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Synthesis and biological evaluation of non-peptide $\alpha_v\beta_3/\alpha_5\beta_1$ integrin dual antagonists containing 5,6-dihydropyridin-2-one scaffolds

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Abstract—Small constrained non-peptidic molecules consisting of a polyfunctionalized rigid core, carrying appendages corresponding to arginine and aspartic acid side chains, have been recently reported to be promising for drug development. In this work, the 5,6-dihydropyridin-2-one was envisaged as a scaffold to turn into potential integrin ligands, introducing a carboxylic acid and a basic appendage. The synthesis and the antiadhesion activity of a small library of peptidomimetics capable to recognize $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins has been herein reported.

1. Introduction

Integrins are a large family of heterodimeric transmembrane glycoproteins involved in the attachment of a cell to the extracellular matrix (ECM) and in signal transduction from the ECM to the cell.[1] These adhesion mechanisms are of fundamental importance in a diverse range of biological processes, including cell differentiation, apoptosis, embryonic cell migration, maintenance of tissue integrity, and blood coagulation.[2] Alterations or aberrations in integrin-mediated cell adhesion have been connected with the pathogenesis of several diseases such as atherosclerosis, osteoporosis, cancer and a variety of inflammatory disorders, making integrins an attractive target for the development of therapeutic agents.[3] The identification of key recognition motifs within integrin ligands is the starting point for the development of antagonists. To date, these motifs have been identified for only a few subtypes. $\alpha_v\beta_3$ integrin has been deeply investigated as it is involved-tumor proliferation and metastasis through the formation of new blood vessels. $\alpha_v\beta_3$ integrin binds to a wide number of ECM components like fibronectin, fibrinogen, vitronectin, and osteopontin through recognition of the Arg-Gly-Asp (RGD) tripeptide sequence.[4] This sequence is also essential for the binding of $\alpha_5\beta_1$ integrin to fibronectin, which has been unambiguously recognized as proangiogenic receptor.[5] $\alpha_5\beta_1$ integrin may regulate the function of integrins $\alpha_v\beta_3$ on endothelial cells during their migration in vitro or angiogenesis in vivo. Activation of $\alpha_5\beta_1$ potentiates $\alpha_v\beta_3$-mediated migration on vitronectin, whereas $\alpha_5\beta_1$ integrin antagonists inhibit $\alpha_v\beta_3$-mediated cell spreading. Therefore, antagonists of both integrins, block the same pathway of angiogenesis.[6] In this paper, we report the design, synthesis, and blockade of fibronectin-mediated cell adhesion of novel $\alpha_v\beta_3/\alpha_5\beta_1$ integrin dual antagonists, whose activity could be synergistically effective in preventing angiogenesis.

The X-ray analysis[7] of the complex between $\alpha_v\beta_3$ integrin and c(RGDfV) ligand shows that the ligand interacts mainly through electrostatic interactions. Arg and Asp form a charged clamp that binds regions with opposite charges in the protein: Asp interacts with a metal cation in the β subunit and Arg with two Asp in the α subunit.

Several efficient classes of ligands, containing the RGD sequence, have been reported in the literature.[8] These structures share as common features conformational

Keywords: $\alpha_v\beta_3$-Integrin; $\alpha_5\beta_1$-Integrin; Dual antagonist; Dihydropyridinone.
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restraints able to give a proper orientation to the peripheral substituents.

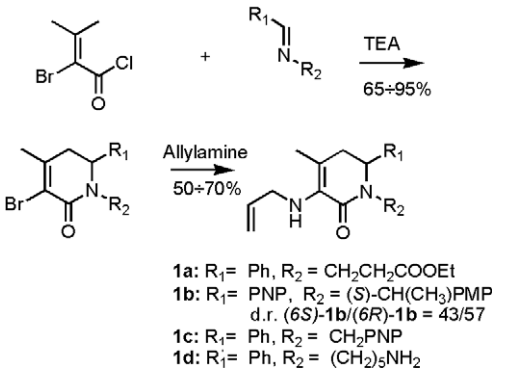
Linear and cyclic peptides containing the RGD sequence, showing high affinity toward $\alpha_v\beta_3$ integrins, have significant therapeutic potential but serious limitations especially for oral dosing. The need for antagonists with higher bioavailability and lower molecular weight has prompted several research groups to develop small constrained non-peptidic molecules mimicking the RGD motif, which would be more promising for drug development.[9]

Most of the structures proposed so far consist of a polyfunctionalized rigid core, linked to appendages corresponding to arginine and aspartic acid side chains.[10] The basicity and the length of the arginine-mimicking group was found to play a central role. Moreover, the presence of a carboxylic function, mimicking the aspartic acid residue in the original binding motif, is a fundamental feature to create anionic interaction with the metal cation in the receptor active site.[11] Many heterocyclic scaffolds have been employed to maintain the acidic and the basic ends of the molecule at the appropriate distance and with the suitable conformation for binding interaction.

We identified the 5,6-dihydropyridin-2-one as scaffold,[12] easily prepared through a short concise synthesis (Scheme 1).

This heterocycle may be converted into a potential integrin ligand introducing the acidic and the basic appendages as reported in Models A, B, and C (Fig. 1).

To evaluate the biological activity of these novel compounds in a cellular environment, we tested their ability to perturb initial cell attachment mediated by $\alpha_v\beta_3$ integrin and $\alpha_5\beta_1$ integrin using cell adhesion assays. The integrin ligand fibronectin (10 μg/ml) was immobilized on tissue culture plates. The ability of human melanoma cell line SK-MEL 24, expressing $\alpha_v\beta_3$ integrin,[13] and human erythroleukemic cell line K562, expressing $\alpha_5\beta_1$ integrin,[14] to adhere to fibronectin in the presence or absence of the assayed compounds was examined. The antiadhesion activity of the well-known integrin antagonist



Scheme 1. Synthetic route to 5,6-dihydropyridin-2-one **1**.

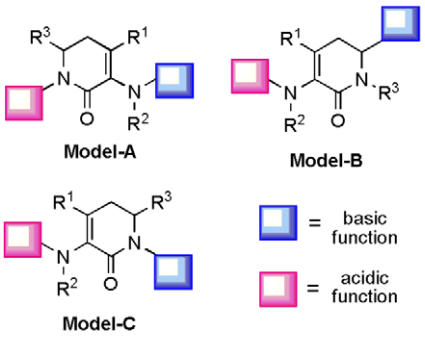


Figure 1. Model A, B, C integrin ligands.

Ac-Asp-Arg-Leu-Asp-Ser-OH (H3534) was measured as a positive control.[15]

2. Results

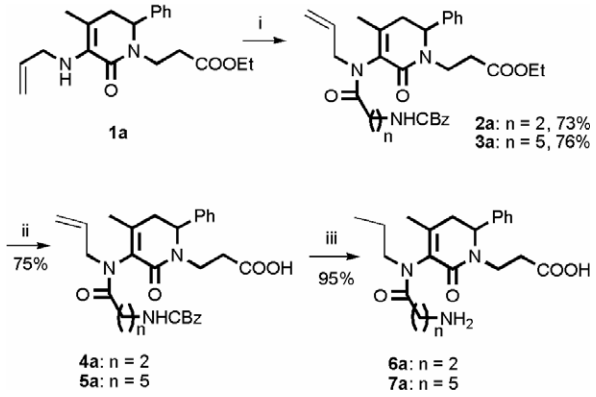
2.1. Synthesis of model A antagonists

The highly functionalized racemic compound **1a**[12] was chosen as precursor in the design of model A $\alpha_v\beta_3$ integrin antagonists. The introduction of the basic function was carried out through nitrogen acylation with Cbz-aminoalkanoic chloride, followed by hydrolysis of the ester function and hydrogenation (Scheme 2).

Compounds **6a** and **7a** were isolated in 55% overall yield and were tested for their ability to perturb initial cell attachment mediated by $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrin. The results obtained are reported in Table 1. All the compounds did not exhibit a potent inhibition of $\alpha_v\beta_3$- and $\alpha_5\beta_1$-mediated cell adhesion (Table 1).

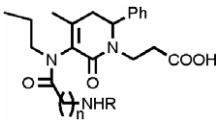
Under these experimental conditions, reference compound H3534 caused a noteworthy inhibition of $\alpha_v\beta_3$-mediated cell adhesion and was less potent toward $\alpha_5\beta_1$-mediated cell adhesion (Table 1).

