A new synthetic approach to biaryls of the rhazinilam type. Application to synthesis of three novel phenylpyridine-carbamate analogues

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The synthesis of three novel racemic phenylpyridine-carbamate analogues of rhazinilam and their biological evaluation as inhibitors of microtubule assembly and disassembly by interaction with tubulin are described. The sterically hindered *ortho*-disubstituted biaryl unit as the challenging key structural element is first obtained by a sequential regiocontrolled nucleophilic addition of a lithium *ortho*-lithiohomobenzylic alkoxide species to 3-bromo-5-oxazolyl pyridine as the electrophile and a subsequent oxidation step. The incorporation of the amino group by replacement of the bromide has been achieved using a Buchwald–Hartwig amination coupling. Ultimate deprotection steps furnished free-amino and free-hydroxyl appendages which were connected by phosgenation to furnish the nine-membered median carbamate ring.

Introduction

(−)-Rhazinilam **1** is a tetracyclic phenyl-pyrrole alkaloid isolated from various *Apocynaceae*.[1] It was found both to induce *in vitro* spiralization of microtubules (vinblastin effect) and to inhibit the cold-induced disassembly of microtubules[1] (paclitaxel effect). As a consequence of these unique antitubulin properties, (−)-rhazinilam showed significant *in vitro* cytotoxicity towards various cancer cell lines but no activity was found *in vivo*.[1] Thus structure–activity relationships on rhazinilam analogues are of considerable interest.[1] Recently three-dimensional quantitative structure–activity relationships (3D-QSAR) from all available analogues were investigated.[2] The biphenyl carbamate analogue (−)-**2** mimicking the structure of (−)-rhazinilam developed by Guéritte *et al.*[3] is currently the most active analogue with a 2-fold activity on microtubule disassembly compared to **1** and a similar cytotoxicity. The synthesis of several biphenyl analogues allowed the establishment of the main structural elements for maximum antitubulin activity which are the presence of the biaryl unit bridged by a nine-membered carbamate ring (ring B) as well as a quaternary center mimicking the stereogenic center of **1**. Our laboratory proposed in 2001 the first phenylpyridine analogues of rhazinilam[4] and their biological evaluation confirmed that the replacement of the lactam by a carbamate function enhances the antitubulin activity. The best biological result was obtained with *rac*-**3** which is however six times less active on the inhibition of microtubule disassembly than (−)-rhazinilam. In continuation of this study, we embarked on a program aimed at the synthesis of new phenylpyridine analogues derived from biphenyl analogue **2** by replacing the aniline moiety (ring A) by an aminopyridine system and keeping the nine-membered carbamate ring and a quaternary center as essential structural elements for the antitubulin activity.

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We expected thus to evaluate the effect of the charge distribution on the aniline moiety of (−)-rhazinilam (ring A) on the antitubulin activity. Here we wish to report the synthesis of three novel racemic phenylpyridine-carbamate analogues of rhazinilam **4a**, **4b** and **4c** (Fig. 1) and their biological evaluation.

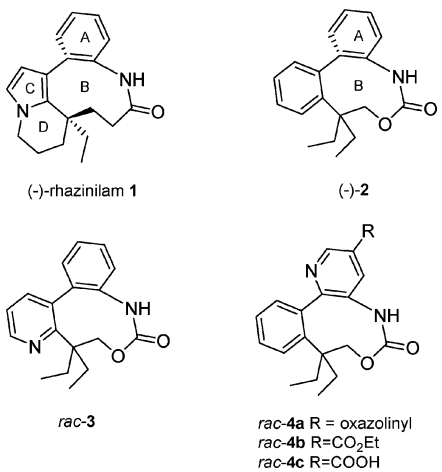
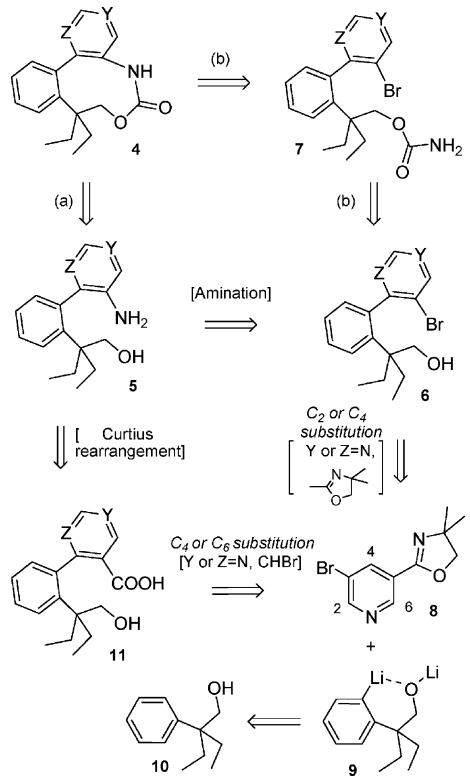


Fig. 1 Analogues of rhazinilam **4a**, **4b** and **4c**.

Results ans discussion

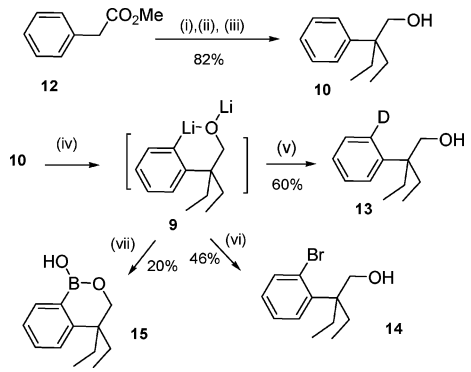
Our planned approach to phenylpyridine-carbamates **4** bearing the nitrogen atom on the aniline moiety (ring A) is shown in Scheme 1. The nine-membered carbamate ring could be installed by ring-closure of the aminoalcohol **5** (route a). The final ring-closure could also be achieved by an intramolecular palladium catalyzed Buchwald–Hartwig amidation of bromocarbamate **7** obtained by carbamoylation of the bromoalcohol **6** (route b). The two *ortho*-substituted biaryl precursors **5**, **6** could be obtained *a priori* using cross-coupling protocols but Guéritte and Baudoin have pointed out the sensitivity of cross-couplings toward steric hindrance in biphenyl series due in particular to the presence



Scheme 1

of the highly hindered quaternary center.[3c] Thus, in order to prepare phenylpyridine analogue *rac*-**3**,[4] Rocca *et al.* opted for a post-alkylation of the picolinic site to install the quaternary carbon after formation of the biaryl unit. However this elegant approach cannot be applied to the preparation of the two biaryl precursors **5** and **6** due to the much lower acidity of the benzylic site compared to the picolinic one. In this paper we envisage the formation of the pivotal *ortho*-substituted biaryl unit using a key nucleophilic addition of the lithium *ortho*-lithioarylalkoxide salt **9** to an adequate activated bromopyridine scaffold **8**, followed by an oxidative step to regenerate the pyridine nucleus.

