Fig. (8). Modulation of the selectivity by tuning the pK_a.

While looking at the side chain as a negative picture of the binding subsite, one can postulate that a negatively charged moiety (probably a carboxylate) on one side (to favour side-on interaction) of a long and hydrophobic subsite (around 7-9 Å) would exist in the $\alpha_V\beta_3$ integrin binding site.

Central Cores (Gly Surrogate)

In medicinal chemistry, conformation and spatial arrangement of the charged groups are crucial to control

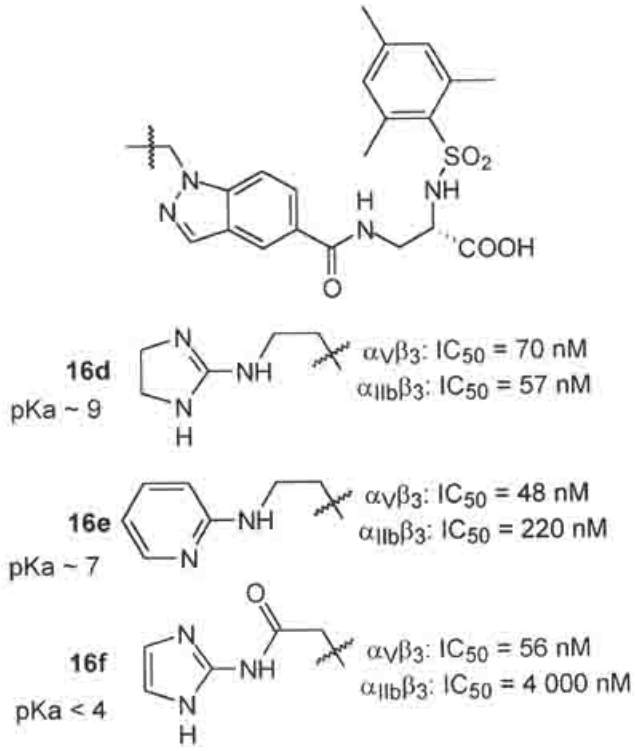

Fig. (9). Basicity, a parameter for activity and selectivity.

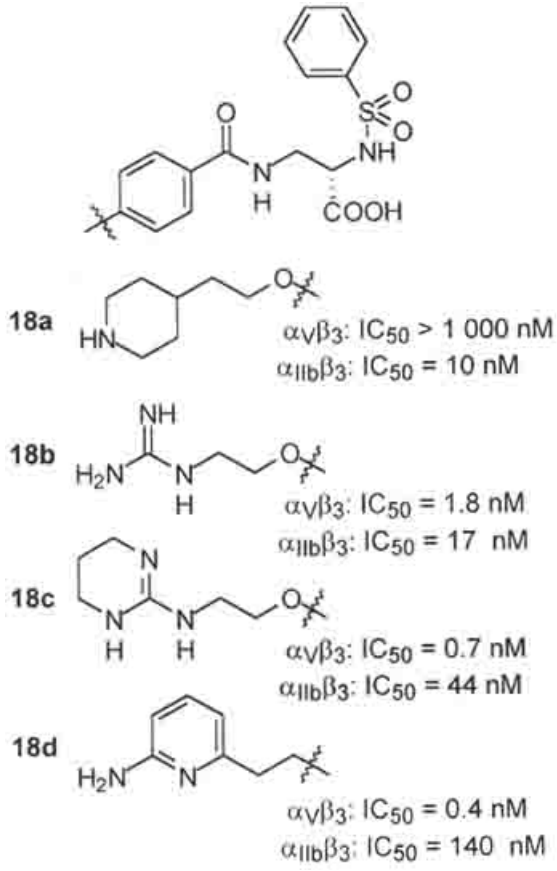

Fig. (10). Reversal of selectivity by modification of the arginine side chain mimetics.