Although compounds **6a** and **7a** were designed with a considerable difference in the distance between acidic



Scheme 2. Reagents and conditions: i—Cl-CO-$(CH_2)_n$NHCbz, pyridine, CH_2Cl_2, rt; ii—LiOH, THF/MeOH/H_2O; iii—H_2, Pd/C, MeOH, rt.

Table 1. $\alpha_v\beta_3$- and $\alpha_5\beta_1$-integrin mediated cell adhesion to fibronectin in the presence of Model-A like ligands



Compound	IC_{50} (μM)[a]	
	$\alpha_v\beta_3$	$\alpha_5\beta_1$
6a	>1000	>1000
7a	>1000	>1000
H3534	0.025	259

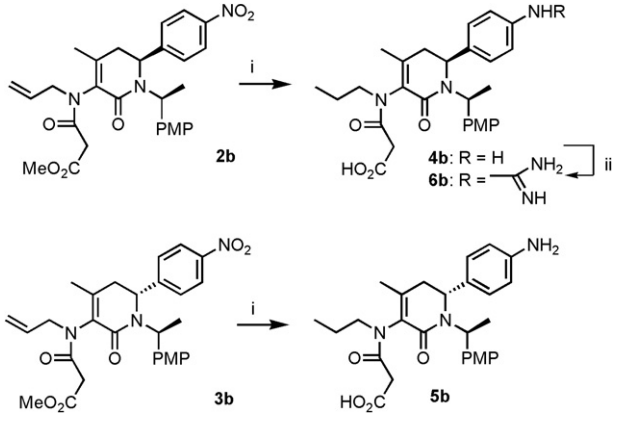
[a] Values are means ± standard error of three experiments.

and basic moieties, they both show a very low affinity toward the two proangiogenic receptors. Thus, we explored the possibility to enhance integrin antagonist properties, modifying our synthetic plan according to Models B and C.

2.2. Synthesis of model B antagonists

As shown in Figure 1, the model B-like antagonists contain the basic function on the C6 side chain of the dihydropyridinone. This function has been introduced in the 5,6-dihydropyridin-2-one **1b** through a nitro-derivative precursor. The choice of (*S*)-*p*-methoxyphenylethylamine as starting building block allowed to obtain dihydropyridinones (6*S*)-**1b** and (6*R*)-**1b** in 43/57 diastereomeric ratio (Scheme 1).[16] The diastereomers were easily separated by flash chromatography on silica gel. Nitrogen acylation with methyl malonyl chloride gave, respectively, the intermediates **2b** and **3b**. Hydrogenation, followed by hydrolysis of the ester, allowed optically active **4b** and **5b** to be obtained in good yield (Scheme 3).

The guanidinic group was introduced by treatment of the intermediate ester deriving from **2b** reduction, with *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carboxamidine in DMF. The guanidino derivative was then transformed into free carboxylic acid by treatment with LiOH in MeOH/THF/H_2O and BOC deprotection was performed in neat trifluoroacetic acid. Enantiomerically pure **6b** was obtained from this reaction sequence in good yield (Scheme 3).



Scheme 3. Reagents and conditions: i—(a) H_2, Pd/C, MeOH, rt; (b) LiOH, THF/MeOH/H_2O, rt: ii—(a) *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carboxamidine, DMF, rt; (b) TFA, rt.

These compounds, carrying a free amino group and the carboxylic acid function, have been tested in cell-adhesion assays and the results are reported in Table 2.

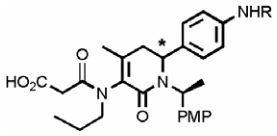
Compound (6*S*)-**4b** showed a significant inhibition of $\alpha_v\beta_3$-integrin mediated cell adhesion with submicromolar IC_{50}. Unfortunately, it was completely uneffective toward $\alpha_5\beta_1$ integrin. On the contrary, the (6*R*)-**5b** showed a lower activity in $\alpha_v\beta_3$ integrin mediated adhesion assays whereas it was a good inhibition of $\alpha_5\beta_1$-mediated cell adhesion. Since dual antagonists, capable to block the adhesion function of both integrins, can be considered more promising as angiogenesis inhibitors, **4b** and **5b** do not appear to be attractive for any further therapeutical development. Finally, guanidino-derivative **6b** resulted inactive toward both integrins. In conclusion, comparison of the results obtained for **4b** and **6b** showed that no advantage could be derived by the introduction of the guanidino moiety.

2.3. Synthesis of model C antagonists

The model C-like antagonists contain the basic function on the amide side chain of the dihydropyiridinone. This function has been introduced in the intermediate **1c**, synthesized via ketene/imine cycloaddition between 2-bromo-3-methyl-chrotonyl chloride and the imine of benzaldehyde and *p*-nitro-benzylamine, followed by treatment with allylamine (Scheme 1).

The affinity and selectivity of a ligand for $\alpha_v\beta_3$ integrin is based on the spatial disposition of the C-terminal carboxylic acid and the N-terminal basic group. The distance has been reported to be optimal when it is about twelve-thirteen bonds;[9a] therefore, we modified the spacer length, introducing methyl malonyl chloride and ethyl fumaryl chloride, to give rise to **2c** and **3c** in 70% yield.

Table 2. $\alpha_v\beta_3$- and $\alpha_5\beta_1$-integrin mediated cell adhesion to fibronectin in the presence of Model-B like ligands



Compound	R	IC_{50} (μM)[a]	
		$\alpha_v\beta_3$	$\alpha_5\beta_1$
4b	H	0.24 ± 0.04	>1000
5b	H	21 ± 4	0.018 ± 0.006
6b		>1000	>1000

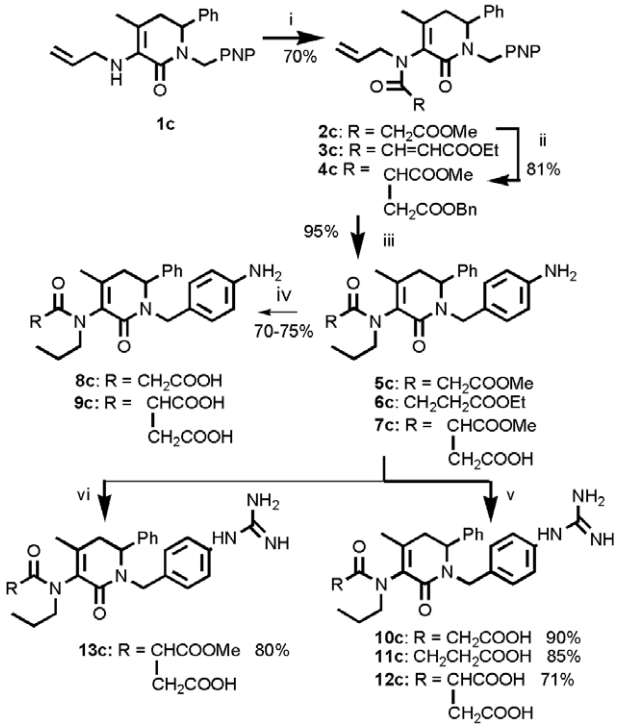
[a] Values are means ± standard error of three experiments.

Moreover, the easy α-alkylation of **2c** with NaH in THF and benzyl bromoacetate gave **4c** in 81% yield. The introduction of the amino function and the consecutive conversion into the corresponding guanidino-derivatives allowed to obtain the first small library of model C-like antagonists. Hydrogenation of **2c** and **4c**, followed by treatment with LiOH in methanol/water/THF solution, gave **8c** and **9c**, having a free amino group and, respectively, one or two free carboxylic acid functions.

The guanidino-derivatives **10c**, **11c**, and **12c** were obtained, starting from hydrogenation products **5c**, **6c**, and **7c**, in excellent yield following the usual procedure. In a similar way, the mono methyl ester **13c** was isolated in 80% yield starting from methyl ester **7c** (Scheme 4).

The small library of model C-like antagonists was then tested for biological activity. The results are reported in Table 3. The IC_{50} was calculated only for compounds showing major activity.