We initially investigated the unreported *ortho*-lithiation of the α,α'-ethylhomobenzylic alcohol **10** ready prepared from methyl 2-phenyl acetate **12** in 82% yield using a double ethylation and reduction sequence depicted in Scheme 2. The α,α'-ethylhomobenzylic alcohol **10** was subjected to a series of strong bases. The lithiation yield was determined by measuring the ratios of starting material and deuterated product (**10** : **13**) after an external D_2O quench



Scheme 2 *Reagents and conditions*: (i) LDA (4 equiv.), THF, −78 °C; (ii) EtI (5 equiv.); (iii) $LiAlH_4$, THF, r.t., 2 h; (iv) *sec*-BuLi (3 equiv), hexane, 70 °C, 6 h; (v) D_2O (see Table 1) then hydrolysis; (vi) 1,2-dibromotetrachloroethane; (vii) $B(OMe)_3$ then aq. HCl.

technique (Table 1). We first applied Meyer and Seebach's conditions reported for the lithiation of α,α'-methylbenzylic alcohol,[5] similar to homobenzylalcohol **10** (Table 1-entry 1). After quenching with D_2O, a mixture of **10** and **13** was obtained in a 4 : 1 ratio. We turned to stronger bases, *sec*-BuLi and *tert*-BuLi. The lithiation was carried out on a broad range of temperatures and using different equivalents of base. After several experiments summarized in Table 1 (entries 2–7), the best result was obtained with the treatment of **10** with 3 equiv. of *sec*-BuLi in hexane at 70 °C for 6 h, which provided a 1 : 9 mixture of **10**–**13** in 60% yield after chromatography (entry 6). The *ortho*-bromo α,α'-ethylhomobenzylic alcohols **14** could be prepared in modest 46% yields using 1,2-dibromo-tetrachloroethane as a halogenating agent. The borylation of the lithium *ortho*-lithioarylalkoxide salt **9** could also be performed with trimethylborate as an electrophile followed by hydrolysis with HCl to give the first prepared six-membered ring oxaborine **15** in 20% yield over two steps.

The 3-bromo-5-oxazolyl pyridine scaffold **8** was prepared on a multigram-scale from commercially available 3-bromo-5-cyano pyridine **16** by treatment with 2-amino-2-methyl propanol **17** in the presence of $ZnCl_2$ as a catalyst[6] (Scheme 3). Although Ottow and co-workers have previously reported the nucleophilic addition of 3-anisylmagnesium bromide to 5-bromo-3-pyridine carboxamide[7] similar to our scaffold **8**, no previous report has given sound support to the nucleophilic addition of aryllithium species to protected 3-bromo-5-carboxypyridine derivatives. Such a nucleophilic addition was explored by reacting 3-bromo-5-oxazolyl pyridine **8** with phenyllithium at room temperature in THF for 1 h as a typical experiment.[8] Subsequent oxidative

Table 1 Lithiation–D_2O trapping of **10**

Entry	Base	Equiv.	*t*/°C	Time/h	Ratio **10**–**13** *x*–*y*[a](%)[b]
1	*n*-BuLi–TMEDA	2	70	12	4 : 1 (—)
2	*sec*-BuLi	2	70	6	7 : 3 (—)
3	*sec*-BuLi	3	r.t.	24	6 : 4 (—)
4	*sec*-BuLi	5	r.t.	24	7 : 3 (—)
5	*sec*-BuLi	3	40	32	3 : 7 (50)
6	***sec*-BuLi**	**3**	**70**	**6**	**1 : 9 (60)**
7	*tert*-BuLi	3	r.t.	32	3 : 7 (55)

[a] NMR conversion to deuterated compound. [b] Isolated yield obtained using the optimal metallation conditions.

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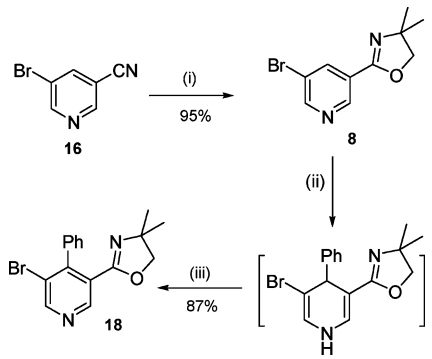
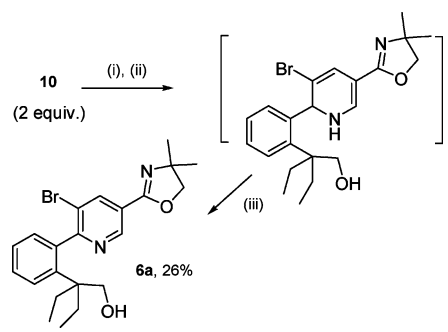


Scheme 3 *Reagents and conditions*: (i) 2-amino-2-methylpropan-1-ol **17**, $ZnCl_2$ (10%mol), PhCl, Δ, 2 days; (ii) PhLi (1 equiv.), THF, r.t., 1 h then NH_4Cl; (iii) chloranil, toluene, Δ, 2 h.

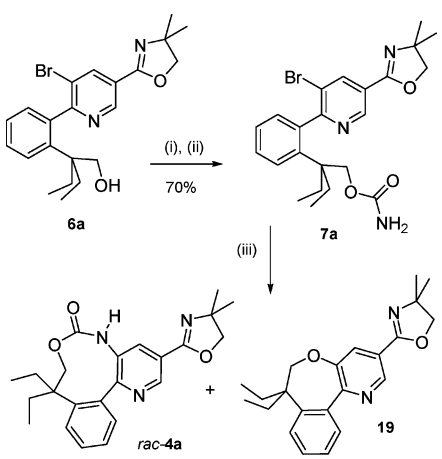
treatment of the crude reaction mixture with chloranil in refluxing toluene for 2 h afforded the expected phenylpyridine **18** in good 87% isolated yield (Scheme 3). The latter showed two characteristic singlets corresponding to the H_2 and H_6 protons in the ^1H NMR spectrum indicating that the phenyl group was exclusively introduced to the C_4 site of the pyridine nucleus in agreement with Ottow's observations.[7] We next investigated the addition of lithium *ortho*-lithioarylalkoxide salt **9** to 3-bromo-5-oxazolyl pyridine **8**. After generation from **10** as previously described, **9** was added to 3-bromo-5-oxazolyl pyridine **8** in THF at room temperature for 1 h.

