Review

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Contemporary nano-architectured drugs and leads for αvβ3 integrin-based chemotherapy: Rationale and retrospect

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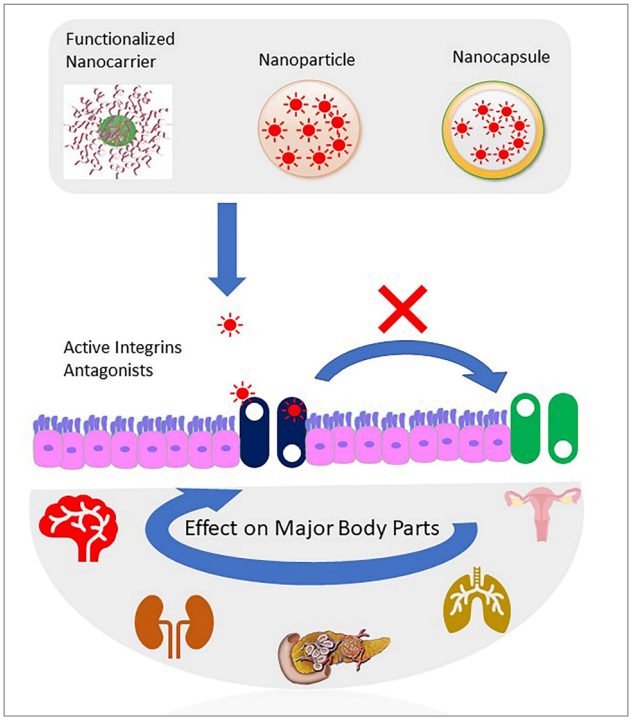
Abstract: The integrins belong to the cell-surface polypeptide family and are the mediating partners among the cells, and extracellular matrix (ECM). They are also involved in the biological processes of cell migration, wound healing, blood clotting, immunological response generation, tissue morphogenesis, leucocyte reticulations, and angiogenesis and are therefore very relevant in stem cell technology and are useful as biomarkers, diagnostic probes, and drug-target ligands. The αvβ3 (*alpha-nu-beta*3) integrin antagonists are an excellent target example for designing and developing newer drug candidates, drug leads and templates for various diseases, and physiological malfunctioning, including cancers. The current review examines the αvβ3 integrin structural features involved in the drug design and its antagonistic ligands and highlights the development of anti-αvβ3 integrin-antagonists as nano-architectural design-based nanomedicine, especially for cancer chemotherapy. The perspectival review discusses the αvβ3 integrin structure, mode of action, involved pathways, and the concepts utilized in nanomedicine design, and ligands related to integrins. It also covers the latest thyrointegrin approaches toward the development of anti-angiogenesis agents and entails the anti-angiogenesis approach to cancer growth inhibition through targeting by the anti-integrin ligands and related chemical entities. The current perspective on the nano-architectural design approach for the known anti-integrin compounds is also outlined.



Graphical abstract: The αvβ3 integrin antagonistic ligands, *i.e.*, drugs as nano-architectural design-based nanomedicine, especially for cancer chemotherapy, are discussed.

Keywords: integrins, αvβ3, antagonists, thyrointegrins, therapeutics, nanomedicine

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1 Introduction

The functioning of multicellular organisms involves complex interactions within the cells, in the extracellular matrix (ECM), surrounding cells, and other bio-entities in the ECM arena, and integrins are the foremost bio-entities involved in these actions [1]. In multicellular

organizations, cells adherence, facilitated through the integrins, has a distinctive and diverse role for a number of biological level feedback, signaling, physico-chemical, physico-mechanical, and biomechanistics aspects of cell and organ functions, such as cell divisions, maintenance of tissue integrity, embryonic cell development during embryo development, cell migration, cell proliferation, blood cell involvement, blood coagulation, and immune system functioning [2]. Any modification in the cellular structure, functions, cellular etiology, and cellular adhesion may cause several diseases including atherosclerosis, inflammatory disorders, and different types of cancers. This has helped to identify the integrins as an appealing target for the discovery and development of new and improved therapeutic agents.

Integrins, the vital component in cells' signal transduction and biochemical functioning at physiological and biochemical levels, have been located in several organs and their tissues and are expressed as part of the cell function requirements, immunological dealings, and signal transduction activities. Several integrin types, with specificity to different receptors, *i.e.*, RGD, collagen, laminin, and leucocyte-specifics, are known (Figure 1). Among the vertebrates, including human's integrins, the αvβ3 (*alpha-nu-beta*3) is the most commonly expressed integrin in proliferative endothelial cell types, vascular smooth muscle cells, macrophages, and the monocytes. These integrins are involved in signal transduction through different signaling pathways within and across the cells, with the ECM components, and in blood cells in various tissues and organs. The integrins are also involved in angiogenesis and tumor cells of several organs in facilitating types of cancer cell proliferation and cancer metastasis [3].

2 Integrins: Structure, heterodimeric injunction, and functional domains

Structurally, the integrins are a family of polypeptidic receptors and mainly function as cell adhesion receptors. The integrins are noncovalently linked, heterodimeric molecules incorporating an α and a β subunit as part of their tertiary structure and are embedded across the plasma membrane. These portions contain a high molecular weight fraction of the integrin structure outside of the cell, and the shorter ratio of the structural part lies in the cytoplasm. Vertebrates' origin integrin entities are composed of 24 α subunit types and 9 β subunits with specified structure types till date with different α–β combinations of receptors with different binding properties

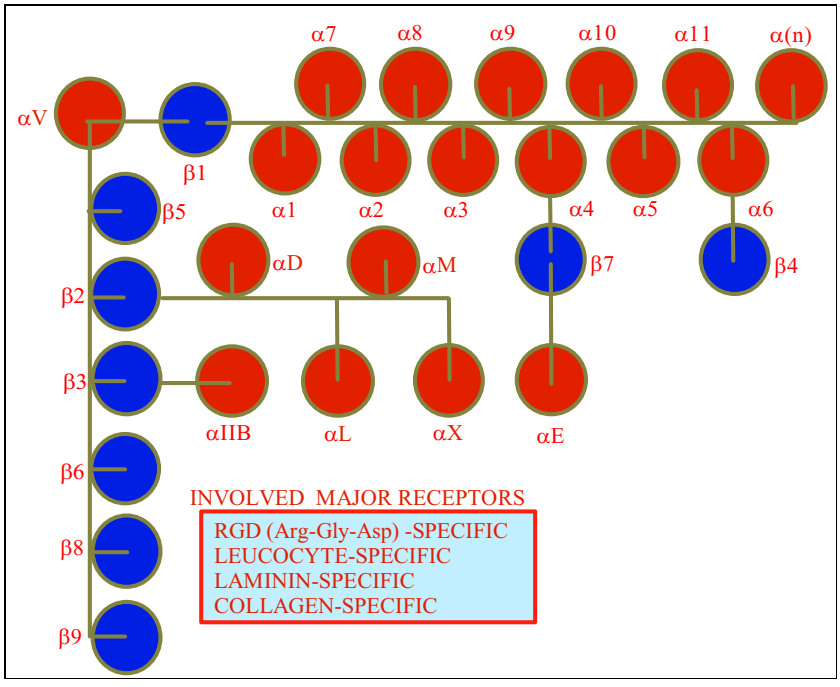


Figure 1: Integrin superfamily of vertebrates' origins including humans. With the α and β subunits combining to form heterodimeric integrins, and the ongoing discoveries, the number of α and β subunits are increasing $\{(\alpha)_n$ and $(\beta)_n\}$ to add to new integrin types.