Starting from **10c**, which showed a weak inhibitory effect, the related compounds **11c**, **12c**, and **13c** differ in the distance between the carboxylic and the guanidino functions and for the structure of the carboxylic chain. The modifications, including elongation and presence of a second carboxylic moiety both as free acid and as methyl ester, did not afford any advantage (Table 3, entries 2,3,4). In fact, elongated compound **11c**, having thirteen bonds between acidic and basic ends, showed



Scheme 4. Reagents and conditions: i—Methyl malonyl chloride or ethyl fumaryl chloride, TEA, CH_2Cl_2, 0 °C to rt; ii—NaH, benzyl bromoacetate, THF, 0 °C to rt; iii—H_2, Pd/C, MeOH, rt; iv—LiOH, THF/MeOH/H_2O, rt; v—(a) *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carboxamidine, DMF, rt; (b) LiOH, THF/MeOH/H_2O, rt; (c) TFA, rt; vi—(a) *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carboxamidine, DMF, rt; (b) TFA, rt.

lower activity toward both integrins. The same behavior was observed for compounds **12c** and **13c**, which maintain the optimal 12-bonds distance but possess a second carboxylic substituent in the acid side chain.

When we turned our attention to the compounds deprived of the guanidinium group, we observed for **7c**, and **8c** (Table 3, entries 6,7) an enhanced activity toward $\alpha_v\beta_3$-integrin mediated cell adhesion. Compound **9c**, corresponding to **12c** deprived of the guanidine moiety, did not show any bioactivity toward the same receptor. Disappointingly, **7c** and **9c** were uneffective to block $\alpha_5\beta_1$ integrin-mediated cell adhesion. The most interesting result was obtained for compound **8c**, having IC_{50} of 0.6 μM (Table 3, entry 5) toward $\alpha_v\beta_3$ integrin and 0.17 μM toward $\alpha_5\beta_1$-integrin-mediated cell adhesion.

The encouraging results observed for compound **8c** $\alpha_v\beta_3$-and $\alpha_5\beta_1$-integrin mediated cell adhesion assays suggest that this substrate could be used as a model to evaluate the influence of the scaffold stereochemistry on inhibitory effect.

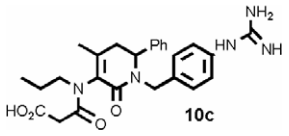
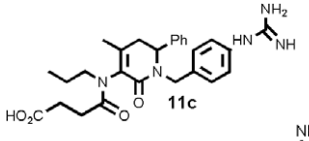
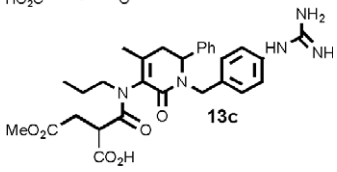
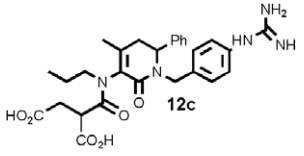
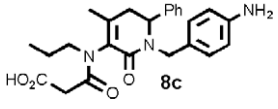
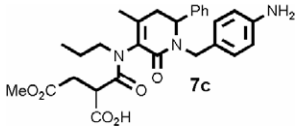
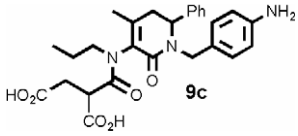
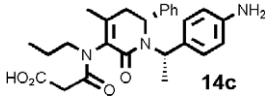
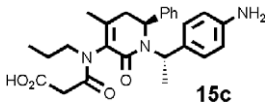
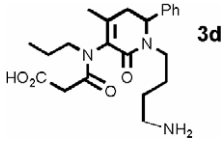
To clarify the conformation induced by the heterocycle stereochemistry, we focused our attention on enantiomerically pure analogs of **8c**. The introduction of (*S*)-*p*-nitro-phenylethylamine allowed diastereomeric compounds **14c** and **15c** to be obtained, showing the critical importance of 5,6-dihydropyridin-2-one C6 configuration on substrate-ligand recognition.[17]

Following the synthetic pathway above reported for model-C antagonists, enantiomerically pure (1′*S*, 6*R*)-**14c** and (1′*S*, 6*S*)-**15c** were obtained in 63:37 d.r., using (*S*)-*p*-nitro-phenylethylamine as precursor of the amino group. The presence of a methyl group in the nitrogen side chain allowed the easy separation of the diastereomers and generated a further conformational constrain.

Both diastereomers (1′*S*, 6*R*)-**14c** and (1′*S*, 6*S*)-**15c** were capable to block $\alpha_V\beta_3$- and $\alpha_5\beta_1$-mediated cell adhesion and, being dual inhibitors could be considered as lead compounds for any further therapeutical and diagnostic development. Interestingly, a 200-fold gain in potency to prevent $\alpha_v\beta_3$ driven cell adhesion and 600-fold gain in potency toward $\alpha_5\beta_1$ were observed for (1′*S*, 6*S*)-**15c** in comparison with the corresponding (1′*S*, 6*R*)-**14c** diastereomer. On this basis, a strong influence to the spatial arrangement of the (*S*)-C6 aromatic substituent on bioactive conformation could be ascribed.

At last, to verify if the substitution of the rigid benzylic aminic appendage with the more flexible butandiamine could afford an improvement with respect to (±)-**8c**, compound (±)-**3d** was synthesized, giving further information. In fact, the possibility to introduce different substituents on the rigid core scaffold offers the opportunity to synthesize other members of this small library of 5,6-dihydropyridin-2-one ligands. On these bases, we changed the heterocyclic nitrogen appendage, with the aim to modulate basicity and lipophilicity. Thus, racemic compound **1d** was synthesized starting from the

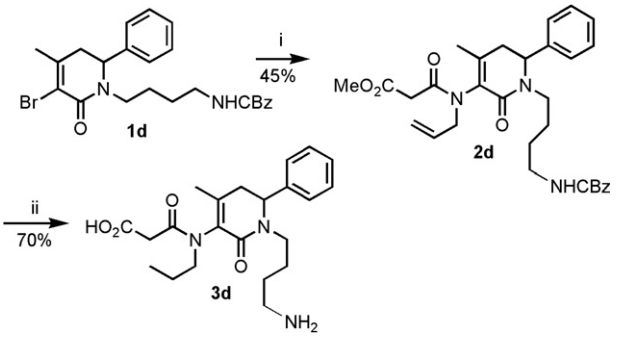
Table 3. $\alpha_v\beta_3$- and $\alpha_5\beta_1$- integrin mediated cell adhesion to fibronectin in the presence of Model-B like ligands

Entry	Compound	IC_{50} (μM)	
		$\alpha_v\beta_3$	$\alpha_5\beta_1$
1	 **10c**	120 ± 17	>1000loffset 0mm
2	 **11c**	>1000	>1000
3	 **13c**	>1000	>1000
4	 **12c**	>1000	>1000
5	 **8c**	0.6 ± 0.1	0.17 ± 0.07
6	 **7c**	45 ± 7	>1000
7	 **9c**	>1000	>1000
8	 **14c**	15.1 ± 6.0	35.1 ± 12.0
9	 **15c**	0.071 ± 0.011	0.057 ± 0.017
10	 **3d**	0.038 ± 0.015	0.043 ± 0.05

[a]Values are means ± standard error of three experiments.

imine of benzaldehyde and *N*-benzyloxycarbonyl-butandiamine. This derivative, having only eleven bonds between acidic and basic functionalities, contains the terminal amino group linked to a more flexible aliphatic side chain in place of the lipophilic aniline moiety. By performing the synthetic sequence reported above, free amino-acid derivative **3d** could be isolated in good yield (Scheme 5).

Compound **3d** gave excellent results in $\alpha_v\beta_3$- and $\alpha_5\beta_1$-integrin mediated cell adhesion assays and turned out to be the best antagonist in the synthesized library (Table 3, entry 10). The dual antagonism toward both pro-angiogenic integrins might be considered for any future anticancer therapy and tumor targeting, even though more potent and selective $\alpha_v\beta_3$ integrin antagonists have already been reported.[18] Further studies on this



Scheme 5. Reagents and conditions: i—(a) allylamine, rt, 3 days; (b) methyl malonyl chloride TEA, CH_2Cl_2, 0 °C to rt; ii—(a) H_2, Pd/C, MeOH, rt; (b) LiOH, THF/MeOH/H_2O, rt.

compound are ongoing to evaluate its antagonistic activity toward other integrins.

In conclusion, we have synthesized and tested in cell adhesion assays small libraries of non-peptide $\alpha_v\beta_3$/$\alpha_5\beta_1$ integrin antagonists, containing the 5,6-dihydropyridin-2-one scaffold. By changing the length, the structure, and the position of the side chains linked to the heterocyclic core, we identified model compound (±)-**8c** that gave excellent results both in $\alpha_v\beta_3$- and $\alpha_5\beta_1$-integrin mediated cell adhesion assays. With the aim to verify the importance of C6 stereochemistry, we synthesized and tested **14c** and **15c**. These last derivatives had excellent affinity toward both receptors, showing a dual inhibitor attitude. Furthermore, comparison of semirigid aromatic derivative (±)-**8c** and (±)-**3d** clearly indicates that both moieties are well tolerated, being their bioactivity in the same range.

