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2,6-Quinolinyl derivatives as potent VLA-4 antagonists

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Abstract—A new series of 2,6-quinolinyl derivatives was prepared leading to potent low nanomolar VLA-4/VCAM-1 antagonists.

During an inflammatory process, white blood cells generally infiltrate the extravascular tissue. This recruitment into areas of inflammation involves the binding of leukocytes to endothelium followed by their transmigration into the tissue. Each step of this process is mediated by specific interactions between adhesion molecules present on the leukocyte cell surface and their counter-ligands expressed on vascular endothelium, epithelium, and matrix proteins.[1]

The integrin α4β1 is predominantly expressed on eosinophils, lymphocytes, monocytes, and basophils. It binds primarily to the vascular cell surface adhesion molecule VCAM-1 that is expressed on the endothelium in response to inflammatory cytokines. This interaction stabilizes rolling, enhances the cell's arrest, and allows the transmigration of these cells into the neighboring tissue.[2]

Several in vitro and in vivo studies have indicated an important role of VLA-4 in cell adhesion-mediated inflammatory pathologies[3] including asthma,[4] multiple sclerosis[5,10c] (MS), rheumatoid arthritis[6] (RA), atherosclerosis,[7] and inflammatory bowel disease[8] (IBD).

Specific inhibitors of the VLA-4 interaction with its ligands VCAM-1 or fibronectin would thus be expected to be of therapeutic benefit, especially in the treatment of asthma (characterized by the accumulation of eosinophils and lymphocytes in bronchial tissue)[9] as well as multiple sclerosis since natalizumab, a humanized monoclonal antibody to α4β1 integrin, has been recently approved for the treatment of multiple sclerosis.[10] This has led a number of companies to search for selective VLA-4 antagonists as new anti-inflammatory agents.

Substituted acylated L-phenylalanine[7,11] derivatives have been reported as highly potent antagonists of VLA-4 binding to VCAM-1, such as SB-683698 (TR-14035, **1**)[11k] or R-411 (**2**) (Fig. 1).

As part of our research directed toward the discovery of new anti-inflammatory agents, we report the synthesis of new orally bioavailable VLA-4 antagonists **3**. These

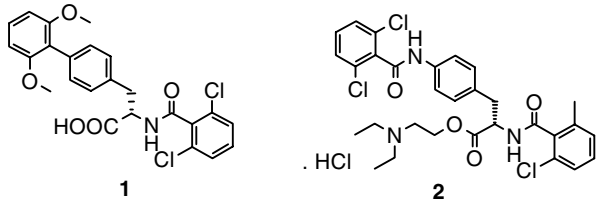

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Figure 1. L-Phenylalanine-containing VLA-4 antagonists.

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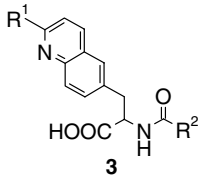
compounds were discovered, in our laboratories, through the development of a combinatorial methodology for quinoline synthesis.[12]



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Compounds **3** were prepared as outlined in Scheme 1 or according to the solid-phase combichem procedure for a few examples.[12]

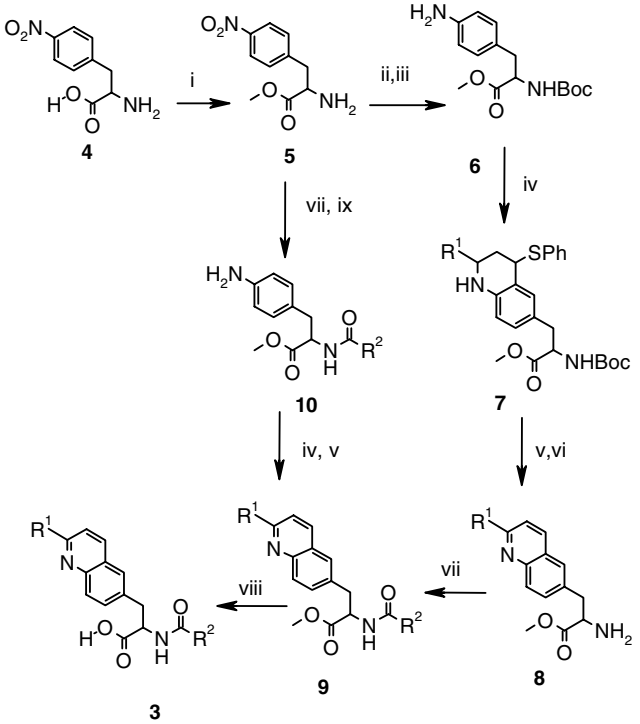
Esterification of 4-nitro-(D,L)-phenylalanine **4** followed by the protection of the amino group and reduction of the nitro group led to **7** in 79% overall yield. The next reaction was carried out according to the procedure described by Kobayashi,[13] using an aldehyde for the introduction of the R^1 group, with a yield of 81% (R^1 = 2,6-diClPh). Oxidation and aromatization of compound **7**, followed by the deprotection of the amino group, provided **8** in 78% overall yield. Introduction of the R^2 group was carried out by acylation of amine **8**. The ester **9** was then hydrolyzed with NaOH in acetonitrile to provide the derivatives **3**.