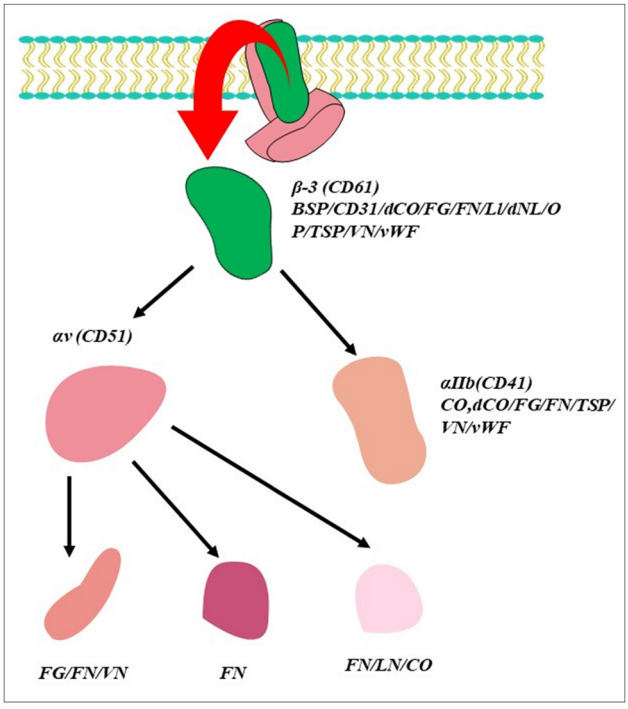


Figure 2: Integrin α–β heterodimers identified and grouped according to the broad families, and the ligands bound by the heterodimer are presented in *italics* either under α subunit, β subunit, or adjacent to the αβ pair. Ligands BSP, bone sialoprotein; CD31, cluster of differentiation antigen 31; CO, collagens; dCO, denatured collagens; FG, fibrinogen; FN, fibronectin; L1, cell adhesion molecule; LN, laminins; dLN, denatured laminin; OP, osteopontin; TN, tenascin; TSP-1, thrombospondin; VN, vitronectin; vWF, von Willebrand fac. The ligands are listed in alphabetical order and are not presented as a major ligand for any of the receptors.

with various tissues distribution [4,5]. The α and β subunits form the outer cell located in ligand-binding domain, where two multidomain longer chains are termed as the "legs" with the two single-pass membrane helices and the two short cytoplasm embedded tails. These α and β subunits show nonuniformity, they do not express homology to each other, and their conserved regions are common among subtypes of both the subunit groups (Figure 2) [6,7]. Generally, an α subunit specifically associates with a particular β subunit only, *e.g.*, α5 subunit only attaches to β1, wherein the β subunits are often more random in their organizations, *e.g.*, the β2 subunit attaches with αM, αL, αX, and αD, except the subunit α 4, which is associated with the β1 and β7, and αV binds to β1, β3, β5, β6, and β8 subunits. Each of these subunits is composed of large extracellularly located amino acid (AA) sequence, together with ~740–780 AAs as part of the β kinds of subunits. There is also a singular domain of the structure located across the membrane consisting of nearly 20 AAs together with a short structure part located in the cytoplasm having a chain length of 40–50 AAs (Figure 2) [8,9]. However, an exceptionally high chain length of 1,000 AAs is found for the β4 subunits [10]. There is a sevenfold repeating unit of about 60 AAs of the α subunits in the *N*-terminal half of the subunit, and these repeating units get folded into a single compact part, wherein they are arranged around a pseudo-symmetry axis to form the structural domain, called β-propeller.

The ligand-binding substructure, the loops in α4β1 were identified by Irie *et al.* [11]. These loops are critical for ligand binding and are available as repeats of 2 and 4 loops on the upper-face side of the β-propeller (Figure 3). For the residues in the α5β1, they are in close proximity with the ligand-binding site of this integrin [12], which was found in close proximity to the propeller near the putative loop. Binding to integrins is achievable through divalent cation dependency. However, the role of the cation needs to be probed in detail. Certain repeats of the α subunit possess multiple cation-binding sites, and these sites were thought to be at the lower surface of the propeller [13]. Around ⅕ of the integrin α subunits possess an I-domain of nearly 200 AA, homologous to von Willebrand factor (vWF), and are located between the blades 2,3 of the β-propeller [14]. These I-domains mimic the ligand-binding characteristics of the intact integrin, and thus, the I-domain, whose structures are well understood, are involved in ligand binding [15–18]. The crystal structures of these domains have been determined for the αM, αL, and α2 subunits. These I-domains form Rossmann dinucleotide-type fold with a central β-sheet, consisting of five parallels and one antiparallel strand encircled by eight α-helices in association with divalent cation that is coordinated through the loops at the top to form metal ion-dependent site for adhesion. The I-domain had no other major structural motifs in the presence of either Mg^{++} or Mn^{++} or in the absence of cations, *i.e.*, Zn^{++} (Figure 3a and b) [19].

Integrin, αvβ3, possess a cluster of differentiation (CD), the antigen 31 for αV and 61 for β3. The X-ray diffraction (XRD) studies devised crystal structure showed αM I-domain in complex formation with a cation that is unusually bound to glutamic acid (Glu) AA residue rather than to the water molecule. The observation has led to speculation that Glu binding is mimicked by the aspartic acid (Asp) AA residue of the RGD (Arg-Gly-Asp) tripeptide, and the aspartic acid residue of another tripeptide LDV (Leu-Asp-Val) of the recognition sequence of the integrin also led to the design and preparation of several drugs and drug candidates as potential αvβ3 integrin inhibitors [20].