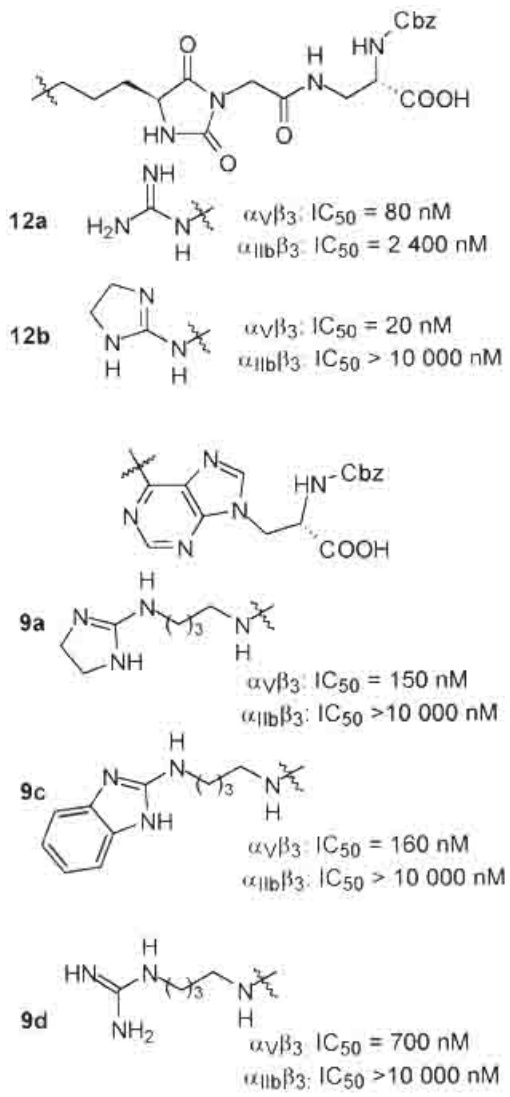

Fig. (11). Introduction of guanidine into cyclic structures.

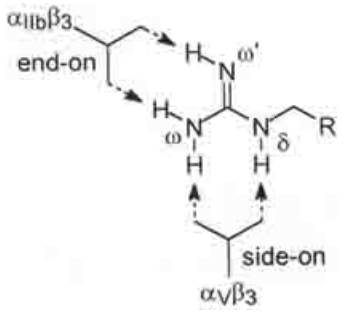

Fig. (12). Side-on/end on interactions.

activity and selectivity. This is the primary role of the central core that correctly positions the charged moieties. Substituting Ala for Gly in peptides resulted in a dramatic loss in potency [60]. This excluded bulky or branched cores at that position. In fact, although a variety of chiral and achiral, aromatic and non-aromatic, cyclic and acyclic scaffolds were envisaged, few highly branched templates were reported as suitable for the preparation of $\alpha_V\beta_3$ antagonists. To date, a few chiral scaffolds, including synthetically challenging tetrahydrofuran and pyranoside rings, were used in the design and synthesis of RGDF-like compounds (Fig. (**13**)). The stereodiversity concept developed by Chapleur and co-workers to explore the required spatial orientation was successfully applied to the combinatorial preparation of xylopyranoside-based libraries deconvoluted into **19a** as active as RGDS on cancer cells [61,62]. Meanwhile, Nicolaou exploited a glucose scaffold to build up RGDF mimics [63] (e.g. **19b**) and Osterkamp synthesized dianhydrohexitol-based [64] and tetrahydrofuran-based [65] integrin antagonists (e.g. **20**, **21**). The configuration of the tetrahydrofuran ring system was studied and showed the *trans* configuration to be more active and *cis* configuration to be more selective [65]. This experimentally showed the crucial role of the spatial arrangement of the essential groups in the selectivity and activity. Other rings with one or two asymmetric carbons have been used such as hydantoin [50] (**12a**, Fig. (**11**)) or benzodiazepine [49] (**17a**, Fig. (**7**)) where the asymmetry came from aminoacids. In contrast, achiral scaffolds have been widely used. For instance, branched rings such as benzoic acid (**18d** [59], Fig. (**10**), **22** [66], Fig. (**14**)), indazolecarboxylic acid [56] (**16b**, Fig. (**7**)) and piperazine [46] (**23**, Fig. (**14**)) or conformationally constrained acyclic chains such as urea [67] (**10b**, Fig. (**4**)) provided active compounds. As exemplified above, mono- and bicyclic cores were used without any distinction. However, the thickness of the cores seems to be a constant. Only flat structures were disclosed, sugars and piperazines being mostly in all-equatorial conformations [61]. This second subsite can be reasonably figured out from this data. Steric interactions that may exist at this location would disfavour the presence of any side chain (bulky or not).