Treatment of the crude reaction with chloranil in refluxing toluene for 2 h provided a biaryl compound in 26% overall yield. Careful analysis surprisingly revealed the introduction of the phenyl moiety at the C_2 site of the pyridine nucleus leading to bromoalcohol **6a** (Scheme 4).

Meyers, Hauck, Knaus and Bourguignon *et al.* previously demonstrated that the regiochemical outcome of the nucleophilic addition of aryllithium species to 3-oxazolylpyridine may occur indifferently at C_2, C_4 and C_6 sites depending mainly on three factors: polarity of the solvent, addition temperature and steric hindrance of the nucleophilic reagent.[8] Unfortunately we were not able to direct the nucleophilic addition of lithio anion **9** at another position whatever the solvent (Et_2O and toluene were used), the temperature or the use of TMEDA. Construction of the nine-membered cyclic carbamate from bromoalcohol **6a** was next investigated. To this purpose carbamate **7a** was first prepared in 70% yield *via* carbamoylation of **6a** in the presence of trichloroacetylisocyanate[9] (Scheme 5) before cyclisation of the *N*-metallated derivative of **7a**. Thus, **7a** was *N*-metallated by treatment with sodium hydride in DMF at room temperature[10] (Table 2-entry 1). However the expected annelated product **4a** was not formed, but instead the seven-membered-ring biaryl-ether **19** was exclusively obtained in excellent 90% yield. We could hypothesize that the competitive elimination of isocyanic acid[11] from the *N*-metallated carbamate produced *in situ* the lithium oxanion which then substituted the bromine atom in an intramolecular way. We then turned to the transition metal-catalyzed carbamatation. Ring-closure *via* Buchwald's amidation by using Cu(I) and a diamine ligand as catalyst[12] (Table 2-entry 2) led to the cleavage of the carbamoyl function affording bromoalcohol **6a** in 70% yield. The Pd(0)-catalyzed intramolecular carbamatation was then tested using two specific ligands, $P(^tBu)_3$[13] and Xantphos[14] (Table 2-entries 3 and 4). In both cases no expected annelated compound *rac*-**4a** could be obtained. Similar to previous observations, decarbamoylation occurred, especially when using Xantphos as a ligand (Table 2-entry 4), and the



Scheme 4 *Reagents and conditions*: (i) *sec*-BuLi (6 equiv.), hexane, 70 °C, 6 h; (ii) **8** (1 equiv.), THF, r.t., 1 h then NH_4Cl; (iii) chloranil, toluene, Δ, 2 h.



Scheme 5 *Reagents and conditions*: (i) trichloroacetylisocyanate, CH_2Cl_2, r.t., 30 min; (ii) K_2CO_3, MeOH, r.t., 3 h; (iii) see conditions and results in Table 2.

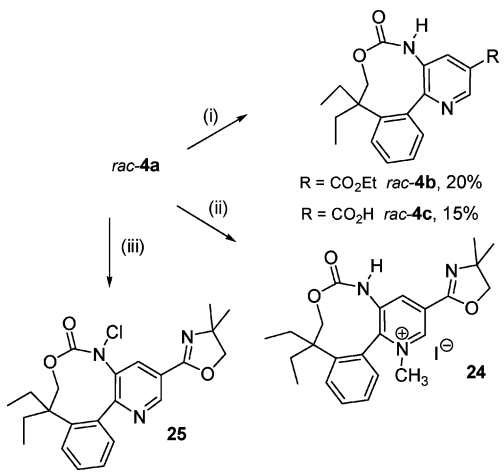
Table 2 Assays of nine-membered ring-closing of **7a**

Entry	Conditions	%-**4a**[a]	%-**6a**[a]	%-**7a**[a]	%-**19**[a]
1	NaH, DMF, r.t., 12 h	None	0	0	90[b]
2	CuI, $(MeNHCH_2)_2$, K_2CO_3, toluene, Δ, 16 h	None	70	30	0
3	$Pd(dba)_2$, $P(^tBu)_3HBF_4$, NaOPh, toluene, Δ,16 h	None	16	60	24
4	$Pd_2(dba)_3$, Xantphos, Cs_2CO_3, dioxane, 16 h	None	60	20	20

[a] NMR conversion except for entry 1. [b] Yield of isolated product.

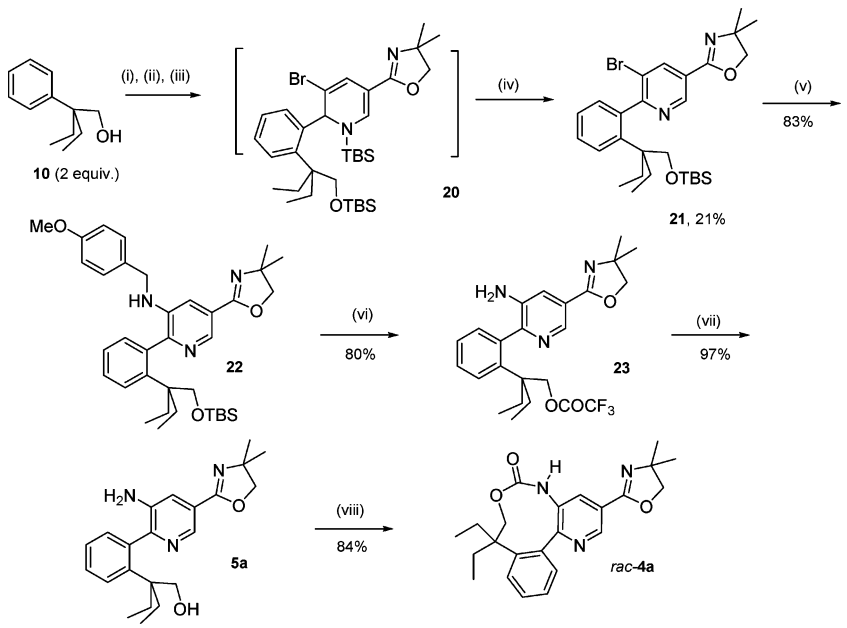
resulting bromoalcohol **6a** was then partially converted in low yields to the seven membered-ring biaryl-ether **19**.