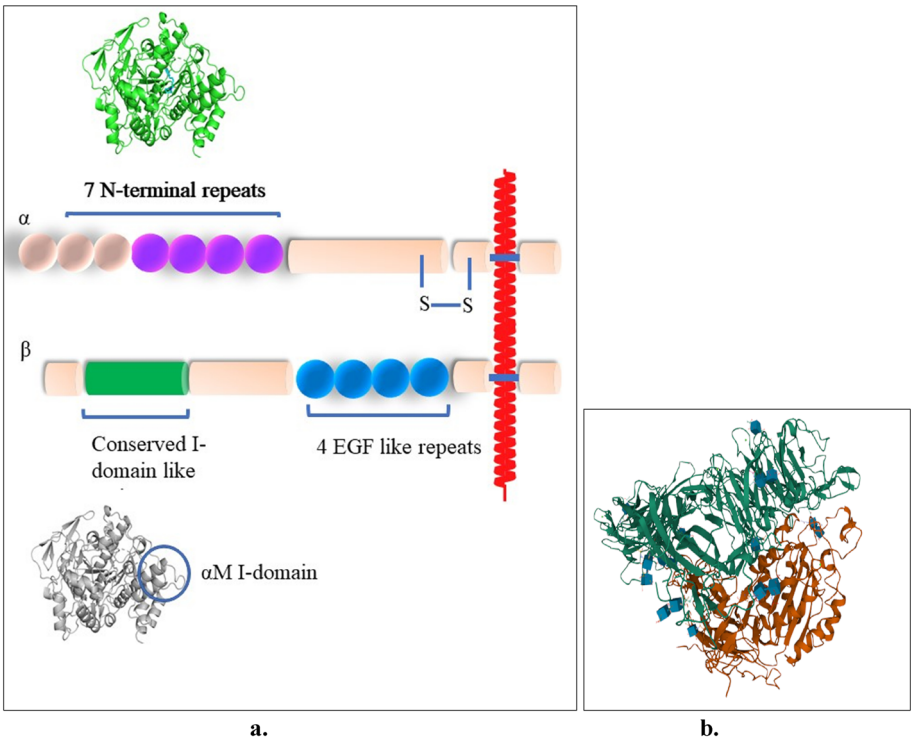


Figure 3: (a) Schematic diagram of an integrin α–β heterodimeric structure. Seven α subunits *N*-terminal repeats with the last four containing EF-hand-like divalent cation-binding sites. The seven repeats fold to form the β propeller part (β-sheets labeled as W1–W7). The putative I-domain-like structure of the integrin β subunit is also shown. The αM I-domains illustrate Rossmann folds as adopted by β I-domains. Down from the putative β I-domain-like motif are located four cysteine-rich epidermal growth factor-like repeats, inspired and with permission from Humphries [7]; (b) the crystal structure of the extracellular segment of the integrin αvβ3 with no bound RGD peptide. Source: Protein Data Bank, PDB code 1JV2) [14,21].

A number of ligands of small molecular weights (SMWs) and macromolecular templates of synthetic, recombinant, and biological origins bind to the integrin αvβ3 for regulating the cancer cell proliferation and metastasis; however, the cross-talks between the different integrin types and other entities of several types involved in signal transduction pathways affect the modulation of cancer proliferation and cancer metastasis by integrin interference. Also, the carcinoembryonic antigen cell adhesion molecule 6 (CEACAM6) is involved in activating the integrin focal adhesion kinase, a nonreceptor tyrosine kinase type toward stimulating many biological activities, including cancer proliferation and metastasis, and hence is of concern in cancer biology. The signaling inhibition of the αvβ3 integrin serves as an important hit point for developing effective therapies for different cancers of several organs and tissues. The role of Tetrac (3,3′,5,5′-tetraiodothyroacetic acid), which provides best receptor binding to the integrin receptor-binding domain, categorically subdues the cancer cell proliferation, and integrin works as a coactivator [3]. Several cancer conditions have been implicated to arise from different factors of structural and functional aberrations, and the αvβ3 integrin molecule, their ligands, and their heightened interactions promote several disease states. The hepatic stellate cells upon activation, liver sinusoidal endothelial cells on capillarization and the angiogenic endothelium, profusely express the αvβ3 integrin and are involved in liver disorders, including intrahepatic angiogenesis, liver fibrosis, and chronic liver diseases. Rationally designed protein ligands have also been developed to successfully reverse liver fibrosis and reduce the activated and capilarized liver cells [22]. Recently, a new class of integrin antibodies has been discovered for fibrosis [23]. The αvβ3 integrin ligand is also known to regulate the quantitative increase in smooth muscles' hyperplasia to restrict Crohn's disease [24]. The severely upregulated αvβ3 integrins in lung fibrosis, where the SSTR2 (somatostatin receptors subtype 2) helped to confirm the fibrosis after 2 weeks of induction, were used for imaging purposes [25]. The cancers of breasts, lungs, and prostate tend to metastasize in the bone and the bone marrow, owing to modulation in αvβ3 integrins' expressions, and the processes of involved signaling, wherein the αvβ3 integrin was overexpressed and followed downstream signaling

pathways to induce osteolysis, have been observed [26]. Integrin dysregulation is the key in tumor-induced bone destruction through metastatic participation of cancers, especially solid tumors [26]. Also, the αvβ3 integrin dysregulation together with the CD47 (cluster of differentiation 47, immunoglobulin, cell surface located, integrin associated) signaling is reported to promote inflammation of the joints, breakdown of cartilage, and osteoarthritic progression [27]. The αvβ3 and αvβ5 integrin receptor involvements in animal models of atherosclerosis and modulation of macrophagic functions through omentin-1 to reverse the plaque vulnerability have been reported recently [28]. Moreover, the αvβ3 integrin in podocyte-mediated kidney disease of chronic nature together with suPAR (soluble urokinase plasminogen activator receptor) and APOL1 (apolipoprotein L1) risk variants as part of a tripartite complex has also been reported [29]. An important understanding related to the structural motif changes in the integrin molecules led to conclude that the aberrant glycosylation of αvβ3 integrin is among one of the causes of progression of melanoma, which has been confirmed through the WM1205Lu cell lines, the highly metastatic variant of the WM793 primary melanoma cell line [30]. Cytomegalovirus, an opportunistic pathogen causing birth defects in neonatal and that altered physiological conditions in immuno-compromised individuals, has a co-receptor in avβ3, together with epidermal growth factor receptor [31]. Moreover, all Parkinson-diseased (PD) and related syndromes showed higher αvβ3 levels in *locus ceruleus* and *substantia nigra pars compacta* in live subjects having incidental Lewy body disease with confirmed Lewy bodies, but the PD and progressive supranuclear palsy conditions exhibited higher αvβ3 levels in post-mortem brain tissues [32]. The αvβ3 integrin has also been proposed as a drug target for rheumatic disorders and rheumatoid arthritis [33]. Activation of αvβ3 integrin-based signaling promotes fibrotic changes in glaucoma and glucocorticoid-induced glaucoma [34]. The inflamed muscles, especially in hypoxia and ischemia, also promote higher expressions of αvβ3, an angiogenic factor [35]. The prominent role of αvβ3 integrin in tumor angiogenesis has led to strategies to counter them for further angiogenesis, tumor growth inhibition, and metastasis of cancer [36].