Acid and Surrounding Residue Substitutes

Not unexpectedly, all structure-activity relationship studies concluded that the acid side chain is crucial for activity. Indeed, mono- or diacid compounds such as **15b** [68] or **24** [69] shown on Fig. (**15**) were reported to bind vitronectin receptor despite the lack of positively charged moiety. Binding to another binding site can be suspected since the arginine guanidinium was shown to be crucial for ligating. Recent work from our group showed that diacids exhibited reduced potency compared to their monoacid counterparts [Henry, C.; Moitessier, N.; Chapleur, Y. unpublished results]. Inversion of the chirality of the atom bearing the acid (**14a** vs. **14b**) resulted in a noticeable loss of activity (Fig. (**6**)). Other examples illustrated on Fig. (**17**) confirmed this fact [56]. It is noteworthy that Genentech developed **25** bearing the acid side chain on a nitrogen though the pyramidal nature of this heteroatom can reproduce the carbon chirality (Fig. (**16**)) [70].

The omnipresence of benzyl carbamates, phenylsulfonamides or other isosteric groups adjacent to the acid deserved comments. These moieties mimicked the hydrophobic aminoacid adjacent to the RGD sequence. They may participate in an extra hydrogen bond with the binding site. As illustrated in Fig. (**17**), this carbonyl/sulfonyl group substantially improved the potency (**16i** vs. **16g** or **16h**) [56]. This influence may also be induced by the alkyl or aryl

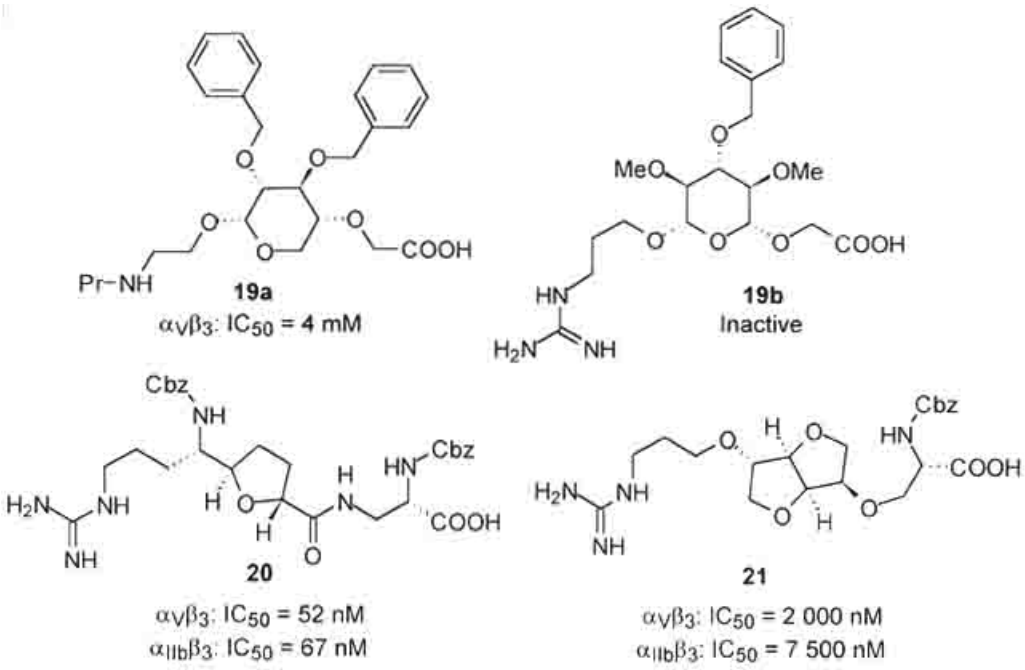

Fig. (13). Asymmetric cores.

moieties bound to it. Expectedly, the better H-bond acceptor thiourea **12d** exhibited enhanced potency (Fig. (**18**)) [50]. The lower affinity of the bulkier sulfonamide indicated a strict demand of the binding site [8,50,51]. However, the postulated H-bond was inconsistent with the noticeable gain in activity resulting from the substitution of the carbonyl group by an aromatic ring (from **10b** to **10c**, Fig. (**19**)) [66]. Although the hypothesised H-bond was lost, an interaction with the aromatic ring was found to be beneficial. SmithKline Beecham has obtained similar results (**14c** vs. **14a**, Fig. (**19**)) [52,71]. An antagonist from Monsanto (**15a**, SC56631) presented in Fig. (**6**) exhibiting nanomolar activity might be the answer to the binding site requirements [55]. The contribution of the pyridine ring suggested that the use of a mixed hydrophobic/hydrogen-bond acceptor functionality was instrumental in mimicking the flanking aminoacid.