At this stage it appeared necessary to protect the free-alcohol function of **6a** before performing the substitution of the bromine by an amino group. The TBS-alcohol protection of **6a** was effected using a standard procedure[15] to give **21** in 67% yield. As Akiba and co-workers have previously shown that *N*-silyldihydropyridine could be readily reoxidized to pyridine through treatment with chloranil,[16] the TBS-alcohol protection was directly performed after the nucleophilic addition of lithium *ortho*-lithioarylalkoxide salt **9** to scaffold **8** *via* subsequent addition of *tert*-butyldimethylsilylchloride (TBSCl). Without isolation, protected *N*-silyldihydropyridine intermediate **20** (Scheme 6) was then subjected to oxidative treatment with chloranil giving rise to **21** in 21% yield through a one-pot four step synthesis. A classical palladium-catalyzed Buchwald–Hartwig amination[17] of **21** provided then the bis-protected biarylic aminoalcohol **22** in excellent 83% yield (Scheme 6). Next, both *N*-PMB and *O*-TBS deprotections were carried out with TFA[18] and the resulting crude free-amino ester **23** thus obtained was immediately hydrolyzed by simple basic treatment with K_2CO_3 in a mixture of MeOH–H_2O to give biarylic aminoalcohol **5a** in 78% yield over two steps (Scheme 6). The final internal carbamatation was first attempted by treating **5a** with triphosgene.[4] Surprisingly this process failed due probably to the poor nucleophilicity of the amino group in the presence of the electron-withdrawing oxazolyl group on the pyridine nucleus. Nucleophilic activation of both free-amino and free-alcohol groups remained unsuccessful after metallation of **5a** with 2.5 equivalents of *n*-BuLi and treatment of the resulting *N*,*O*-dilithio anions with diethylcarbonate[19] at room temperature for 16 h. Finally, the direct phosgenation of **5a** in the presence of NEt_3[20] was achieved providing the desired phenylpyridine carbamate *rac*-**4a** in an excellent 84% yield (Scheme 6). The corresponding ethyl ester *rac*-**4b** and carboxylic acid *rac*-**4c** were obtained *via* H_2SO_4-induced cleavage[21] of the oxazolyl group in EtOH or in H_2O respectively but in low 20 and 15% yields due to the undesired hydrolysis of the carbamate group (Scheme 7). Milder methods for oxazoline hydrolysis involving the prior formation of oxazolinium salts[22] and subsequent treatment with NaOH couldn't be applied as the treatment of *rac*-**4a** with CH_3I exclusively afforded the *N*-methylpyridinium salt **24**. Treatment of *rac*-**4a** with NaOCl also remained unsuccessful leading only to the *N*-chlorocarbamate analogue **25** (Scheme 7).



Scheme 7 *Reagents and conditions*: (i) H_2SO_4–EtOH or H_2O (1 : 9), Δ, 5 h; (ii) CH_3I, CH_3CN, r.t., 12 h; (iii) NaOCl, Bu_4NHSO_4, AcOEt, r.t., 4 h.

The cytotoxicity and the antitubulin activity of the new phenylpyridine analogues **4a**, **4b** and **4c** were evaluated and compared to those of (−)-**1** (Table 3). The seven-membered-ring



Scheme 6 *Reagents and conditions*: (i) *sec*-BuLi (6 equiv.), THF, 70 °C, 6 h; (ii) **8** (1 equiv.), THF, r.t., 1 h; (iii) TBSCl, r.t., 16 h; (iv) chloranil, toluene, Δ, 2 h; (v) *p*-methoxybenzylamine (1.2 equiv.), Pd_2dba_3, BINAP, ^{t}BuONa, toluene, Δ, 16 h; (vi) TFA, r.t., 16 h; (vii) K_2CO_3, MeOH–H_2O, r.t., 1 h; (viii) phosgene (1 equiv.), NEt_3, THF, 0 °C to 25 °C, 1 h.

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Table 3 Cytotoxicity and antitubulin activity of (−)-rhazinilam, *rac*-**4a–c** and **19**

Compound	Cytotox. KB cell line $IC_{50}/\mu M$[a]	Cytotox. MCF7 cell line $IC_{50}/\mu M$[a]	Inhibition of microtubule disassembly $IC_{50}/\mu M$[b]	Inhibition of microtubule assembly $IC_{50}/\mu M$[b]
1	0.6	4.0	3.7	6.7
4a	in	in	1%[c]	32%[c]
4b	in	in	12%[c]	18%[c]
4c	in	in	in	in
19	in	in	190	110

[a] IC_{50} is the concentration of compound corresponding to 50% growth inhibition after 72 h incubation. [b] IC_{50} is the concentration of compound required to inhibit 50% of the rate of microtubule assembly or disassembly (in = inactive). [c] Percentage of inhibition of assembly or disassembly at 10 mg L^{-1} (IC_{50} could not be measured).

bridged biaryl-ether **19** was also submitted to the same test as the ring structure analogue of the antimitotic (−)-colchicine. Phenylpyridine analogues **4a**, **4b** and **4c** were weakly active in the polymerization and depolymerization of microtubules. In addition, no cytotoxicity was found on KB cancer cells as well as on human breast adeno-carcinoma MCF7. It was previously demonstrated that the addition of sterically hindered substituents on the aniline moiety (ring A) of (−)-**2a** lowers the interaction with tubulin.[1] This suggests that the inactivity of *rac*-**4a**, *rac*-**4b** and *rac*-**4c** is imputable to the substitution of the pyridine nucleus rather than to its electron-deficient character. The biological evaluation of the unsubstituted pyridine analogue would be necessary to verify this assumption. The seven-membered-ring biaryl-ether **19** was respectively 15 and 50 times less active than (−)-**1** in tubulin polymerization and depolymerization and no cytotoxicity towards adeno-carcinoma MCF7 as well as KB cancer cells was observed.