The thyroid-regulated disorders and involvement of the αvβ3 integrin are well known [37–42]. The angiogenic signaling in multipotent stem cells through the αvβ3 integrin is also influenced by the thyroid hormones. The proven role of Tetrac, an ingredient of thyroid hormones, in the antiangiogenic role in the tumor microenvironment has also been established [43]. The thyroid hormonal role in chronic lymphocytic leukemia [44] is well known. The role of thyroid hormone–integrin αvβ3 and the therapeutic strategies for colorectal cancer has been reported recently [37]. The crosstalk between the αvβ3 integrin and the estrogen receptor is implicated in the proliferation of ovarian cancer [38] and human lung carcinoma [45].

Thyroid hormones, *e.g.*, T3 (3,5,3′-triiodo-L-thyronine) and T4 (L-thyroxine), produce nongenomic effects and are well known to control several cellular and subcellular functions, thereby affecting multiple organs. The effects are primarily maintained through αvβ3 integrin together with other receptors, not to mention the TRα and TRβ. The cancer cells, capable of reprogramming their metabolism, adopt aerobic glycolysis instead of oxidative phosphorylation, thereby dysregulating the PKM2 (pyruvate kinase isoform M2, cellular energetics mediator), the rate-limiting enzyme of glycolysis, and due to several biochemical processes and signal transduction activities, the cancer cells produce more reactive oxygen species (ROS) to survive and propagate. Thyroid hormones are also associated with oxidative injury in hyperthyroidism where increased production of ROS and reactive nitrogen species is observed. The inhibition of αvβ3 signaling, through ligand binding, has a prominent role in mediating the dysregulation and finally the cancer progression by stopping the increased angiogenesis. The involvement of thyroid constituents, T3 and T4, in liver cancer has been described [46]. The implications of the thyroid hormones and the integrin over expression are well debated and have led to the focus primarily on the development of novel drugs, of which both traditional and contemporary nano-architectural originating drugs for anti-integrin therapies in conjunction with the thyroid hormones are designed and produced. The thyroid hormones, T3 and T4, including other thyroid hormone agonist analogs [47] are pro-angiogenic in nature [48]. The pro-angiogenic activity removal of thyroid hormone at cell surface receptor is thought to regress the tumor xenografts by ~50% [49–51] and hence can shrink the tumor significantly. As the thyroid hormones are the key regulators of several cellular processes of cell proliferation, differentiation, apoptosis, and metabolism, their association with the cancer mass has been suggested very earlier [52]. The clinical observations have supported the notion that hormonal deficiency and hypothyroidism inhibit tumor growth [24,53,54]. These actions are facilitated through several nongenomic pathways, which include activation of integrin αvβ3. The αvβ3 integrin, containing binding sites, S1 and S2 [55], binds to the thyroid components, T3 and T4, with a lower affinity for T4 than T3. The physiologically present T3 specifically binds to S1 and activates the phosphoinositide 3-kinase pathway, while the T4 binds at the S2 receptor site and

activates the MAPK3 and MAPK1, or ERK1 and ERK2 (44 and 42 kDa Ser/Thr kinases) pathways involving the Ras-Raf-MEK-ERK cascade of signal transduction, which participates in the regulation of adhesion, progression, migration, survival, differentiation, proliferation, transcription, and metabolism [56]. Thus, the αvβ3 integrin enables the proliferative action of thyroid hormones on cancer cells and participates in angiogenesis involving the blood vessel cells [35]. In the nutshell, the dysregulation of physiologically bioavailable thyroid hormones affects cancer development and progression and escalates the risk of solid tumors of different organs and tissues through higher availability of T3, together with the T4 thyroid hormones, thereby increasing the integrin binding, which has been mainly supported by clinical and subclinical studies [57]. The reduction in the biological presence of thyroid hormones or lesser bioavailability, their inhibition, and their restricted and reduced binding to the integrin receptor through antagonists have led to newer anticancer agents. In this context, the unraveling of the 3D structure of the αvβ3 integrin, its regulation of the ligand binding, and binding affinity manipulated through antagonistic molecules of low and high molecular weight with the capability to stabilize certain specific conformations of the integrin receptor and the signaling to the cell; the molecules that may antagonistically inhibit certain intercellular adhesion functions have been proposed as the rationale for integrin-based drug design. The heterodimeric structure, being capable of recognizing several different types of structural motifs, together with regulating the binding affinity, directs the conformational changes at the receptor site and establish communication between the extracellular and intracellular domains of the cells. Thus, the ligand binding influences the allosteric changes in the integrin conformation, and the integrin's information feeds up about the external cellular environment to the cell. Therefore, the integrins that serve as sensors of the extracellular matrix, and their surroundings at the molecular level, together with working as an effector system for certain cytoskeletal forces, including the blood vessels, effectively make the sensor-effector system based on its heterodimeric structure and its amino acid sequence employed in different functions of the cells [58]. Moreover, as the thyroid hormones support the proliferation of cancer cells [59–62], any change in the tumor size suggested several plausible mechanisms with the hormonal activity being reduced at the tumor site [57]. Importantly, the pro-angiogenic activity of T3 and T4 hormones originate at the surface of the cellular receptor, integrin αvβ3, partly found extracellularly on the cell membrane whose mechanism has been understood on the chick chorioallantoic membrane (CAM) model-based assays [62], and the integrins have been shown to express multiple functions that connect to the ECM proteins [63], cell surface, and within the cells located growth factor receptors [64], as well as in the specific gene transcriptions [65]. Also, the iodothyronine receptors on the integrin have been found to regulate the cancer-relevant angiogenesis and are considered as the key for cancer cells' survival through the involved pathways. The iodothyronine receptor can be covered with certain drugs and their nanoscale covalent conjugate [66,67] to provide antitumor effects through regressed or terminated angiogenesis.

3 Anti-αvβ3 integrin-based drugs for cancer chemotherapy

The tumor cells repenetrate the vessels or walls and continue to multiply forming another clinically detectable tumor over a period, which is characterized as metastatic tumors [68]. Alterations in the adhesive nature of the tumor cells can bring significant changes in the metastasis of these cancers. Thus, limiting the role of the molecules involved in various pathological activities, such as tumor's neo-vascularization and metastasis, can bring significant therapeutic effects. An encouraging target for cancer treatment, integrin αvβ3, is capable of binding to several ECM components, *i.e.*, fibrinogen, fibronectin, and so on to provide the desired effects on cell proliferation, cell adhesion, and control on the further development of the cells colony. The αvβ3 is expressed on the malignant tumor cells that have made them an attractive target for developing anti-αvβ3 antagonists' molecular templates and biologically active new chemical entities. The antagonists of αvβ3 receptor protein by inducing the apoptosis of the new blood vessel can block tumor-associated angiogenesis and thereby leaves the malignant cells dysfunctional. Figure 4 shows selected αvβ3 antagonists developed by various groups and pharmaceutical concerns.