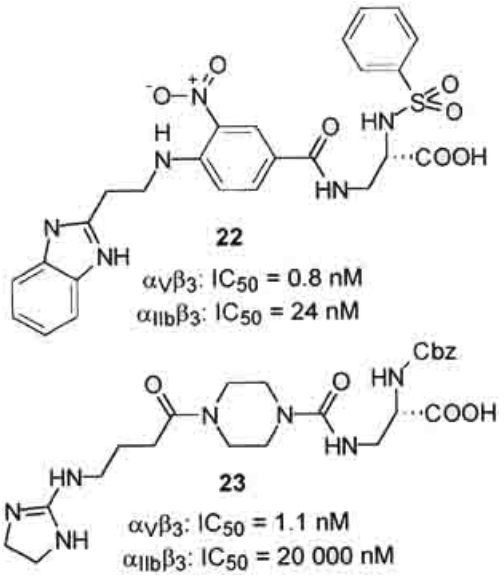

Fig. (14). Achiral cores.

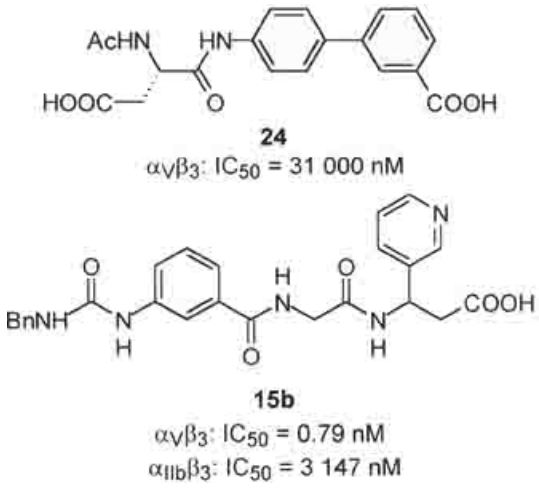

Fig. (15). Potent vitronectin receptor antagonist lacking the guanidinium mimic.

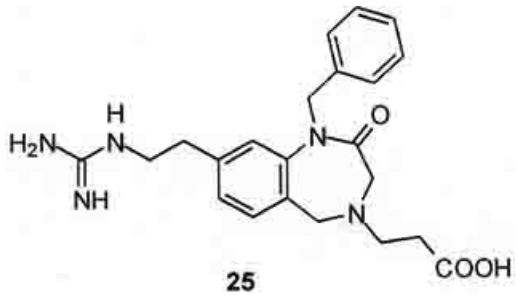

Fig. (16). Achiral RGDF mimetic.

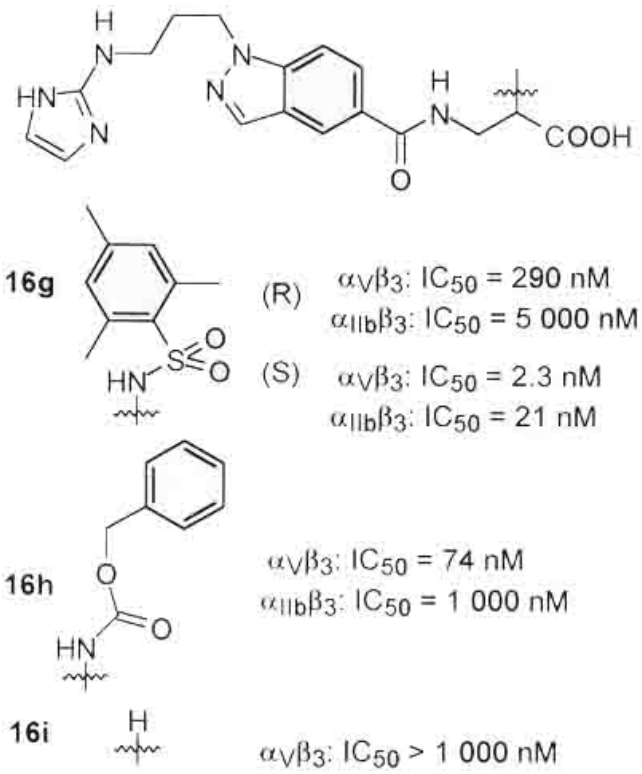

Fig. (17). Benzyl carbamate of aryl sulfonamide as adjacent Phe mimetics.