Conclusion

The hindered rhazinilam-like phenylpyridine carbamates were prepared for the first time by using a one-pot three step sequence with the generation of the lithium *ortho*-lithioarylalkoxide salt **9** by *ortho*-lithiation, subsequent nucleophilic addition to the 3-bromo-5-oxazolyl pyridine scaffold **8** at the C_2 position and a final oxidative step. The method was directly applied to the preparation of three novel phenyl-3-carboxypyridyl-carbamate analogues **4a**, **4b** and **4c** of rhazinilam as racemic mixtures in 11, 2.2 and 1.6% overall yields respectively. These new analogues proved to be inactive in the inhibition of the polymerization and depolymerization of tubulin. Other substituted as well as unsubstituted phenylpyridine carbamates will be synthesized by extension of the nucleophilic addition of the lithium *ortho*-lithioarylalkoxide salt **9** to other activated pyridine scaffolds.

Experimental

General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded on a Bruker AM 300 spectrometer with residual protic solvent as the internal reference. Chemical shifts are quoted in ppm and coupling constants in Hz. IR spectra were recorded using KBr cells on a Perkin-Elmer FT IR 205 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 apparatus. High-resolution mass spectra (HRMS) were recorded by the department service. THF was distilled from benzophenone–Na. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. The compounds **12** and **17**, the solutions of *n*-BuLi, *sec*-BuLi and *tert*-BuLi and the ligands $P(^tBu_3)HBF_4$, Xantphos were used as received.

2-Ethyl-2-phenylbutan-1-ol (10). A solution of *n*-BuLi (48 ml of 2.5 M solution in hexane, 120 mmol) was slowly added, at −78 °C under N_2, to a stirred solution of 2,2′-bipyridyl (4 mg, 0.02 mmol) and *N*-diisopropylamine (DIPEA) (16.8 ml, 120 mmol) in THF (120 ml). The mixture was stirred for 15 min at −78 °C and a solution of methyl 2-phenylacetate **12** (4.31 ml, 30 mmol) in THF (50 ml) was added. After an additional 30 min stirring period, EtI (12 ml, 150 mmol) was added. The mixture was allowed to warm to r.t. for 3 h and H_2O (100 ml) was added. The product was extracted with CH_2Cl_2 (3 × 70 ml) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was dissolved in THF (50 ml) and the above deprotonation–ethylation sequence was repeated (LDA (60 mmol) in THF (60 ml) and EtI (6 ml, 75 mmol)). The residue was purified by flash chromatography (Cy–EA 98 : 2) to give 2-methyl-2-ethylphenylbutanoate (5.7 g, 92%) as a pale yellow oil. To a solution of 2-methyl-2-ethylphenylbutanoate (500 mg, 2.4 mmol) in THF (10 ml) was slowly added a solution of $LiAlH_4$ (91 mg, 2.4 mmol) in THF (5 ml) at 0 °C. The mixture was stirred at 25 °C for 2 h under N_2 and cooled at 0 °C before H_2O (91 µl), NaOH (2 M, 91 µl) and H_2O (270 µl) were successively added. After filtration though a short pad of celite, the product was extracted with AcOEt (3 × 10 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by distillation (112 °C, 2 mbar) to give **10** (384 mg, 90%) as a colorless oil (Found: C, 80.79; H, 10.23. Calc. for $C_{12}H_{18}O$: C, 80.85; H, 10.18%); IR ν_{max}/cm^{-1} 3307 (OH), 2969; ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.75 (6 H, t, *J* 7.2, 2 × CH_2CH_3), 1.07 (1 H, s, OH), 1.74 (4 H, m, 2 × CH_2CH_3), 3.74 (2 H, d, *J* 6.0, CH_2OH), 7.22 (1 H, m, 4-H), 7.33 (4 H, m, Ph); ^1H NMR δ_H (300 MHz, DMSO): 0.59 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.64 (4 H, m, 2 × CH_2CH_3), 3.61 (2 H, d, *J* 4.9, CH_2OH), 4.48 (1 H, t, *J* 4.9, OH), 7.12 (1 H, m, 4-H), 7.26 (4 H, m, Ph); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 7.9 (2 × CH_3), 26.0 (2 × CH_2), 46.0 ($C(Et)_2$), 67.1 (CH_2OH), 125.9 (CH_{ar}), 126.9 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 144.4 (C_{Ar}).

2-(2-Deuteriophenyl)-2-ethyl-butan-1-ol (13). A solution of *sec*-BuLi (2.6 ml of 1.3 M solution in cyclohexane–hexane 98 : 2, 3.36 mmol) was slowly added, at r.t. under N_2, to a stirred solution of 2-ethyl-2-phenylbutan-1-ol (**10**, 200 mg, 1.12 mmol) in

hexane (2 ml). The mixture was refluxed for 6 h and cooled to 0 °C before D_2O (0.6 ml, 30 mmol) was added. The temperature was slowly allowed to warm to r.t. and water (2 ml) was added. The product was extracted with AcOEt (3 × 5 ml) and the combined organic extract was washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (Cy–EA 8 : 2) to give **13** (125 mg, 60%) as a colorless oil. ^{1}H NMR δ_H (300 MHz, DMSO): 0.59 (6 H, t, *J* 7.1, 2 × CH_2CH_3), 1.64 (4 H, m, 2 × CH_2CH_3), 3.61 (2 H, d, *J* 4.9, CH_2OH), 4.48 (1 H, t, *J* 4.9, OH), 7.12 (1 H, m, 4-H), 7.26 (3 H, m, Ph).

2-(2-Bromophenyl)-2-ethyl-butan-1-ol (14). A solution of *sec*-BuLi (2.6 ml of 1.3 M solution in cyclohexane–hexane 98 : 2, 3.36 mmol) was slowly added, at r.t. under N_2, to a stirred solution of 2-ethyl-2-phenylbutan-1-ol (**10**, 200 mg, 1.12 mmol) in hexane (2 ml). The mixture was refluxed for 6 h and cooled to 0 °C before a solution of 1,2-dibromotetrachloroethane (1.82 g, 5.6 mmol) in THF (3 ml) was added. The temperature was allowed to warm to 25 °C and the mixture was stirred for 16 h. Water (2 ml) was added and the product was extracted with AcOEt (3 × 5 ml). The combined organic extract was washed with brine, dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (Cy–EA 8 : 2) to give **14** (134 mg, 46%) as a colorless oil (Found: C, 56.34; H, 6.65. Calc. for $C_{12}H_{17}BrO$: C, 56.04; H, 6.66%); IR ν_{max}/cm^{-1} 3380, 2965; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 0.71 (6 H, t, *J* 7.2, 2 × CH_2CH_3), 1.20 (1 H, t, *J* 6.0, OH), 1.98 (2 H, m, CH_2CH_3), 2.10 (2 H, m, CH_2CH_3), 4.08 (2 H, d, *J* 6.0, CH_2OH), 7.05 (1 H, t, *J* 6.8, 4-H), 7.26 (2 H, m, 5-H, 6-H), 7.60 (1 H, d, *J* 7.5, 3-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.9 (2 × CH_3), 25.3 (2 × CH_2), 48.5 ($C(Et)_2$), 64.7 (CH_2OH), 122.8 (C_{ar}), 127.5 (CH_{ar}), 128.2 (CH_{ar}), 131.4 (CH_{ar}), 136.4 (CH_{ar}), 142.1 (C_{ar}).