On the molecular level, the thyroid hormone analog molecules, T3 and T4, also termed thyrointegrins, work and selectively activate the extracellularly available integrin receptors. The recognition site, Arg-Gly-Asp (RGD), is in close approach within the receptor [69], and the receptors, thyroid-hormone, and αvβ3, structurally and functionally are neither analogous nor related to each other, but triggering of the thyrointegrin receptors located on the cell surface results in nuclear mediation to elicit pro-angiogenic activity. The radio-ligand binding studies have confirmed the preferences of the purified αvβ3 receptor, which is higher to T4 than T3 [70]. Sources also demonstrated that the activation and nuclear translocation of mitogen-activated

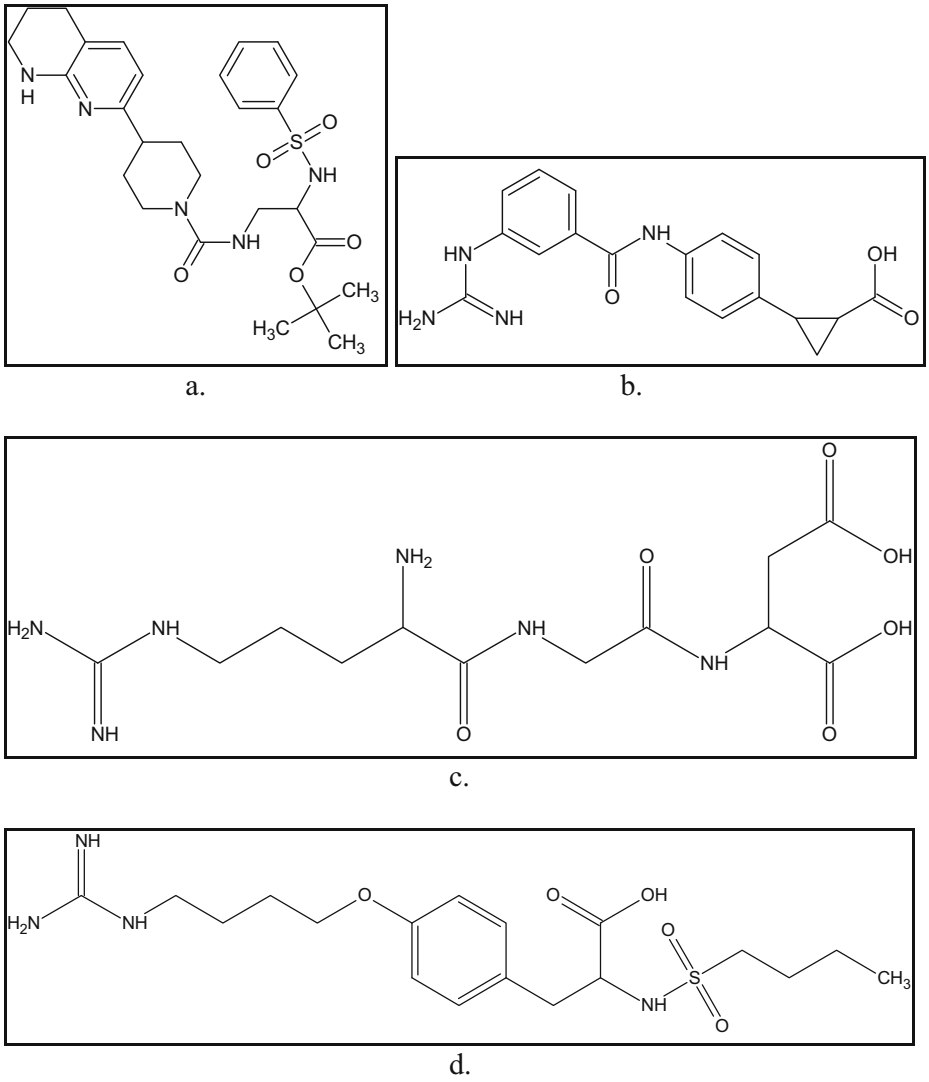


Figure 4: Major αvβ3 antagonists; (a) Merck & Co, patent WO 9818461-A1: 4-(δ-6,7,8-tetrahydro-[l,8]naphthyridin-2-yl)piperidin-l-yl-carbonyl-2-(*S*)-phenylsulfonylamino-β-alanine-*t*-butylester; (b) searle, patent WO 9736858-A1: 2-[3-[[[[3-[(amino-imino methyl)-amino] phenyl] carbonyl]-amino] methyl] phenyl]-cyclopropane carboxylic acid (trifluoro acetate salt); (c) Merck KGaA, patent DE 19548709-A: 2(*S*)-2-[[2-[[(2*S*)-2-amino-5-(diamino methylidene amino)]amino]acetyl]amino] butanedioic acid; (d) (*S*)-2-butylsulfonamido-3-[4-(3-amino-propoxy) phenyl]-propionic acid.

protein kinases (MAPKs) and hormone-induced angiogenesis is comparatively higher because of the thyroid hormone T4 compared to the T3. The role of thyrointegrin is imperative in these senses. The binding of the T4 to the integrin receptor is inhibited by the integrin αvβ3 antagonists, which thereby prevents the activation of MAPK signals, which were conclusively based on the spotting of the binding site for iodothyronine on the integrin receptor, and well relates to the functional aspects of the MAPK signal cascade activation by the thyroid hormone. The thyroid hormone derivative, 3-iodothyronamine, is also reported to conjugate with a trace amine receptor (TAR-I), but operationally, the entity is opposite to thyroid hormones, T3 and T4 [71]. The binding domains of the integrin αvβ3 constitute two binding domains for the thyroid hormone [72]. Domain 1 is an RGD tripeptide-sensitive site, and it has no relation to cellular proliferation. However, the RGD-recognition site, which contributes to the interaction of different proteins, connects the integrin systemically and mechanistically with the ECM proteins. However, domain 2, is an insensitive RGD tripeptide site and contributes to cellular proliferation as well as angiogenesis, thereby making both the sites structurally distinct and functionally altogether different. The thyroidal receptor and the RGD tripeptide recognition sites are nearly overlapping in their situational domains. The site of the thyroid hormone also functions in a unique way in the process of gene

expression during the tumor cell proliferation and contributes its role effectively [73,74]. Moreover, these receptors (thyroid hormone receptors) present on the cell membrane are G protein sensitive [75].