3. Experimental

3.1. General synthetic methods

All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in sure seal bottles over molecular sieves and used without further drying. Flash chromatography was performed on silica gel (230–400 mesh). NMR Spectra were recorded with 200, 300, or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77.0$ (^{13}C NMR). Melting points are uncorrected. MS analyses were performed on a liquid chromatograph coupled with an electrospray ionization–mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 *m*/*z*, fragmentor 70 V, gradient elution program from 80% water to 70% acetonitrile in 8 min.).

3.2. General procedure for acylation of 5,6-dihydro-4-methyl-6-phenyl-pyridin-2-ones 1

To a stirred solution of dihydropyridinone in CH_2Cl_2 (10 mL) at 0 °C, under argon, TEA (1.5 equiv) and the acyl chloride (1.5 equiv) were added. The temperature was allowed to slowly warm to rt. The reaction was followed by TLC and then quenched with HCl 0.1 M (10 mL). The layers were separated and the aqueous layer was extracted twice with dichloromethane (10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the desired compound, that was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2).

3.3. General procedure for hydrogenation of nitro-derivatives

To a solution of nitroderivative in MeOH, Pd/C (1 equiv) was added in one portion. The reaction mixture was stirred vigorously at rt in a hydrogen atmosphere overnight. The solution was filtered to remove catalyst and evaporated to afford hydrogenated product, which was used without purification in the following step.

3.4. General procedure for the reaction of free amines with *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carbox-amidine

To a stirred solution of the amino derivative in DMF at room temperature, *N*,*N*′-Bis(*t*-butoxycarbonyl)-1-H-pyrazole-1-carboxamidine (1.2 equiv) was added in one portion. The reaction was followed by TLC and then quenched with 0.1 M HCl. The mixture was diluted with ethyl acetate and extracted (three times). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate 5/5), to afford the desired compound.

3.5. General procedures for ester hydrolysis

To a stirred solution of ester in a 3.6:1:1 mixture of THF/MeOH/H_2O at room temperature, LiOH (3 equiv) was added. The reaction was followed by TLC and then concentrated in vacuo to afford the acid, which was purified by chromatography on basic ion-exchange resin.

3.6. General procedure of Boc deprotection

The Boc-derivative was dissolved in CF_3COOH (9 equiv). The reaction was followed by TLC and then concentrated in vacuo. The residue was diluted with toluene and concentrated in vacuo (three times) to afford the desired pure compound.

Compound **1a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.26 (t, 3H, $J = 6.9$ Hz), 1.74 (s, 3H), 2.33 (dd, 1H, $J = 1.8$, 17.4 Hz), 2.55 (dd, 1H, $J = 6.0$, 15.0 Hz), 2.78 (dt, 1H, $J = 7.2$, 15.0 Hz), 3.04–3.16 (m, 3H), 3.42–3.51 (m, 2H), 4.04–4.16 (m, 3H), 4.76 (dd, 1H, $J = 1.6$, 7.5 Hz), 5.07 (dq, 1H, $J = 1.5$, 11.7 Hz), 5.17 (dq, 1H, $J = 1.5$, 17.1 Hz), 5.89 (ddt, 1H, $J = 11.7$, 17.1, 5.7 Hz), 7.16–7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 18.9, 33.4, 37.5, 43.2, 51.1, 59.6, 60.5, 115.6, 120.9, 126.3, 127.4, 128.5, 133.5, 136.7, 141.1, 164.9, 172.1; LC-ESI-MS rt 11.86 min, *m*/*z* 343 (M+1), 365 (M+Na), 707 (2M+Na).

Compound **2a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.24 (t, 3H, J = 7.2 Hz), 1.64 (s, 3H), 2.19–2.37 (m 2H), 2.41–2.59 (m, 2H), 2.61–2.80 (m, 1H), 2.99–3.22 (m, 2H), 3.41–3.50 (m, 2H), 3.83 (dd, 1H, J = 7.2, 15.6 Hz), 4.05 (m, 1H), 4.11 (q, 2H, J = 6.0 Hz), 4.23 (dd, 1H, J = 6.6, 15.6 Hz), 4.89 (bd, 1H, J = 6.9 Hz), 4.97–5.14 (m, 4H), 5.70–5.81 (m, 1H), 7.14–7.20 (m, 2H), 7.24–7.37 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.0, 19.4, 20.1, 33.3, 37.2, 43.4, 50.2, 58.5, 60.5, 66.2, 118.0, 126.0, 127.8, 128.3, 128.6, 133.3, 136.7, 139.8, 140.0, 144.6, 156.3, 162.2, 171.9, 172.3; LC-ESI-MS rt 13.72 min, m/z 548 (M+1), 570 (M+Na).

Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.11 (t, 3H, J = 7.9 Hz), 1.20–1.45 (m, 6H), 1.56 (s, 3H), 1.81-1.93 (dt, 1H J = 6.9, 15.3 Hz), 2.03 (dt, 1H, J = 7.8, 15.3 Hz), 2.21–2.45 (m, 3H), 2.55–2.67 (m, 1H), 2.90–3.12 (m, 5H), 3.70 (dd, 1H, J = 7.2, 14.5 Hz), 3.91–4.02 (m, 3H), 4.13 (dd, 1H, J = 5.7, 14.5 Hz), 4.71–5.04 (m, 3H), 4.97 (bs, 2H), 5.59–5.77 (m, 1H), 7.02–7.24 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 14.1, 19.7, 24.3, 26.3, 29.5, 33.2, 33.6, 37.3, 40.8, 43.5, 50.3, 58.7, 60.6, 66.4, 117.8, 118.0, 126.1, 127.9, 128.0, 128.4, 128.7, 128.9, 130.0, 133.7, 140.1, 144.1, 156.4, 162.4, 172.0, 173.4; IR (film) ν 3328, 2934, 1723, 1639, 1529, 1399, 1249 cm^{-1}; LC-ESI-MS rt 19.22 min, m/z 590 (M+1), 612 (M+Na).

Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.68 (s, 3H), 2.24 (m, 1H), 2.39–2.59 (m, 2H), 2.50 (bd, 1H, J = 18.0 Hz), 2.67–2.77 (m, 1H), 2.97–3.04 (m, 2H), 3.26 (dd, 1H, J = 7.5, 18.0 Hz), 3.37–3.48 (m, 2H), 3.83 (dd, 1H, J = 7.2, 14.4 Hz), 4.26 (dd, 1H, J = 6.6, 14.4 Hz), 4.87 (bd, 1H, J = 7.5 Hz), 4.97–5.19 (m, 4H), 5.75 (m, 1H), 5.86 (t, 1H, J = 5.1 Hz), 7.15–7.40 (m, 10H), ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 19.5, 33.2, 37.0, 37.2, 43.2, 50.8, 58.0, 60.3, 66. 6, 118.6, 126.1, 127.9, 128.4, 128.8, 129.0, 129.2, 133.2, 136.5, 139.9, 145.3, 157.0, 163.1, 172.4, 172.9; LC-ESI-MS rt 11.29 min, m/z 520 (M+1), 542 (M+Na).

Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.12–1.66 (m, 6H), 1.72 (s, 3H), 1.98–2.21 (m, 2H), 2.51 (bd, 1H, J = 14.8 Hz), 2.60 (m, 1H), 2.75–2.85 (m, 1H), 3.02–3.24 (m, 5H), 3.84 (dd, 1H, J = 7.4, 14.4 Hz), 4.08 (m, 1H), 4.27 (m, 1H), 4.82 (bd, 1H, J = 7.0 Hz), 4.90–5.18 (m, 4H), 5.40 (bs, 1H), 5.70–85.95 (m, 1H), 7.15–7.40 (m, 10H), 8.60 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 19.6, 24.3, 26.1, 29.4, 32.9, 37.2, 40.9, 43.1, 43.5, 50.4, 51.0, 58.6, 66.5, 118.0, 126.0, 127.8, 127.9, 128.4, 128.7, 129.5, 129.7, 133.5, 140.1, 144.6, 162.5, 173.5, 175.0; LC-ESI-MS rt. 13.4 min, m/z 562 (M+1), 584 (M+Na).