3,4-Dihydro-1-hydroxy-4,4-diethyl-(2,1)-benzoxaborine (15). A solution of *sec*-BuLi (2.6 ml of 1.3 M solution in cyclohexane–hexane 98 : 2, 3.36 mmol) was slowly added, at r.t. under N_2, to a stirred solution of 2-ethyl-2-phenylbutan-1-ol (**10**, 200 mg, 1.12 mmol) in hexane (2 ml). The mixture was refluxed for 6 h and cooled to −78 °C before trimethyl borate (1.35 ml, 12.00 mmol) was added. The solution was allowed to warm to 25 °C and the mixture was continued for 16 h. Saturated NH_4Cl (15 ml) was added. The separated aqueous extract was then acidified with HCl (3 M) to pH = 1, extracted with AcOEt (3 × 10 ml) and the combined organic extract was washed with NaOH (2 N, 3 × 10 ml). The aqueous extract was acidified with HCl (3 M) to pH = 5 and extracted with AcOEt (3 × 15 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo to give **15** (46 mg, 20%) as a white solid without further purification; mp 145 °C (Found: C, 70.47; H, 8.52. Calc. for $C_{12}H_{17}BO_2$: C, 70.63; H, 8.40%); IR ν_{max}/cm^{-1} 3215 (OH), 1459, 805 (B–C); ^{1}H NMR δ_H (300 MHz, DMSO): 0.71 (6 H, t, *J* 7.5, 2 × CH_2CH_3), 1.55–1.66 (4 H, m, 2 × CH_2CH_3), 3.90 (2 H, s, CH_2OB), 7.22 (2 H, m, Ph), 7.43 (1 H, t, *J* 7.2, Ph), 7.69 (1 H, d, *J* 7.5, Ph), 8.42 (1 H, s, OH); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.6 (2 × CH_3), 29.0 (2 × CH_2), 43.0 ($C(Et)_2$), 71.5 (CH_2O), 125.1 (CH_{ar}), 125.8 (CH_{ar}), 131.2 (CH_{ar}), 133.6 (CH_{ar}), 151.3 (C_{ar}).

3-Bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridine (8). To a suspension of zinc chloride (371 mg, 2.73 mmol) in chlorobenzene (55 mL) was added, at r.t. under N_2, 5-bromonicotinonitrile (5 g, 27.3 mmol) and 2-amino-2-methylpropan-1-ol (**17**, 2.74 mL, 28.6 mmol). The resulting mixture was refluxed for 48 h and solvent was removed under vacuo. The residue was dissolved in CH_2Cl_2 (30 mL) and the resulting organic phase was washed with H_2O (30 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (EA) to give **8** (6.61 g, 95%) as white powder; mp 91 °C (Found: C, 47.14; H, 4.33; N, 10.83. Calc for $C_{10}H_{11}BrN_2O$: C, 47.08; H, 4.35; N, 10.98%); IR ν_{max}/cm^{-1} 3033, 2870, 1935, 1651; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 1.39 (6 H, s, 2 × CH_3), 4.15 (2 H, s, CH_2), 8.38 (1 H, dd, *J* 1.9 and 2.2, 4-H), 8.74 (1 H, d, *J* 2.2, 2-H), 9.02 (1 H, d, 1H, *J* 1.9, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 28.7 (2 × CH_3), 69.0 ($C(Me)_2$), 80.1 (CH_2), 120.5 (C_{ar}), 125.8 (C_{ar}), 138.1 (CH_{ar}), 147.5 (CH_{ar}), 152.0 (CH_{ar}), 159.1 (CN).

3-Bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-4-phenylpyridine (18). PhLi (0.39 ml of 2 M solution in Bu_2O, 0.78 mmol) was slowly added, at r.t. under N_2, to a solution of 3-bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridine **8** (200 mg, 0.78 mmol) in THF (6 ml). The solution was stirred at r.t. for 1 h. Saturated NH_4Cl (10 ml) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude residue was then dissolved in toluene (30 ml) and subsequently treated with chloranil (193 mg, 0.78 mmol). The mixture was refluxed for an additional 2 h and washed successively with aqueous NaOH (12%, 3 × 30 ml) and water (30 ml). The separated organic layer was dried ($MgSO_4$), filtered and concentrated under vacuo. The crude residue was purified by flash chromatography (P–EA 3 : 7) to give **18** (224 mg, 87%) as a yellow oil (Found: C, 58.29; H, 8.07; N, 4.62. Calc. for $C_{16}H_{15}BrN_2O$: C, 58.02; H, 8.46; N, 4.56%); IR ν_{max}/cm^{-1} 2964, 1651; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 1.03 (6 H, s, 2 × CH_3), 3.56 (2 H, s, CH_2), 7.13 (2 H, m, Ph), 7.27 (3 H, m, Ph), 8.64 (1 H, s, Py), 8.72 (1 H, s, Py); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 28.3 (2 × CH_3), 68.3 ($C(Me)_2$), 79.9 (CH_2), 122.6 (C_{Ar}), 127.1 (C_{Ar}), 128.6 (CH_{Ar}), 128.8 (CH_{Ar}), 129.0 (C_{Ar}), 137.2 (CH_{Ar}), 149.0 (CH_{Ar}), 149.7 (C_{Ar}), 153.9 (CH_{Ar}), 160.4 (CN).