The Tetrac blocked the effects of T4 and T3. Thyroid hormone analogs, when applied locally, promoted the desirable neovascularization, *e.g.*, in healing the wounds or to prevent the undesirable angiogenesis that supports the growth of tumors and can be inhibited by using Tetrac. The polymer conjugates and nanoparticle formulations of thyroid hormones and their analogs were also prepared to test the inhibition of angiogenesis [76]. Other anti-angiogenic agents and their derivatives with the polymeric entities, liposomes, nano, and microstructured materials have been prepared and studied. mAb LM609 Tetrac, Triac, and XT 199 are a few illustrations of such anti-angiogenic thyroid hormone antagonists (Figure 5). The nanoparticles were attached through a hydroxyl group. Among the well-known thyroid agonists, the di iodo thyro propionic acid and the GC-I, GC-1 agonist's linking was also achieved. The ether bond, as found in T3, T4, Triac, and Tetrac, does not seem to be essential [77] for the activity exhibition. However, the intervening carbon is required rather than the ethereal bond. The 3′ iodine of the outer ring is also not necessary according to the structure–activity relationship (SAR) requirements. Similarly, position 3′ need not be modified [78] for any elicitation of the biological activity. Through the amide bond embedded in the nanoparticles, the linker was linked to the nanoparticle and thus contributed to the development of novel nano-formulations containing αvβ3 antagonists. The synthesis of guanidine, urea, methylamine, and propylamine derivatives of the Tetrac has also shown anti-angiogenic bioactivity in the CAM model from 65% to 73% inhibitions at the dose of 0.25–2.0 μg/mL [79].

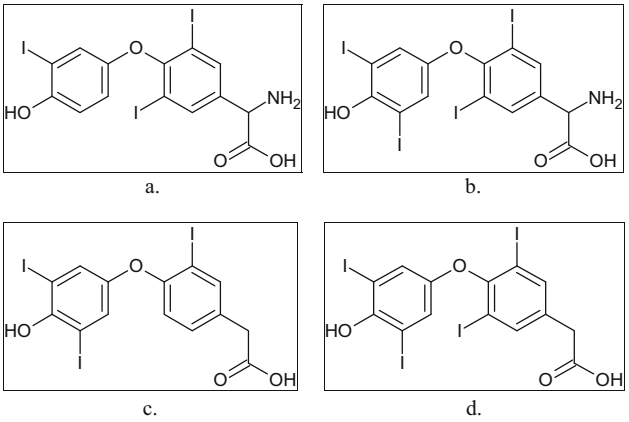


Figure 5: Thyroid hormone compounds, its analogs, and thyrointegrin antagonist; (a) T3, (b) T4, (c) Triac, and (d) Tetrac.

4 Contemporary nano-architectured drugs

Nanoparticulate formulations of thyroid hormones and analogs were synthesized with additional polymeric conjugations. To locally deliver the thyroid hormone and its analogs, the nanoparticles delivery modalities together with polymeric conjugates were used as a carrier and delivery/transportation matrices. The chronologically defined delivery at the targeted tissue and cell sites with the nano-sized entities was achieved, wherein the prepared nano-enabled antagonist drugs were between ~150 and 250 nm in size [80]. The nanoparticles or the thyroid analog-conjugated polymers can also target cancers in various body sites, including the skin. In addition, the thyroid hormone analogs and their antagonist can also be employed for hematopoietic, as well as stem cell-related malfunctions and disorders.

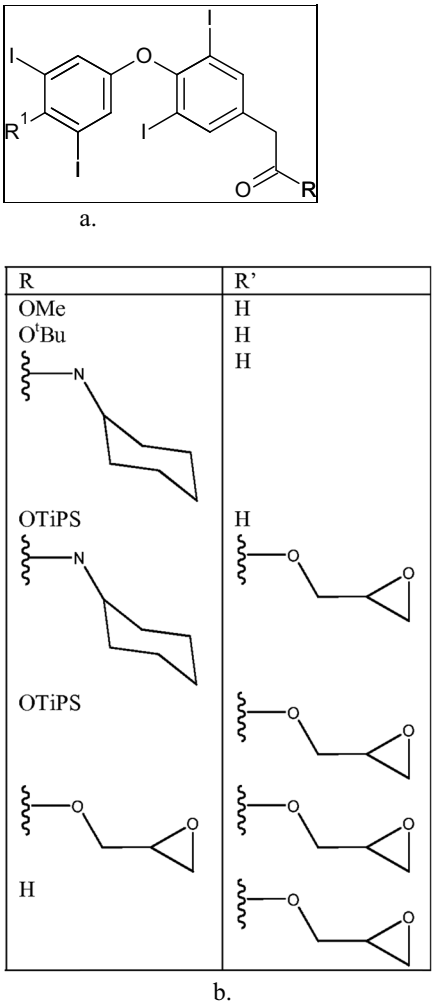


Figure 6: Tetrac and related products: (a) Tetrac (R^1 = R = OH) and (b) various semisynthetic products.

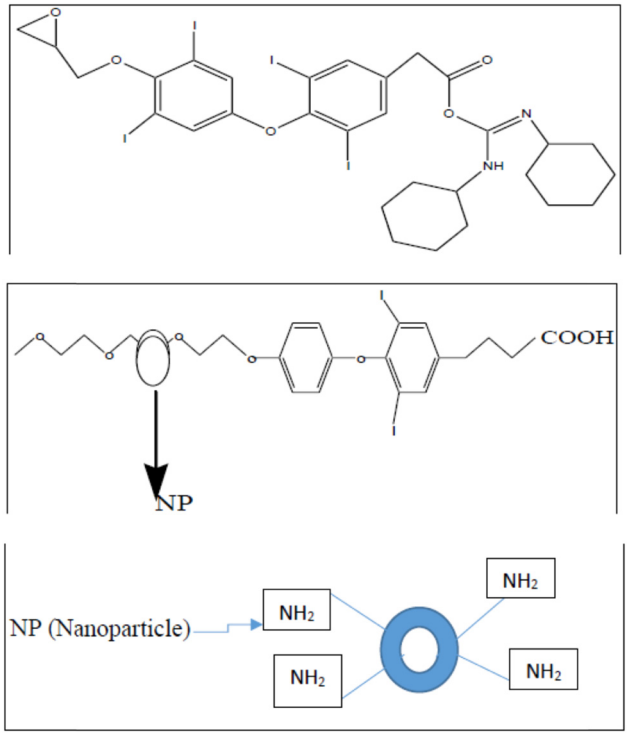


Figure 7: Nano-Tetrac drug model.

These formulations have been recommended for delivery for faster cell reproduction at the time of bone marrow transplant. The semisynthetic precursors of Tetrac (Figure 6a, and b) were also researched to find and institute the best product for angiogenesis [81,82].

In addition, with the help of various RNA microarray techniques, the genomic activities within thyroid hormones, specifically at αvβ3 receptors, were studied in various cancer cell lines obtained from human samples [37,83–86]. Previous studies have also established the anticancer ability of the Tetrac, which antagonizes the proliferation of cancer cells. The thyroid hormone is anti-apoptotic [87], whereas the Tetrac has pro-apoptotic characteristics [39]. The Tetrac analog-treated tumors have been investigated in detail for apoptosis-related and differently regulated gene contributions. The unchanged moieties of Tetrac and Triac molecules were covalently conjugated with nanoparticles that inhibited entrance into the cells and effectively destructed the MDA-MB-231 cells (estrogen receptor-negative human breast cancer cells). The genes, *BCL2L14* and *CASP2*, were also accelerated, but the Tetrac formulation diminished the expressions of anti-apoptotic *MCLI* and *XIAP* genes [88,89].