The role of the aminoacid adjacent to Arg was also investigated. Nitroaryl compounds such as **22** (Fig. (**14**)) were considered by Nicolaou *et al.* and can be thought as isosteric for the backbone carbonyl group of this extra aminoacid, though the role of the nitro group was not examined [66]. Biscarbamate compounds were also designed that could mimic both aminoacids flanking RGD sequence (**20**, Fig. (**13**)) [65].

Three main features are believed to occur within this part of the binding site. One can suspect a protonated lysine, a protonated arginine or a calcium ion interacting with the ligands. An hydrogen bond donor group and a partially hydrophobic surface are probably involved as well. However, the weight of each interaction in the overall free energy of binding and their location remain obscure. The overlap of the features suggested by the aforementioned contributions complicated the picture of this subsite.

NMR and Modelling Conformational Studies and Pharmacophore

The studies summarised all along this review probed the receptor and revealed a negative picture of the binding site. Molecular modelling studies focused mainly on fibrinogen receptor antagonists [72]. However, particular attention was given to the spatial relationship between the Arg and Asp side chains. These geometric data served to figure out the binding pockets of both integrins. Two-dimensional pharmacophores were constructed with an optimal distance between the *C*-terminal carboxylate and the *N*-terminal guanidino group of twelve bonds [47,50]. NMR studies on cyclic peptides proposed a "turn-extended-turn" conformation

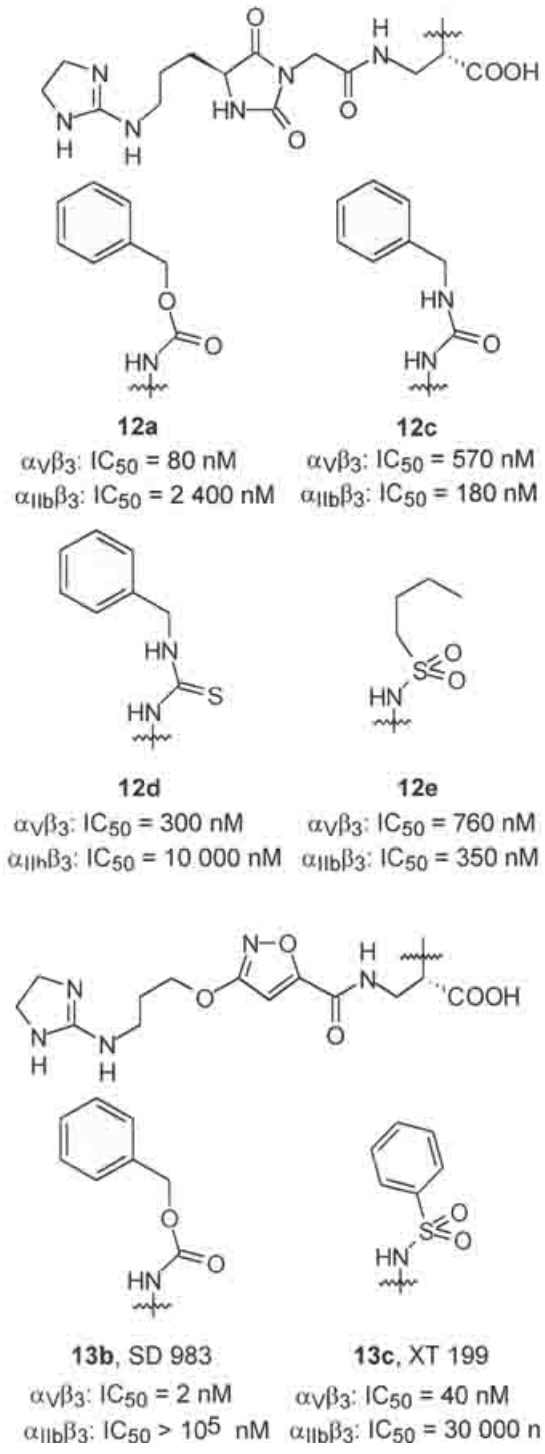

Fig. (18). Effect of the flanking residue mimetics.

for $\alpha_{IIb}\beta_3$ antagonists and a "cupped" presentation for $\alpha_V\beta_3$ antagonists [23]. Indeed, most of the solution conformation of active RGD-containing cyclic peptides invoked a γ-turn centred on G (*vide infra*) or/and β-turn centred on GD [73]. Our molecular modelling contribution led to two models for both $\alpha_V\beta_3$ and $\alpha_{IIb}\beta_3$ antagonists with guanidinium – carboxylate distances of 6-13Å in water [61,62].