Compound **6a**: ^{1}H NMR (300 MHz, CD_3OD) δ_H 0.83 (t, 3H, J = 7.2 Hz), 1.20–1.32 (m, 2H), 1.73 (s, 3H), 2.47–2.63 (m, 3H), 2.69–2.75 (m, 2H), 2.83–3.01 (m, 2H), 3.22–3.46 (m, 3H), 3.48–3.60 (m, 1H), 4.32–4.34 (m, 1H), 4.93 (t, 1H, J = 6.0 Hz), 7.14–7.27 (m, 2H), 7.27–7.37 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ_C 11.4, 19.4, 20.7, 31.8, 34.9, 35.2, 37.5, 44.1, 49.1, 50.3, 58.0, 125.8, 127.6, 128.6, 137.3, 140.0, 145.6, 162.6, 171.5, 174.5. LC-ESI-MS: rt 5.13 min, m/z 388 (M+1), 410 (M+Na).

Compound **7a**: ^{1}H NMR (300 MHz, CD_3OD) δ_H 0.84 (t, 3H, J = 7.2 Hz), 1.20–1.70 (m, 8H), 1.74 (s, 3H), 2.10–2.24 (m, 1H), 2.59–3.06 (m, 7H), 3.10–3.20 (m, 1H), 3.30–3.38 (m, 1H), 3.61–3.67 (m, 1H), 4.14–4.21 (m, 1H), 5.03 (bd, 1H, J = 7.2 Hz), 7.24 (d, 2H, J = 6.9 Hz), 7.31–7.44 (m, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.0, 20.2, 22.12, 25.56, 27.1, 28.4, 33.9, 34.5, 34.5, 38.4, 40.9, 45.0, 50.7, 59.8, 127.4, 127.8, 129.2, 130.1, 130.3, 131.0, 141.6, 147.7, 164.6, 176.2. LC-ESI-MS: rt 5.66 min, m/z 444 (M+1), 466 (M+Na).

Compound **(6*S*)-1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.58 (d, 3H, J = 7.1 Hz), 1.642 (d, 3H, $J_{1,3}$ = 1.5 Hz), 2.08 (d, 1H, J = 17.1 Hz), 3.09 (ddq, 1H, J = 17.1 7.1, 1.5 Hz), 3.47–3.54 (m, 2H), 3.58 (s, 3H), 4.57 (d, 1H, J = 7.1 Hz), 5.09 (ddd, 1H, J = 10.2, 1.4, 2.9 Hz), 5.21 (ddd, 1H, J = 17.1, 1.8, 3.0 Hz), 5.83–5.96 (m, 1H,), 5.96 (q, 1H, J = 7.1 Hz), 6.45–6.47 (m, 2H), 6.90–6.93 (m, 2H), 7.00–7.03 (m, 2H), 7.80–7.83 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.6, 18.8, 37.9, 50.9, 51.6, 53.0, 55.2, 113.1, 113.4, 115.7, 118.2, 122.5, 123.0, 127.0 127.2, 129.7, 129.5, 130.1, 134.4, 136.7, 146.4, 149.5, 159.0, 163.6. LC-ESI-MS: rt 14.3 min, m/z 422 (M+1), 444 (M+Na), 865 (2M+Na+). $[\alpha]_D$ = −53.9 ($CHCl_3$ c 0.5).

Compound **(6*R*)-1b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.14 (d, 3H, J = 7.2 Hz), 1.62 (s, 3H), 1.98 (d, 1H, J = 17.1 Hz), 2.82 (dd, 1H, J = 17.1, 7.2 Hz), 3.42–3.58 (m, 2H), 3.8 (s, 3H), 4.38 (d, 1H, J = 7.2 Hz), 5.09 (d, 1H, J = 10.2 Hz), 5.20 (d, 1H, J = 17.1 Hz), 5.82–5.97 (m, 1H), 6.06 (q, 1H, J = 7.2 Hz), 6.86–6.89 (m, 2H), 7.20–7.23 (m, 2H), 7.31–7.34 (m, 2H), 8.11–8.13 (m, 2H). ^{13}C NMR (75 MHz, CDCl3): δ_C 16.5, 18.6, 37.6, 50.7, 51.0, 52.9, 55.0, 113.4, 113.8, 115.5, 118.3, 123.2, 123.6, 127.2, 127.5, 128.0, 128.1, 132.9, 134.0, 136.7, 147.0, 150.5, 158.9, 164.0. LC-ESI-MS: rt 14.8 min, m/z 422 (M+H), 444 (M+Na), 865 (2M+Na). $[\alpha]_D$ = +75.3 ($CHCl_3$ c 0.7).

Compound **2b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.59 (d, 3H, J = 6.9 Hz), 1.68 (s, 3H), 2.33 (d, 1H, J = 17.8 Hz), 3.19 (dd, 1H, J = 17.8, 7.2 Hz), 3.27–3.30 (m, 2H), 3.56 (s, 3H), 3.69 (s, 3H), 4.05–4.12 (m, 2H), 4.72 (d,1H, J = 7.2 Hz), 5.07–5.13 (m, 2H), 5.77–5.90 (m, 1H), 5.93 (q, 1H, J = 6.9 Hz), 6.44–6.47 (m, 2H), 6.93–7.02 (m, 4H), 7.80–7.83 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$): δ_C 17.5, 19.4, 37.7, 41.2, 50.7, 51.8, 52.1 (2), 55.0, 113.1, 113.3, 117.8, 122.6, 122.8, 126.9 (2), 129.5, 129.6, 129.7, 129.8, 133.6, 144.2, 146.5, 148.3, 159.1, 160.9, 166.7, 167.8. LC-ESI-MS: rt 11.6 min, m/z 522 (M+H), 544 (M+Na), 1065 (2M+Na). $[\alpha]_D$ = −92.3° ($CHCl_3$ c 0.8).

Compound **3b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ_H 1.15 (d, 3H, J = 7.1 Hz), 1.67 (s, 3H), 2.22 (d, 1H, J = 17.8 Hz), 2.9 (dd,1H, J = 17.8, 6.7 Hz), 3.31–3.32 (m, 2H) 3.68 (s, 3H), 3.80 (s, 3H), 4.01 (dd,1H, J = 15.0, 6.6 Hz) 4.20 (dd, 1H, J = 15.0, 6.4 Hz), 4.48 (d, 1H, J = 6.7 Hz), 5.09–5.18 (m, 2H), 5.75–5.95 (m, 1H), 6.04 (q, 1H,

J = 7.1 Hz), 6.87–6.91 (m, 2H), 7.18–7.22 (m, 2H), 7.35–7.39 (m, 2H), 8.11–8.16 (m, 2H).^{13}C NMR (50 MHz, $CDCl_3$): δ_C 16.5, 19.5, 37.7, 41.3, 50.8, 51.3, 52.1, 52.2, 55.2, 113.8, 114.0, 117.8, 123.6, 123.7, 127.2, 128.1, 130.1, 132.5, 133.6, 144.5, 147.4, 149.3, 159.1, 161.4, 166.7, 167.8. LC-ESI-MS: rt 12.2 min, *m/z* 522 (M+H), 544 (M+Na). $[\alpha]_D$ = +46.4° ($CHCl_3$ *c* 0.87).

Compound **4b**: ^{1}H NMR (300 MHz, CD_3OD): δ_H 0.90 (t, 3H, J = 7.4 Hz), 1.41-1.45 (m, 2H), 1.67 (d, 3H, J = 7.1 Hz), 1.92 (s, 3H), 2.46 (bd,1H, J = 17.4 Hz), 3.10–3.28 (m, 3H), 3.38 (s, 2H), 3.69 (s, 3H), 4.80 (bd,1H, J = 6.3 Hz), 5.74 (q,1H, J = 7.1 Hz), 6.48–6.51 (m, 2H), 6.62–6.68 (m, 4H), 7.18–7.21 (m, 2H).^{13}C NMR (75 MHz, CD_3OD): δ_C 12.1, 18.9, 20.3, 22.1, 39.9, 51.1, 54.7, 56.0, 68.3, 114.6, 123.8, 129.3, 130.4, 131.0, 131.6, 143.3, 147.9, 160.5, 163.0, 169.9, 169.7. LC-ESI-MS: rt 7.6 min, *m/z* 480 (M+H), 502 (M+Na).$[\alpha]_D$ = −144.7 ($CHCl_3$ *c* 0.6).