Angiogenesis in cancers involves downregulation of thrombospondin-1 (TSP-1), which is an endogenous inhibitor of angiogenesis. The transformation of genetic lesions through the expression of mutant RAS oncogene, which is intrinsic to the cancer cells, induces the TSP-1 downregulation. However, the effect of the mutant *RAS* gene on tumor neo-vascularization is confined not only to angiogenic modulation in cancer cells but also to the RAS with different signaling mechanisms and also to elicit proangiogenic effects [90]. The Rab18 and Rab1B were among various RAS oncogenes, which were considered to be highly affected by the nanoparticles of Tetrac [90]. The Rab18 was downregulated, whereas RablB was upregulated. The RablB expression is considered responsible for the differentiation of malignant cells, *e.g.*, the monocytes in promyelocyte leukemia [91]. The agonist thyroid hormone-supported proangiogenic activity is blocked by Tetrac, an anti-angiogenic product. The microarray results

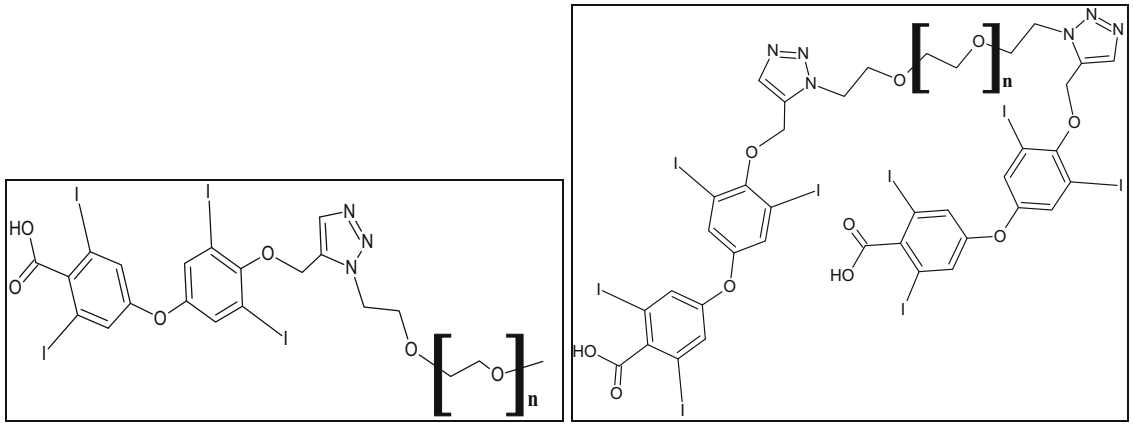
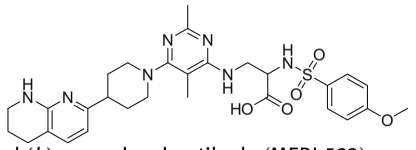
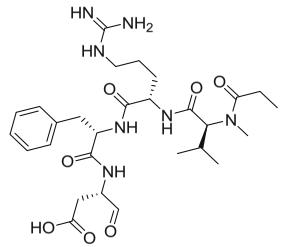
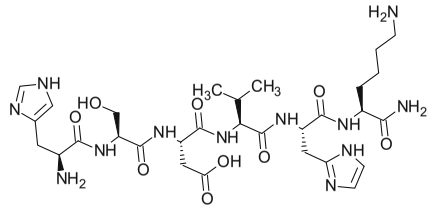


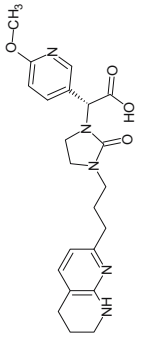
Figure 8: Chemical structures of PEG (polyethylene glycol) conjugated Tetrac: (a) PEG-conjugated one Tetrac unit conjoined through single triazole unit (PEG-triazole-Tetrac, P-mono-TAT); (b) two Tetrac units) conjoined through distantly placed two triazole structures (Tetrac-triazole-PEG-triazole-Tetrac [P-bi-TAT]); *n* means the average number of repeating oxy ethylene units (90) of the polymer PEG, PEG A_V MW 4,000 amu.

Table 1: Drug candidates based on integrin antagonists under development

Category	Compound/code	Target and structure	Application/description	Ref.
Small molecule	GLPG 0187	Targets αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, and α5β1 	Selective 1.3 nM IC_{50} for αvβ1, RGD binding, clinical trial for liver cancer	[108]
Monoclonal antibodies	*h*-Vitaxin (*h* humanized)	αvβ3, humanized (*h*) monoclonal antibody (MEDI-523)	Clinical trials for metastatic melanoma and prostate cancers, phase I and II trials	[109]
	Etaracizumab	αvβ3, humanized monoclonal antibody (MEDI-522)	Clinical trials for melanoma, prostate, and ovarian cancers, phase II trials	[110]
	Abituzumab (ITGAV)	αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, humanized IgG2 monoclonal antibody	Clinical trials for colorectal, multiple sclerosis, interstitial lung, and prostate cancers, phase I and II trials	[111]
Peptidic	Cilengitide (EMD 121974)	Selective for αvβ3, αvβ5 	Clinical trials for multiple cancers, phase I, II, and III trials	[112]
	HSDVHK-NH_2	αvβ3, antagonist of integrin αvβ3-vitronectin interaction 	Site-specific RGD recognition, antagonist against αvβ3-GRGDSP, integrin αvβ3-vitronectin interaction, with an IC_{50} of 1.74 pg/mL	[113,114]
	Echistatin and its TFA (trifluoro acetic acid) salt	αvIbβ3, αvβ3, and α5β1, smallest active RGD protein, disintegrin type – derived from viper snake venom; sequence structure with disulfide bridges at Cys^2–Cys^{11}; Cys^7–Cys^{32}; Cys^8–Cys^{37}; Cys^{20}–Cys^{39}:AA (amino acid) sequence: ECESGPCCRNCKFLKEGTICKRARGDDMDDYCNGKTCDCPRNPHKGPAT	An integrin antagonist developed to inhibit osteoclastic bone resorption	[115]

(*Continued*)