The R^2-substituent could also be introduced earlier in the synthesis. In this route, reduction of the nitro group to provide compound **10** was carefully conducted, otherwise unwanted side reactions could be observed at R^2, for example, reduction of halogenated aryl groups.

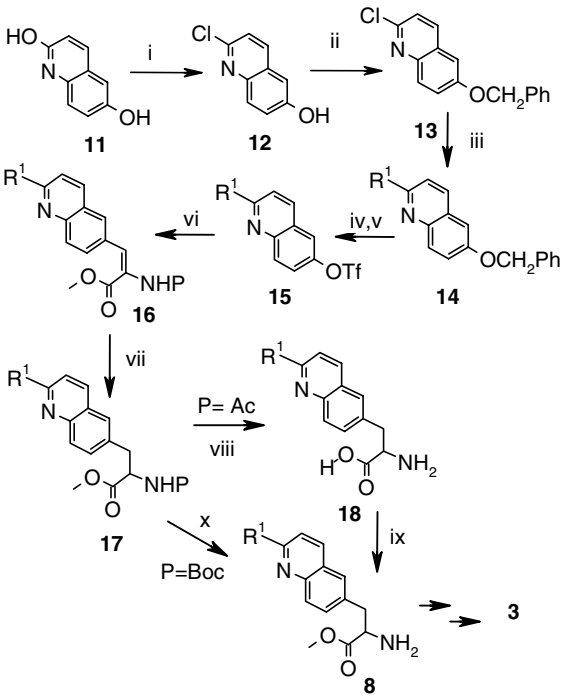
Enantiopure compounds were obtained either by synthesis starting from (*S*) or (*R*)-4-nitro-phenylalanine or by chiral chromatographic separation of racemic esters **9**.[14]

Another racemic synthetic procedure was developed in order to allow further modifications of R^1 or of the amidic function of compounds **3** as shown in Scheme 2.

Reaction of 2,6-quinolinediol **11** with $POCl_3$ provided 2-chloro-6-quinolinol **12** in 98% yield. Addition of cesium carbonate and benzyl bromide led to the *O*-protected derivative **13** in 94% yield. Introduction of R^1-groups was carried out by substituting the quinoline moiety of **13** with various boronic acids in the presence of $Pd(PPh_3)_4$ (62% yield when R^1 = 2,6-diClPh). Deprotection of the hydroxy group and triflate formation provided compounds **15** in quantitative yield. The next reaction was performed according to experimental conditions listed by Arcadi.[15] The derivatives $CH_2{=}C(COOCH_3)NHP$ are either commercially available or may be prepared by dehydration of the corresponding 2-amino-protected 3-hydroxypropanoate esters.[16] Hydrogenation of the double bound in **16** followed by deprotection of the amino group provided the synthetic intermediates **8** used to obtain compounds **3** according to the synthetic procedure described in Scheme 1.



Scheme 1. Reagents and conditions: (i) $SOCl_2$, CH_3OH; (ii) Boc_2O, NaOH, THF; (iii) NH_4HCO_2, CH_3OH, Pd/C; (iv) R^1CHO, $CH_2{=}CHSPh$, $Yb(OTf)_3$, CH_3CN, CH_2Cl_2; (v) 1—$NaIO_4$, 2—80 °C; (vi) TFA, CH_2Cl_2; (vii) R^2COCl, DIPEA, CH_2Cl_2 or R^2COOH, HATU, DIPEA, DMF; (viii) NaOH 0.1 N/CH_3CN/H_2O; (ix) Pt(S)/C, CH_3OH, H_2.



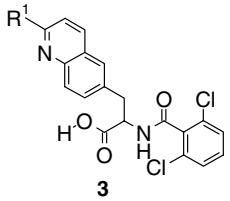
Scheme 2. Reagents: (i) $POCl_3$, DMF; (ii) $PhCH_2Br$, Cs_2CO_3, DMF; (iii) $R^1B(OH)_2$, $Pd(PPh_3)_4$, $NaHCO_3$, toluene, EtOH; (iv) BBr_3, CH_2Cl_2; (v) Tf_2O, CH_2Cl_2; (vi) $CH_2{=}C(COOCH_3)NHP$, $Pd(OAc)_2$, *n*-Bu_4NCl, NEt_3, DMF; (vii) H_2, Pd/C, CH_3OH; (viii) HCl (6N); (ix) $SOCl_2$, CH_3OH; (x) TFA, CH_2Cl_2.