2-(2-(3-Bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridin-2-yl)phenyl)-2-ethylbutan-1-ol (6a). A solution of *sec*-BuLi (7.75 ml of 1.3 M solution in cyclohexane–hexane 98 : 2, 10.11 mmol) was added dropwise, at r.t. under N_2, to a stirred solution of 2-ethyl-2-phenylbutan-1-ol (**10**, 600 mg, 3.37 mmol) in hexane (6 ml). The mixture was refluxed for 6 h, cooled to 25 °C and a solution of 3-bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridine (**8**, 430 mg, 1.69 mmol) in THF (6 ml) was added. The resulting mixture was stirred at 25 °C for 1 h before saturated NH_4Cl (10 ml) was added. The product was extracted with AcOEt (3 × 10 ml) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo.* The residue was dissolved in toluene (34 ml) and chloranil (416 mg, 1.69 mmol) was added. The mixture was refluxed for an additional 2 h. The cooled solution was washed with NaOH (12%, 3 × 30 ml) and water (30 ml) and the separated organic phase was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 9 : 1) to give **6a** (190 mg, 26%) as a brown solid; mp 46 °C (Found: C, 61.27; H, 6.61; N, 6.10. Calc. for $C_{22}H_{27}BrN_2O_2$: C, 61.26; H, 6.31; N, 6.49%); IR ν_{max}/cm^{-1} 3364

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(OH), 1651; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 0.64 (3 H, t, *J* 7.5, CH_2CH_3), 0.88 (3 H, t, *J* 7.2, CH_2CH_3), 1.25 (2 H, m, CH_2CH_3), 1.42 (6 H, s, 2 × CH_3), 1.74 (1 H, m, CH_2CH_3), 1.83 (1 H, m, CH_2CH_3), 3.16 (1 H, d, *J* 10.9, CH_2OH), 3.31 (1 H, s, OH), 3.46 (1 H, d, *J* 10.9, CH_2OH), 4.18 (2 H, s, CH_2), 6.99 (1 H, d, *J* 7.5, 6-H), 7.28 (1 H, t, *J* 7.5, 5-H), 7.43 (1 H, t, *J* 8.3, 4-H), 7.55 (1 H, d, *J* 8.3, 3-H), 8.57 (1 H, d, *J* 1.7, 4′-H), 8.99 (1 H, d, *J* 1.7, 6′-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.8 (2 × CH_3), 27.3 (CH_2), 27.6 (CH_2), 28.7 (2 × CH_3), 48.9 ($C(Et)_2$), 67.7 (CH_2OH), 68.4 ($C(Me)_2$), 79.8 (CH_2), 121.9 (C_{ar}), 124.8 (C_{ar}), 126.0 (CH_{ar}), 129.0 (CH_{ar}), 130.2 (CH_{ar}), 131.7 (CH_{ar}), 139.4 (C_{ar}), 140.7 (CH_{ar}), 141.9 (C_{ar}), 146.3 (CH_{ar}), 159.1 (CN), 164.6 (C_{ar}).

2-(2-(3-Bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridin-2-yl)phenyl)-2-ethylbutyl carbamate (7a). Trichloroacetyl isocyanate (101 μl, 0.85 mmol) was slowly added, at 0 °C under N_2, to a stirred solution of compound **6a** (280 mg, 0.65 mmol) in freshly dry CH_2Cl_2 (6 ml). The mixture was allowed to warm to room temperature and stirred for an additional 30 min. After removal of the solvent under vacuo, the crude product obtained was dissolved in methanol (6 ml) and the resulting solution was treated with potassium carbonate (196 mg, 1.42 mmol). The mixture was stirred for 3 h and water (10 ml) was then added. The mixture was extracted with ethyl acetate (3 × 15 ml) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuo. The crude material was purified by flash chromatography (DCM–Ac 9 : 1) to give **7a** (216 mg, 70%) as an orange solid; mp 70 °C (Found: C, 58.16; H, 6.02; N, 8.93. Calc. for $C_{23}H_{28}BrN_3O_3$: C, 58.23; H, 5.95; N, 8.86%); IR ν_{max}/cm^{-1} 3338 (NH_2), 1725; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 0.72 (6 H, m, 2 × CH_2CH_3), 1.42 (6 H, s, 2 × CH_3), 1.53 (4 H, m, 2 × CH_2CH_3), 4.03 (1 H, d, *J* 10.9, CH_2OCO), 4.15 (1 H, d, *J* 10.9, CH_2OCO), 4.17 (2 H, s, CH_2), 4.56 (2 H, s, NH_2), 7.01 (1 H, dd, *J* 7.5 and 1.5, 6-H), 7.28 (1 H, t, *J* 7.5, 5-H), 7.37–7.47 (2 H, m, 3-H, 4-H), 8.52 (1 H, d, *J* 1.9, 4′-H), 9.03 (1 H, d, *J* 1.9, 6′-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.9 (CH_3), 9.0 (CH_3), 28.0 (CH_2), 28.4 (CH_2), 28.7 (2 × CH_3), 47.2 ($C(Et)_2$), 68.1 (CH_2OCO), 68.4 ($C(Me)_2$), 79.8 (CH_2), 122.0 (C_{ar}), 124.5 (C_{ar}), 126.1 (CH_{ar}), 128.7 (CH_{ar}), 129.3 (CH_{ar}), 131.8 (CH_{ar}), 139.7 (C_{ar}), 140.2 (CH_{ar}), 141.7 (C_{ar}), 146.5 (CH_{ar}), 157.2 (CO), 159.3 (CN), 164.7 (C_{ar}).

7,7-Diethyl-6,7-dihydro-4,5-dihydro-3-(4,4-dimethyloxazol-2-yl)benzoxepino[1,2,*b*]pyridine (19). To a stirred solution of compound **7a** (70 mg, 0.15 mmol) in DMF (1 ml) were added small portions of NaH (13 mg of 60% in mineral oil, 0.32 mmol). The resulting mixture was allowed to warm to 100 °C for 16 h and saturated NH_4Cl (2 ml) was added. The product was extracted with AcOEt (3 × 5 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The crude material was purified by flash chromatography (DCM–Ac 9 : 1) to give **19** (46 mg, 90%) as a yellow oil. IR ν_{max}/cm^{-1} 2968, 1652; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): 0.76 (6 H, m, 2 × CH_2CH_3), 1.40 (6 H, s, 2 × CH_3), 1.67 (2 H, m, CH_2CH_3), 1.89 (2 H, m, CH_2CH_3), 4.13 (2 H, s, CH_2), 4.26 (2 H, s, CH_2OAr), 7.38 (3 H, m, Ph), 7.80 (1 H, d, *J* 1.9, 4-H), 8.59 (1 H, m, Ph), 8.91 (1 H, d, *J* 1.9, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 9.0 (2 × CH_3), 28.8 (2 × CH_3), 31.9 (2 × CH_2), 48.3 ($C(Et)_2$), 68.2 ($C(Me)_2$), 79.6 (CH_2OAr), 79.7 (CH_2), 123.7 (C_{ar}), 126.9 (CH_{ar}), 127.2 (CH_{ar}), 128.4 (CH_{ar}), 129.0 (CH_{ar}), 132.4 (CH_{ar}), 136.3 (C_{ar}), 143.2 (CH_{ar}), 145.1 (C_{ar}), 149.0 (C_{ar}), 155.1 (C_{ar}), 160.3 (CN); HRMS (IC$^+$, *tert*-butane) calcd. for $C_{22}H_{27}N_2O_2$ [(M + H)$^+$] 351.2072, found 351.2065.