Table 1: *Continued*

Category	Compound/code	Target and structure	Application/description	Ref.
Nonpeptide	MK-0429 (L-000845704)	Selective antagonist, orally active, targets αvβ1, αvβ3, αvβ5, αvβ6, αvβ8, and α5β1 	Pan-integrin antagonist	[116]

have proposed another mechanism for Tetrac, wherein it is supposed to inhibit angiogenesis through upregulation of *THBSI* gene expression [92]. The prohibition of tumor cells growth is supported by the pure, un-modified Tetrac and its different nano-preparations (Figure 7) through upregulation of THBSI expression. The expressions of *CBYI*, *XIAP*, and *THBSI* genes are affected by Tetrac nanoparticles. In addition, the nanoparticle formulations of Tetrac helped in showing MDA-MB-231 cell gene expressions, which are part of the cell survival mechanism [89]. This suggested that the pure, unchanged Tetrac and its nanoformulations can fit in the integrin-binding site, which is slightly different. The thyroid hormone receptor domain contains closely related receptor sites, and either of these two acts through specific transduction. Therefore, the fact of distinction between nanoparticulate and unmodified Tetrac by receptor domains is not surprising. The other possibility is that the structurally unchanged Tetrac might have triggered actions that offset to initiate the integrin αvβ3 receptor site activation and binding. Interestingly, in the absence of T3 and T4, the coherent behaviors of the antibasic fibroblast growth factor and the anti-vascular endothelial growth factor, with Tetrac involvement, have been found in the endothelial cells [93,94]. Therefore, the nanoparticle-loaded Tetrac's action at triple-negative breast cancer, the most malignant tumor, is not surprising.

These novels Tetrac nanodrugs also inhibit the human cancers' major oncogenic Wnt signaling pathway. It also happens to be conjoined with downregulation of *CTNNAI* and *CTNNA2* expressions, the catenin genes [95], along with the concurrent up-regulation of the *CBYl* gene, the nuclear antagonist for the catenin activity. Also, there are 13 differentially regulated RAS oncogenes reported [96], of which 8 are downregulated after the Tetrac and its nano-sized formulated drugs through interfering with the oncogenic-signaling pathways, and this is a clear indication of the signaling pathways and the integrin involvement in anticancer activities. The cross-talks add to the complex signaling and can lead to cells' unpredictable fate and therapeutic outcomes [97].

Among other products mimicking the Tetrac in completely binding to the αvβ3 integrin, and with the thyroid hormone receptor, to restrict cancer proliferation, the analog of (*E*)-stilbene, resveratrol, is worth mentioning. Nanotechnical advances in preparing the RGD (Arg-Gly-Asp) tripeptide conjugate with gadolinium-molybdenum dioxide (RGD-Gd-MoO_2) for magnetic resonance imaging (MRI) and cancer therapy, as an ideal theranostic agent, the derivative of Tetrac, the 150–200 nm sized PLGA-encapsulated N-DAT (Nano-Diamino-Tetrac-PLGA), and nano-resveratrol (N-RES) for targeting the integrin αvβ3

for cancer controls are reported [98]. The diamino-Tetrac-PLGA conjugates (DAT-PLGA) and the PLGA-encapsulated nano-DAT (N-DAT-PLGA, or N-DAT) effects on different cancer cell lines, *i.e.*, pancreatic, breast, lungs (non-small cell), colorectal, hepatocellular, glioblastoma, bladder, and gastric, namely, SUIT-2, MPanc96, MDA-MB-231, MCF-7, H1299, HepG2, U87, 253JBV, and AGS in the *in vitro* and *in vivo* xenograft models, were of downregulating nature for the αvβ3 expressions. Reduction and viability were exhibited in N-DAT-treated glioblastoma xenografts, and N-DAT was found to be safe at higher doses [99]. The N-DAT and Tetrac together are known to induce antiproliferation activity through αvβ3 intermediacy in different K-RAS (K-RAS-mutant HCT116 cells and K-RAS-wild type HT-29 cells) colorectal cancer [100]. In addition, the cyclic RGD-based pentapeptide derivative {*cyclo*-(Arg-Gly-Asp-D-Phe-Lys)}, the c-$(RGDfK)_2$, conjugates of poly-L-glutamic acid (PGA) and polyethylene glycol (PEG) with an anticancer agent, paclitaxel (PTX), as PGA-PTX-E-[c(RGDfK)2] and PTX-PEG-E-[c(RGDfK)2] conjugates exhibited boosted anticancer activity against MDA-MB-231 tumor cells [101]. The PLGA-PEG-NPs {poly-(D,L-lactic-*co*-glycolic acid)-*block*-polyethylene glycol nanoparticles} in conjunction with the c-(RGDfK) motifs were utilized to nano-formulate another anticancer agent, cisplatin, to target integrin αvβ3 at RGD-binding domain in cancer cells [102]. The interesting observation of shape effects of the constructs, including nano, micellar, cyclic, and linear formulation products, was remarkable and noteworthy. The solubilization capacity, and the stability in kinetic terms of lower energy status, provided the cyclic RGD derivatives improved targeting, while the linear RGD constructs were less pronounced in their targeting efficiency [103]. The nanoparticulate shape provided better-enhanced cytotoxicity in comparison to the non-nano formulations for the cisplatin in prostate and breast cancer cell lines [104]. The nanoparticle-shaped molecular entities also exhibited selective efficiency and potent activation through enhancements in their permeability retentions [105].

Recently (12/2021), PEG-conjugated two Tetrac units (Tetrac-triazole-PEG-triazole-Tetrac) conjoined through distantly placed two triazole entities, together with PEG-conjugated one Tetrac unit conjoined through a single triazole unit (PEG-triazole-Tetrac) (Figure 8) [106], were reported for their pharmacokinetics and biodistribution studies in animal models' serum through utilizing a concurrently developed bioanalytical method for the purpose. The product, P-bi-TAT, was found to be involved in downregulating several signaling pathways, including the NF-kB, and was suggested for acute myeloid leukemia and other malignancies owing to their high thyrointegrin αvβ3 affinity [107].

A list (Table 1) of drug candidates' structural classes types under evaluations at different phases of clinical trials (phase I–III) also discusses the applications and integrin receptor specificity along with their molecular structures developed as integrins, especially αvβ3 inhibitors.

5 Summary and future prospects

Significant knowledge about the role of integrins in various pathological and physiological conditions led to the invention of various therapeutic agents. The nano-sized formulated αvβ3 antagonist drugs certainly play an important role in several biological activities in therapeutically relevant pathways, which needs further and deeper studies, to pinpoint αvβ3 inhibition targets. The Tetrac model is an initiating point in developing αvβ3 antagonist drugs as nano modalities that might form part of the combination therapy as an anticancer agent. Opportunities for other cross-reactive and closely related thyrointegrin antagonists may also be searched to lead the design of newer and specifically targeted new chemical entities at specific locations in the receptor. Efforts to design and develop new chemical entities fitting the receptor binding site, and pharmacophore-based model products exists which could be transformed in future into nanostructural motifs, and conjugates of a plethora of biodegradable and biocompatible polymers of natural, synthetic, and semi-synthetic origins.

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