Compound **5b**: ^{1}H NMR (300 MHz, CD_3OD): δ_H 0.94 (t, 3H, J = 7.4 Hz), 1.28 (d, 3H, J = 7.1 Hz), 1.42–1.53 (m, 2H), 1.72 (s, 3H), 2.31 (bd, 1H, J = 17.2 Hz), 2.95 (dd, 1H, J = 17.2, 6.6 Hz), 3.11–3.21 (m, 1H), 3.35 (s, 2H), 3.84 (s, 3H), 4.46 (bd,1H, J = 6.6 Hz), 5.96 (q, 1H, J = 7.1 Hz), 6.71–6.74 (m, 2H), 6.95–6.99 (m, 4H), 7.31–7.34 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ_C 13.6, 17.2, 20.6, 23.1, 38.6, 50.7, 53.4, 57.1, 66.9, 113.8, 123.6, 129.6, 130.2, 131.0, 131.3, 143.0, 148.2, 149.1, 160.6, 164.8, 168.9, 170.1. LC-ESI-MS: 2.4 min, 480 (M+H), 502 (M+Na).$[\alpha]_D$ = +23.5 ($CHCl_3$ *c* 0.2).

Compound **6b**: ^{1}H NMR (300 MHz, CD_3OD): δ_H 0.90 (t, 3H, J = 7.0 Hz), 1.29–1.43 (m, 1H), 1.69 (d, 3H, J = 6.9 Hz), 1.73 (s, 3H), 2.52 (d, 1H, J = 17.4 Hz), 3.10–3.20 (m, 3H), 3.38 (m, 2H), 3.78 (s, 3H), 5.10 (bd, 1H), 5.88 (q, 1H, J = 7 Hz), 6.60–6.63 (m, 2H), 6.97–7.00 (m, 4H), 7.19–7.22 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ_C 12.0, 18.5, 20.1, 22.3, 27.9, 31.1, 39.4, 53.8, 54.2, 56.0, 114.6, 125.7, 129.2 (2), 131.4 (2), 131.8, 135.2, 141.4, 145.9, 147.9, 153.1, 160.8, 162.6, 163.9, 180.1. LC-ESI-MS: rt 3.6 min, *m/z* 522 (M+H), 544 (M+Na). $[\alpha]_D$ = −64.9° ($CHCl_3$ *c* 0.26).

Compound **1c**: Mp 75 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.78 (s, 3H), 2.39 (dd, 1H, J = 3.4, 17.4 Hz), 2.99 (dd, 1H, J = 7.5, 17.4 Hz), 3.51 (dd, 2H, J = 1.5, 4.4 Hz), 3.80 (d, 1H, J = 15.8 Hz), 4.47 (dd, 1H, J = 3.4, 7.5 Hz), 5.11 (dd, 1H, J = 1.6, 10.2 Hz), 5.22 (dd, 1H, J = 1.6, 17.1 Hz), 5.44 (d, 1H, J = 15.8 Hz), 5.80–6.01 (m, 1H), 7.13 (d, 2H, J = 8.4 Hz),7.21–7.39 (m, 5H), 8.14 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 18.9, 37.3, 48.4, 51.0, 58.1, 115.7, 121.9, 123.7, 126.6, 127.8, 128.3, 128.6, 136.5, 139.9, 145.3, 147.1, 165.1. LC-ESI-MS rt 12.9 min, *m/z* 378 (M+1), 400 (M+Na).

Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.81 (s, 3H), 2.55 (dd, 1H, J = 2.0, 11.9 Hz), 3.18 (dd, 1H, J = 7.0, 11.9 Hz), 3.33 (s, 2H), 3.72 (s, 3H), 3.83 (d, 1H, J = 15.5 Hz), 4.04–4.26 (m, 2H), 4.59 (dd, 1H, J = 2.0, 7.0 Hz), 5.06–5.38 (m, 2H), 5.52 (d, 1H, J = 15.5 Hz), 5.80–6.00 (m, 1H), 7.18 (d, 2H, J = 8.4 Hz), 7.35–7.45 (m, 5H), 8.20 (d, 2H, J = 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 19.9, 37.3, 41.8, 48.5, 50.9, 52.2, 57.0, 118.6, 123.9, 126.6, 128.3, 128.6, 128.9, 129.1, 133.1, 138.7, 144.8, 146.0, 147.4, 162.4, 166.3, 167.7; LC-ESI-MS rt 11.1 min, *m/z* 478 (M+1), 500 (M+Na).

Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.28 (t, 3H, J = 7.0 Hz), 1.73 (s, 3H), 2.57 (dd, 1H, J = 2.6, 18.4 Hz), 3.18 (dd, 1H, J = 7.6, 18.4 Hz), 3.81 (d, 1H, J = 15.4 Hz), 4.04–4.37 (m, 4H), 4.60 (dd, 1H, J = 2.6, 7.6 Hz), 5.05–5.23 (m, 2H), 5.45 (d, 1H, J = 15.4 Hz), 5.73–5.96 (m, 1H), 6.81 (d, 1H, J = 15.2 Hz), 6.99 (d, 1H, J = 15.0 Hz), 7.15 (d, 2H, J = 8.8 Hz), 7.28–7.40 (m, 5H), 8.12 (d, 2H, J = 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 13.9, 19.6, 37.3, 48.6, 50.6, 57.0, 60.9, 118.6, 123.8, 126.1, 128.1, 128.4, 128.5, 128.8, 129.2, 130.9, 132.7, 134.0, 138.9, 144.7, 146.0, 147.2, 162.3, 164.6, 165.6. LC-ESI-MS rt 11.54 min, *m/z* 504 (M+1), 526 (M+Na).

Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.88 (s, 3H), 2.58 (dd, 1H, J = 17.0, 1.4 Hz), 3.30 (dd, 1H, J = 17.0, 6.2 Hz), 3.60 (m, 1H), 3.68 (s, 3H), 3.72 (d, 1H, J = 15.6 Hz), 3.90–4.05 (m, 3H,), 4.23 (dd, 1H, J = 14.6, 6.4 Hz), 4.56 (dd, 1H, J = 1.4, 6.2 Hz), 5.49 (d, 1H, J = 15.6 Hz), 5.05–5.22 (m, 2H), 5.78–5.98 (m, 2H), 7.12–7.38 (m, 12H), 8.13 (d, 2H, J = 8.2); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 20.3, 37.9, 41.0, 47.4, 50.3, 54.1, 54.3, 58.0, 59.6, 118.8, 121.0, 123.6, 126.9, 127.2, 127.6, 128.0, 128.4, 128.9, 129.1, 131.3, 132.8, 138.0, 142.1, 145.9, 146.1, 162.3, 165.9, 168.1, 169.2. LC-ESI-MS rt 12.9 min, *m/z* 626 (M+1), 648 (M+Na).

Compound **5c**: Mp 59 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 0.88 (t, 3H, J = 7.5 Hz), 1.35–1.66 (m, 2H); 1.82 (s, 3H); 2.44 (bd, 1H, J = 17.0 Hz), 3.05 (dd, 1H, J = 7.6, 17.0 Hz), 3.30 (d, 1H, J = 15.0 Hz), 3.37 (d, 1H, J = 15.0 Hz), 3.46–3.62 (m, 2H,), 3.53 (d, 1H, J = 15.0 Hz), 3.73 (s, 3H), 4.59 (d, 1H, J = 7.6 Hz), 5.53 (d, 1H, J = 15.0 Hz), 6.67 (d, 1H, J = 8.4 Hz); 7.04 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.7 Hz), 7.33–7.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 11.3, 19.6, 20.8, 37.3, 41.5, 48.0, 49.8, 52.1, 55.1, 115.1, 125.9, 126.9, 127.8, 128.9, 129.5, 130.0, 139.5, 144.5, 146.0, 162.1, 166. 7, 168.2. LC-ESI-MS rt 9.9 min, *m/z* 450 (M+1), 472 (2M+Na).