All compounds were tested in a VLA-4 dependent U937/VCAM-1 adhesion test.[17]

Table 1 summarizes the results obtained following the introduction of various (hetero)aryl groups at the R^1 position.

A very weak activity was observed when an unsubstituted phenyl ring was introduced at the R^1 position (**26**). Substituting the 2,6-positions of the aromatic ring with chlorine (**19**) led to one of the most active compounds within this series. Interestingly, substitutions of the two chlorine atoms at the 2,4-positions of the phenyl ring gave rise to the less potent molecule **21**. Less potent compounds were obtained when two fluorine (**22**) or methyl (**23**) groups replaced the two chlorine atoms. However, replacement of chlorine by methoxy provided **20** displaying a similar activity to that of **19**. One of the chlorine atoms at the ortho position could be replaced by a fluorine atom (**24**) or by a nitro group (**25**) while keeping the same level of activity. On the other hand, monosubstitution at the ortho position of the phenyl ring with bromine (**27**) or trifluoromethyl (**28**) led to less active molecules. Lastly, introduction of the electron-withdrawing group methylsulfonyl at the para position (**30**) induced an important loss of activity. We next investigated replacement of the phenyl ring by other potential isosteric groups. Thus, replacing the phenyl moiety by a substituted naphthyl (**29**) or a 2,6-diCl-4-pyridyl group (**32**) gave rise to potent low nM antagonists. On the contrary, introduction of an unsubstituted 4-pyridyl-moiety (**31**) or a 1,3-thiazole ring (**33**) was detrimental to the anti-VLA-4 activity.

Table 1. SAR on R^1 position of **3** (R^2 = 2,6-diClPh)



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Compound	R^1	Cell Adh. VLA-4 (IC_{50}, nM)
19	2,6-DiClPh	7.8
20	2,6-Di(OCH_3)Ph	20
21	2,4-DiClPh	748
22	2,6-DiFPh	371.5
23	2,6-Di(CH_3)Ph	102
24	2-F, 6-ClPh	20
25	2-NO_2, 6-ClPh	6.5
26	Ph	24% inh. at 1 μM
27	2-BrPh	153.5
28	2-CF_3Ph	92
29	2-OCH_3-1-naphthyl	7.3
30	*p*-(Methylsulfonyl)Ph	82% inh. at 1 μM
31	4-Pyridinyl	381
32	2,6-DiCl-4-pyridinyl	8.6
33	1,3-Thiazol-2-yl	38% inh. at 1 μM
34	2-Cl-5-(CF_3)Ph	208.5

These results confirm the need for 2,6-disubstitution with bulky groups (Cl ⩾ F, OMe > Me ≫ H) in order to generate a non-planar orientation between the phenyl and the quinoline rings.

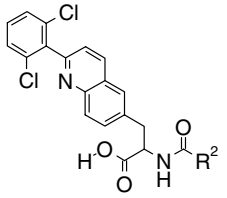
The need for an H-bond acceptor in that area, as reported in the case of TR-14035 where the methoxy group proved to be crucial for the interaction,[11k] is also met thanks to the quinoline nitrogen as confirmed by the much lower affinity of the corresponding naphthyl analogue to **19** (unpublished results).

We then explored the introduction of diverse (hetero)aryl groups at the R^2 position of **3** (Table 2).

Introduction of a phenyl ring led to a poorly active compound (**41**) while one of the most potent compounds (**19**) was obtained following disubstitution with chlorine at the 2,6-positions. As noticed for the R^1 position, chlorine could be replaced by methyl (**36**), while replacing this atom by a methoxy group (**35**) or fluorine atom (**37**) led to less potent derivatives. Moreover, replacement of the 2-Cl atom by a methyl group (**38**) allowed keeping a quite potent antagonism. Interestingly, mono-chloro substitution was allowed when substituting the para position of the phenyl ring with the methylsulfonyl moiety as in **39**. Replacement of the phenyl ring by a substituted 4-pyridyl-ring (**40**) also led to a potent antagonistic activity. The 1-substituted cyclopentanyl group described by other researchers[11c,18] also proved to be useful in our series, leading to the potent molecule **42**.

As a general conclusion, we observed that the SAR generated from the chemical modulations at the R^1or R^2 positions were rather similar and are consistent with other reported data.