Fig. (**20**) presents a cartoon of pharmacophore including chemical and conformational properties gleaned all along this review.

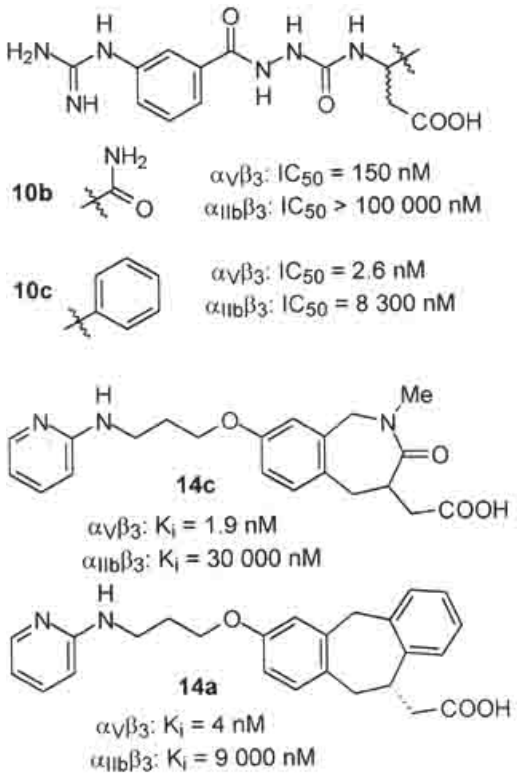

Fig. (19). Adjacent residue mimics.

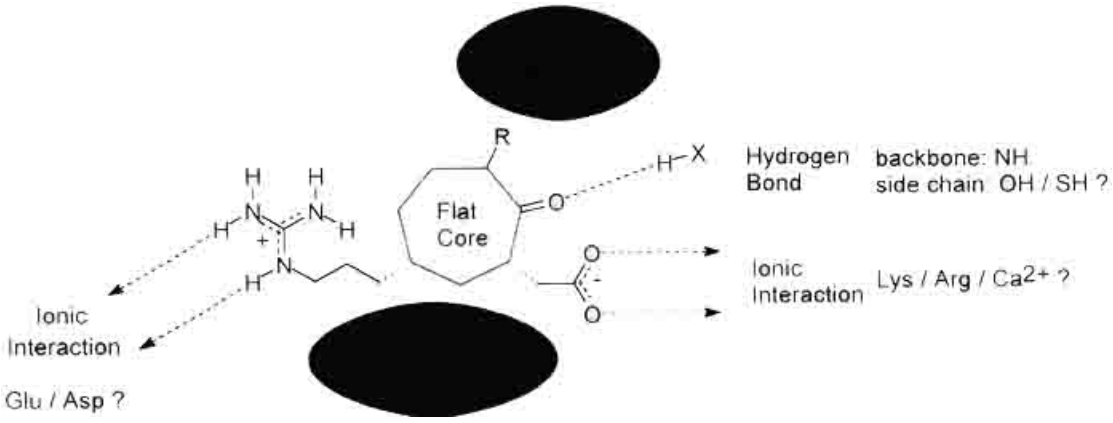

Fig. (20). Proposed pharmacophore/binding site interactions.

CONCLUDING REMARKS

$\alpha_V\beta_3$ integrin was found to be a relevant drug target in cancer or osteoporosis treatments. Small synthetic antagonists would therefore provide potential drugs. Such compounds, namely peptidic, pseudo peptidic or non-peptidic, followed general structural and chemical rules although examples to the contrary were reported. Since the receptor three-dimensional structure was not known yet, rational design remained tricky. However, systematic search and preparation of "me-too" led to highly active and selective $\alpha_V\beta_3$ antagonists. A critical survey of the literature was described and provided a model of the pharmacophore gathering the common features or patterns. The extracted model afforded in turn a negative picture of the binding site.

NOTE ADDED IN PROOF

While this review was processing, an X-ray crystal structure of the extracellular part of the receptor was disclosed and would be of great interest for further design of new inhibitors and to construct a model of their interaction with the binding site [74].

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