Compound **6c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 0.85 (t, 3H, J = 7.4 Hz); 1.27 (t, 3H, J = 7.3 Hz), 1.35–1.52 (m, 2H); 1.77 (s, 3H); 2.32–3.21 (m, 6H), 3.42–3.47 (m, 1H); 3.48 (d, 1H, J = 14.2 Hz); 3.62–3.76 (m, 1H); 4.14 (q, 2H, J = 7.2 Hz), 4.58 (bd, 1H, J = 8.0 Hz Hz); 5.53 (d, 1H, J = 14.2 Hz); 6.62–6.69 (m, 2H); 7.03 (d, 2H, J = 8.2 Hz); 7.13–7.22 (m, 3H); 7.34–7.39 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) major conformer δ: 11.3, 14.6, 19.3, 20.3, 27.1, 29.3, 37.6, 48.4, 49.8, 55.6, 60.4, 115.1, 125.8, 126.3, 127.6, 128.6, 129.3, 129.8, 139.5, 143.8, 145.9, 160.1, 171.9, 173.2. LC-ESI-MS rt 11.77 min, *m/z*: 478 (M+1), 501 (M+Na), 977 (2M+Na).

Compound **7c**: ^{1}H NMR (300 MHz, CD_3OD) δ_H 0.86 (t, 3H, J = 7.2 Hz), 1.21-1.30 (m, 2H); 1.88 (s, 3H);

2.46 (bd, 1H, $J = 16.8$ Hz), 3.02 (dd, 1H, $J = 7.0$, 16.8 Hz), 3.41 (m, 1H), 3.56–4.02 (m, 4H), 3.74 (s, 3H), 3.78 (d, 1H, $J = 15.3$ Hz), 4.66 (d, 1H, $J = 7.0$ Hz), 5.51 (d, 1H, $J = 15.3$ Hz), 6.95–7.10 (m, 2H); 7.08–7.41 (m, 5H), 7.50–7.62 (m, 2H), 7.33–7.39 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 11.8, 18.9, 22.4, 34.2, 36.9, 43.4, 50.6, 53.1, 124.1, 126.5, 127.3, 127.9, 128.2, 128.8, 131.2, 133.4, 136.1, 139.4, 158.1, 162.1, 166.7, 172.1. LC-ESI-MS rt 8.4 min, *m*/*z* 508 (M+1), 530 (M+Na).

Compound **8c**: ^{1}H NMR (300 MHz, CD_3OD): δ: 0.88 (t, 3H, $J = 7.5$ Hz); 1.30–1.44 (m, 2H); 1.79 (s, 3H); 2.51 (bd,1H, $J = 17.4$ Hz); 3.16 (dd, 1H, $J = 6.6$, 17.4 Hz); 3.22 (m, 1H); 3.55 (m, 1H); 3.64 (d, 1H, $J = 15.0$ Hz); 4.71 (bd, 1H, $J = 6.6$ Hz); 5.34 (d, 1H, $J = 15.0$ Hz); 6.68–6.72 (m, 2H), 7.19–7.21 (m, 2H), 7.30–7.41 (m, 3H). ^{13}C NMR (50 MHz, CD_3OD) δ: 11.3, 18.7, 20.8, 37.3, 40.0, 48.2, 49.8, 58.1, 64.1, 115.1, 125.9, 126.9, 127.8, 128.9, 129.5, 130.0, 134.2, 139.5, 144.5, 150.9, 161.9, 168. 3, 174.4, LC-ESI-MS rt 3.55 min, *m*/*z*: 436 (M+1), 458 (M+Na).

Compound **9c**: ^{1}H NMR (300 MHz, D2O): δ: 0.64 (t, 3H, $J = 6.9$ Hz); 1.09–1.22 (m, 2H); 1.59 (s, 3H); 2.36 (dd,1H, $J = 16.2$, 10.2 Hz); 2.53–2.68 (m, 3H) 3.03–3.11 (m, 2H), 3.29 (m, 2H); 3.54 (d, 1H, $J = 15.3$ Hz); 4.52 (m, 1H), 5.00 (d, 1H, $J = 15.3$ Hz); 6.75–6.78 (m, 2H), 6.79–6.97 (m, 5H), 7.11–7.19 (m, 2H). ^{13}C NMR (75 MHz, D_2O) δ: 12.0, 19.9, 22.6, 30.9, 39.0, 43.1, 44.2, 51.9, 124.5, 126.8, 127.1, 127.8, 128.2, 128.5, 130.0, 132.1, 138.1, 139.4, 157.1, 163.0, 175.1, 177.1. LC-ESI-MS rt 3.20 min, *m*/*z*: 494 (M+1), 516 (M+Na).

Compound **10c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ: 0.87 (t, 3H, $J = 7.2$ Hz); 1.21-1.25 (m, 2H); 1.79 (s, 3H); 2.69 (bd,1H, $J = 17.2$ Hz); 3.11–3.31 (m, 2H); 3.23–3.46 (m, 1H); 3.52 (s, 2H); 3.59 (d, 1H, $J = 15.8$ Hz); 4.23 (bd, 1H, $J = 5.4$ Hz); 5.40 (d, 1H, $J = 15.8$ Hz); 7.21–7.47 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 12.6, 20.9, 22.6, 39.0, 42.9, 48.6, 59.1, 87.0, 125.3, 128.0, 128.6, 128.7, 129.7, 130.7, 131.1, 131.4, 134.4, 140.5, 141.6, 149.9, 154.1, 168.1, 170.4. LC-ESI-MS rt 10.05 min, *m*/*z*: 478 (M+1), 501 (M+Na).

Compound **11c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 0.81 (t, 3H, $J = 6.9$ Hz); 1.20–1.40 (m, 2H); 1.81 (s, 3H); 2.31 (bd,1H, $J = 16.8$ Hz); 2.42–2.77 (m, 4H); 3.08 (dd, 1H, $J = 6.5$, 16.8 Hz); 3.22 (m, 1H); 3.70 (m, 1H); 3.86 (d, 1H, $J = 15.0$ Hz); 4.78 (bd, 1H, $J = 6.5$ Hz); 5.41 (d, 1H, $J = 15.0$ Hz); 7.20–7.50 (m, 9H); 9.81 (bs, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.7, 18.9, 20.8, 28.4, 28.9, 37.1, 49.5, 50.7, 57.2, 125.6, 126.2, 126.7, 127.8, 128.7, 129.3, 134.2, 136.1, 139.2, 147.2, 151.2, 156.9, 163.3, 173.4. LC-ESI-MS rt 11.84 min, *m*/*z*: 492 (M+1), 514 (M+Na).

Compound **12c**: ^{1}H NMR (200 MHz, CD_3OD): δ: 0.87 (t, 3H, $J = 7.6$ Hz); 1.29–1.45 (m, 2H); 1.88 (s, 3H); 2.68 (bd, $J = 16.8$ Hz); 2.91 (dd, 1H, $J = 12.4$, 16.8 Hz), 3.20–2.80 (m, 1H), 3.51–3.98 (m, 4H); 3.82 (d, 1H, $J = 15.0$ Hz); 4.74 (d, 1H, $J = 12.4$ Hz), 5.40 (d, 1H, $J = 15.0$ Hz), 7.19–7.40 (m, 9H). ^{13}C NMR (50 MHz, CD_3OD) δ: 13.2, 20.1, 23.5, 37.5, 40.0, 40.6, 48.3, 58.9, 80.0, 124.6, 128.1, 128.7, 128.8, 129.7, 130.0, 131.5, 134.3, 140.8, 148.6, 151.8, 157.4, 163.1, 175.9, 176.4. LC-ESI-MS rt 3.1 min, *m*/*z*: 536 (M+1), 558 (M+Na).

Compound **13c**: ^{1}H NMR (200 MHz, $CDCl_3$): δ: 0.87 (t, 3H, $J = 7.2$ Hz); 1.43–1.55 (m, 2H); 1.83 (s, 3H); 2.50 (bd,1H, $J = 17.4$ Hz); 2.99 (dd, 1H, $J = 6.9$, 17.4 Hz); 3.16 (m, 2H); 3.21–3.45 (m, 2H); 3.50 (d, 1H, $J = 15.3$ Hz); 3.93 (dd, 1H, $J = 10.5$, 4.2 Hz); 4.56 (bd, 1H, $J = 6.9$ Hz); 5.60 (d, 1H, $J = 15.3$ Hz); 7.16–7.58 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 11.8, 18.9, 21.5, 37.2, 39.8, 41.0, 47.1, 53.8, 58.8, 78.9, 122.8, 128.0, 128.6, 128.7, 129.7, 130.7, 131.1, 134.2, 142.7, 149.9, 152.8, 156.1, 163.2, 169.6, 176.4. LC-ESI-MS rt 7.2 min, *m*/*z*: 550 (M+1), 572 (M+Na).