Table 2. SAR on R^2 position of **3** (R^1 = 2,6-diClPh)



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Compound	R^2	Cell Adh. VLA-4 (IC_{50}, nM)
19	2,6-DiClPh	7.8
35	2,6-Di(OCH_3)Ph	53.7
36	2,6-Di(CH_3)Ph	37.2
37	2,6-DiFPh	435
38	2-CH_3, 6-ClPh	3.9
39	2-Cl, p-(methylsulfonyl)Ph	3.5
40	2,4-DiCl-6-CH_3-3-pyridinyl	7.9
41	Ph	5640
42	1-(4-ClPh)cyclopentanyl	6.6
43	(2*S*)-1-benzyl-5-oxopyrrolidinyl	15.3

Table 3. Influence of stereochemistry on VLA-4/VCAM adhesion

Compound	Stereochemistry	R^1	R^2	Cell Adh. VLA-4 (IC_{50}, nM)
19	(*S*,*R*)	2,6-DiClPh	2,6-DiClPh	7.8
19a	(*S*)	2,6-DiClPh	2,6-DiClPh	3.9
19b	(*R*)	2,6-DiClPh	2,6-DiClPh	> 3200

Table 4. In vitro properties of **19a**

Compound	U937-VCAM adhesion (IC_{50}, nM)	Jurkat/fibronectin adhesion (IC_{50}, nM)	CD3-VCAM T-cell activation (CD25 expression) (IC_{50}, nM)	α4β1 human whole blood (IC_{50}, nM)
19a	3.9	1.6	43	95
1	18	—	99	414

Table 5. In vivo PK properties of **19a**

Compound	Cl (L/h/kg)	V_{dss} (L/kg)	C_{max} (ng/mL)	F (%)			
				Mouse	Rat	Dog	Monkey
19a	1.1	10	119	35	41	59	23

Compound **19** has been selected for further profiling on the basis of these preliminary results. In order to assess the influence of stereochemistry, both enantiomers have been prepared starting from the corresponding amino acids. As shown in Table 3, and as expected on the basis of numerous reported results, enantiomer **19a** (2*S*) proved to be the most potent.

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Compound **19a** has been further characterized in secondary in vitro assays and compared to TR-14035 **1**. It displays a higher activity in the U937-VCAM cell adhesion assay, on CD25 expression, and in the α4β1 human whole blood assay[19] (Table 4).

Compound **19a** has been screened against more than 40 different receptors, enzymes, and other integrins, and no significant interactions were observed at 10 μM. No cytotoxicity was observed up to 10 μM.

On the basis of its excellent affinity, selectivity, and adequate physicochemical properties (S = 1.5 mg/mL at pH 7.4, log D = 1.47, no plasma hydrolysis), **19a** was then evaluated in early DMPK. It is characterized by a very low metabolic clearance on rat, dog, and human microsomes, and by low transformation rate by rat hepatocytes. Moreover, no significant interaction (at 50 μM) was observed in vitro with the major cytochrome P450 subtypes (2D6, 2C9, 2C19, and 3A4).

Furthermore, compound **19a** displays an adequate in vivo PK profile including acceptable oral bioavailability across species. This constitutes a clear advantage compared to most reported programs that, by default, resort to a pro-drug strategy to achieve acceptable oral exposure (Table 5).

As a conclusion, new 2,6-quinolinyl derivatives were prepared and proved to be potent, original, selective, and orally bioavailable VLA-4/VCAM antagonists.[20] One preferred compound, **19a**, is presently under extensive pharmacological characterization. The results of this study will be reported in due course.

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14. For R^1 and R^2 = 2,6-diClPh: Chiralpak AD 100×500 mm, flow: 300 mL/min, wavelength: 220 nm; hexane/ethanol 50/50 as eluent.
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17. The VLA-4 expressing cell line U937 (ATCC *n*°: CRL 1593) was cultured in RPMI 1640 medium supplemented with fetal bovine serum 10%. Prior to the assay, cells were washed, resuspended in HBSS BSA 0.1% at 5×10^6 cells/mL, and loaded with the fluorescent dye Calcein-AM at a final concentration of 10 μmol/L for 15 min at 37 °C. After washing, cells were resuspended in RPMI at 2×10^6 cells/mL for assay. Cells were plated in 96-well microtiter plates, precoated with soluble human recombinant VCAM-1 (2.5 μg/mL in DPBS), in the presence of test compounds or vehicle (DMSO, 1% final concentration). Plates were then incubated at room temperature for 45 min. After washings, adherent cells were quantified by fluorescence measurement and expressed in percentage of total cells. Adhesion inhibition was calculated for each test compound concentration run in triplicate. IC_{50} were evaluated from three independent titration curves and expressed as mean value.
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