Compound **14c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.91 (t, 3H, $J = 7.2$ Hz), 1.21 (d, 3H, $J = 7.1$ Hz), 1.38–1.45 (m, 2H), 1.62 (s,3H), 2.26 (bd,1H, $J = 17.4$ Hz), 2.85 (dd, 1H, $J = 17.4$, 6.8 Hz), 3.01 (m, 1H), 3.12 (d, 1H, $J = 19.1$ Hz), 3.44 (d, 1H, $J = 19.1$ Hz), 3.85 (m, 1H), 4.46 (d, 1H, $J = 6.8$ Hz), 6.00 (q, 1H, $J = 7.1$ Hz), 6.68–6.72 (m, 2H), 7.07–7.15 (m, 4H), 7.31–7.33 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ_C 16.4, 18.1, 19.5, 20.6, 22.2, 38.5, 50.0, 51.6, 52.5, 125.9, 127.7, 128.3, 128.4, 128.5, 138.4, 141.9, 143.7, 146.2, 149.5, 160.8, 161.9, 167.2. LC-ESI-MS: rt 2.3 min *m*/*z* 450 (M+H), 472 (M+Na), 921 (2M+Na). $[\alpha]_D = +14.6°$ (CH_3OH *c* 1.1).

Compound **15c**: ^{1}H NMR (300 MHz, CD_3OD): δ_H 0.85 (t, 3H, $J = 7.4$ Hz), 1.26–1.41 (m, 2H), 1.63 (s, 3H), 1.67 (d, 3H, $J = 7.8$ Hz), 2.45–2.55 (m, 1H), 3.05–3.21 (m, 2H), 3.34–3.36 (s, 2H), 3.55–3.65 (m, 1H), 4.70 (m, 1H), 5.71–5.79 (q, 1H, $J = 7.8$ Hz), 6.42–6.44 (m, 2H), 6.90–7.12 (m, 5H), 7.36–7.41 (m, 2H).^{13}C NMR (75 MHz, CD_3OD): δ_C 12.0, 18.9, 20.3, 22.1, 29.6, 39.7, 52.7, 54.2, 54.7, 116.6, 127.4, 128.0, 129.6, 130.0, 130.6, 131.6, 142.0, 147.6, 148.1, 163.7, 164.6, 170.6. LC-ESI-MS: rt 7.47 min *m*/*z* 450 (M+H), 472 (M+Na). $[\alpha]_D = -120.0°$ (CH_3OH *c* 0.2).

Compound **1d**: Isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.54–1.57 (m, 2H); 1.58–1.60 (m, 2H); 1.95 (s, 3H); 2.55 (dd, 1H, $J = 17.4$, 2.4 Hz), 2.76 (m, 1H), 3.08 (dd, 1H, $J = 17.4$, 7.2 Hz), 3.18–3.22 (m, 2H), 4.01 (m, 1H), 4.63 (dd, 1H, $J = 2.4$, 7.2), 4.98 (bs, 1H), 5.11 (s, 2H), 7.14–7.18 (m, 3H), 7.32–7.39 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 24.1, 25.1, 26.9, 39.1, 40.3, 46.4, 57.6, 66.2, 118.7, 126.0, 126.1, 127.7, 127.8, 128.1, 128.2, 128.6, 139.6, 144.7, 156.3, 160.3. LC-ESI-MS rt 10.0 min, *m*/*z*: 471–473 (M+1), 493–495 (M+Na).

Compound **2d**: Isolated as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.51-1.60 (m, 4H); 1.79 (s, 3H); 2.51 (d, 1H, $J = 17.2$ Hz); 3.05 (d, 1H, $J = 17.2$ Hz); 3.16 (m, 2H); 3.19 (m, 2H); 3.27 (m, 2H); 3.69 (s, 3H); 4.00 (m, 2H); 4.66 (bd, 1H, $J = 7.27$ Hz); 5.11 (m, 4H); 5.81 (m, 1H); 7.14–7.19 (m, 2H); 7.29–7.37 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 19.8, 25.1, 26.9, 29.9,

37.5, 40.1, 40.3, 45.1, 50.6, 51.1, 56.7, 67.3, 118.9, 125.8, 125.9, 129.2, 129.3, 130.1, 130.7, 131.5, 133.0, 137.2, 139.9, 145.5, 156.2, 162.2, 167.3. LC-ESI-MS rt 9.2 min, *m*/*z*: 548 (M+1), 571 (M+Na).

Compound **3d**: ^{1}H NMR (300 MHz, CD_3OD): δ_H 0.85 (t, 3H, $J = 7.2$ Hz); 1.54–1.63 (m, 2H); 1.70–1.75 (m, 2H); 1.80 (m, 3H), 2.65–2.70 (m, 1H); 2.70–2.78 (m, 1H), 2.85–3.02 (m, 2H), 3.10–3.15 (m, 1H), 3.17 (m, 1H); 3.40 (s, 1H), 3.69 (m, 1H); 4.09 (m, 1H), 5.0 (m, 1H), 7.21–7.30 (m, 2H); 7.31–7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 12.0, 20.8, 26.3, 26.9, 38.4, 41.3, 47.1, 47.5, 49.3, 49.7, 51.0, 59.0, 127.6, 129.1, 130.3, 130.6, 141.3, 141.8, 148.7, 164.4, 169.8, 172.2, 173.9, 175.5. LC-ESI-MS rt 2.9 min, *m*/*z*: 402 (M+1), 424 (M+Na).

3.7. Materials for bioassays

Trypsin/EDTA, non-essential amino acids, minimum essential medium (MEM), RPMI-1640 with L-glutamine, antibiotic, and antimycotic solution, and glycine were purchased from Invitrogen (Carlsbad, CA, USA). Fetal bovine serum (FBS) and phosphate buffered saline (PBS) were from Cambrex (Walkersville, MD, USA). Citrate buffer solution, EDTA, DMSO, Triton-X-100, 4-nitrophenyl *N*-acetyl-β-D-glucosaminide, phorbol 12-myristate 13-acetate (PMA), pyruvic acid, fibronectin from human plasma were obtained from Sigma–Aldrich SRL (Milan, Italy). SK-MEL-24 (human malignant melanoma) and K-562 (human erythroleukemia) cell lines were obtained from American Tissue Culture Collection (ATCC, Rockville, MD, USA).

3.8. Cell culture

SK-MEL-24 cells were routinely grown in MEM medium supplemented with 10% FBS, non-essential amino acids and sodium pyruvate. K-562 cells were maintained as a stationary suspension culture in RPMI-1640 + L-glutamine with 10% FBS. Cells were kept at 37 °C in a 5% CO_2 humidified atmosphere. Fourty-hour before the experiment K-562 cells were treated with 25 ng/mL of PMA to induce differentiation with increased expression of cell surface antigens.[19]

3.9. Adhesion assays

Plates (96-well) (Corning, New York, NY, USA) were coated by passive adsorption with fibronectin (10 μg/mL) overnight at 4 °C. Cells were counted and exposed to different concentrations of the drug for 30 min at room temperature to allow the ligand–receptor equilibrium. Stock solutions (10^{-2} M) of the assayed compounds were prepared in 33% DMSO and 66% PBS (v/v); further dilutions were done in PBS alone. The highest rate of DMSO in the assays was 1% of the stock solution. Control cells were exposed to the same concentration of DMSO. At the end of the incubation time, the cells were plated (50,000 cells per well) and incubated at room temperature for 1 h. Then, all the wells were washed with PBS to remove the non-adherent cells, and 50 μL of the substrate of the exosaminidase (4-nitrophenyl *N*-acetyl-β-D-glucosaminide dissolved at 7.5 mM in 0.09 M citrate buffer solution, pH 5, and mixed with an equal volume of 0.5% Triton X-100 in water) was added. This product is a chromogenic substrate for β-*N*-acetylglucosaminidase that is transformed in 4-nitrophenol whose absorbance is measured at 405 nm. As previously described,[20] there is a linear correlation between absorbance and enzymatic activity. It is, therefore, possible to identify the number of adherent cells in treated wells, interpolating the absorbance values of the unknowns in a calibration curve.

The reaction was blocked by adding 100 μL of a stopping solution (50 mM glycine, 5 mM EDTA, pH 10.4) and the plate was read in a Victor^2 Multilabel Counter (Perkin-Elmer, Waltham, Massachusetts, USA).

Experiments were carried out in quadruplicate. Data analysis and IC_{50} values were calculated using GraphPad Prism 3.0 (GraphPad Software Incorporated, San Diego, CA, USA).

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