3-Bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-2-(2-(3-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)pentan-3-yl)phenyl)pyridine (21).

*Method A (from compound **6a**).* *Tert*-butylchlorodimethylsilane (82 mg, 0.55 mmol) was added to a stirred solution of compound **6a** (214 mg, 0.50 mmol) and 1*H*-imidazole (54 mg, 0.80 mmol) in DMF (1 ml). The resulting mixture was stirred at 25 °C under N_2 for 2 h and water (10 ml) was added. The product was extracted with CH_2Cl_2 (3 × 15 ml) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 9.5 : 0.5) to give **21** (183 mg, 67%) as an orange oil. IR ν_{max}/cm^{-1} 2961, 1653, 1085; ^{1}H NMR δ_H (300 MHz, $CDCl_3$): −0.14 (3 H, s, MeSi), −0.12 (3 H, s, MeSi), 0.64–0.70 (6 H, m, 2 × CH_2CH_3), 0.80 (9 H, s, $(CH_3)_3Si$), 1.42 (6 H, s, 2 × CH_3), 1.45–1.71 (4 H, m, 2 × CH_2CH_3), 3.36 (1 H, d, *J* 9.2, CH_2OSi), 3.44 (1 H, d, *J* 9.2, CH_2OSi), 4.17 (2 H, s, CH_2), 6.99 (1 H, dd, *J* 7.5 and 1.3, 3′-H), 7.22 (1 H, td, *J* 8.3 and 1.3, 4′-H), 7.35–7.44 (2 H, m, 5′-H, 6′-H), 8.51 (1 H, d, *J* 1.9, 4-H), 9.03 (1 H, d, *J* 1.9, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): −5.4 (MeSi), −5.3 (MeSi), 9.2 (CH_3), 9.3 (CH_3), 18.5 (CMe_3), 26.1 (3 × CH_3), 28.7 (2 × CH_3), 29.1 (CH_2), 30.1 (CH_2), 49.4 ($C(Et)_2$), 64.1 (CH_2OSi), 68.4 ($C(Me)_2$), 79.8 (CH_2), 122.0 (C_{ar}), 124.4 (C_{ar}), 125.6 (CH_{ar}), 128.5 (CH_{ar}), 129.6 (CH_{ar}), 131.2 (CH_{ar}), 139.8 (C_{ar}), 139.9 (CH_{ar}), 142.4 (C_{ar}), 146.3 (CH_{ar}), 159.3 (CN), 165.1 (C_{ar}); HRMS (DIC$^+$, *tert*-butane) calcd. for $C_{28}H_{42}N_2O_2SiBr$ [(M + H)$^+$] 545.2199–547.2183, found 545.2206–547.2174.

*Method B (one-pot procedure from compound **10**).* A solution of *sec*-BuLi (1.25 ml of 1.3 M solution in cyclohexane–hexane 98 : 2, 1.68 mmol) was slowly added, at r.t. under N_2, to a stirred solution of 2-ethyl-2-phenylbutan-1-ol (**10**, 200 mg, 0.56 mmol) in hexane (1 ml). The mixture was refluxed for 6 h, cooled to 25 °C and a solution of 3-bromo-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridine (**8**, 72 mg, 0.28 mmol) in THF (1 ml) was added. The resulting mixture was stirred at r.t. for 1 h before a solution of *tert*-butylchlorodimethylsilane (253 mg, 1.68 mmol) in THF (1 ml) was added. The mixture was stirred for 16 h, water (2 ml) was added and the product was extracted with AcOEt (3 × 5 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in toluene (7 ml) and chloranil (69 mg, 0.28 mmol) was added. The mixture was refluxed for an additional 2 h and the cooled solution was washed with NaOH (12%, 3 × 5 ml) and water (5 ml). The separated organic phase was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 9.5 : 0.5) to afford **21** (30 mg, 21%) as an orange oil with the same characteristic analysis as above.

***N*-(4-Methoxybenzyl)-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-2-(2-(3-(((1,1-dimethylethyl)dimethylsilyloxy)methyl)pentan-3-yl)-phenyl)pyridin-3-amine (22).** To a stirred solution of compound **21** (300 mg, 0.55 mmol) in dry toluene pre-degassed by argon bubbling for 30 min (3 ml) were added 4-methoxybenzylamine (87 μl, 0.66 mmol), sodium *tert*-butoxide (73 mg, 0.76 mmol), BINAP (14 mg, 0.02 mmol) and Pd_2dba_3 (8 mg, 0.008 mmol). The resulting mixture was refluxed for 16 h under N_2. After filtration through a short pad of celite, the solvents were removed under vacuo and the residue was purified by flash chromatography

(DCM–Ac 9 : 1) to give **22** (274 mg, 83%) as a yellow oil. IR ν_{max}/cm^{-1} 3416 (NH), 1651, 1084; ^1H NMR δ_H (300 MHz, $CDCl_3$): −0.11 (6 H, s, 2 × MeSi), 0.57–0.67 (6 H, m, 2 × CH_2CH_3), 0.80 (9 H, s, $(CH_3)_3Si$), 1.40 (6 H, s, 2 × CH_3), 1.47–1.61 (2 H, m, CH_2CH_3), 1.69–1.74 (2 H, m, CH_2CH_3), 3.45 (2 H, s, CH_2OSi), 3.71 (1H, m, NH), 3.77 (3 H, s, OMe), 4.12 (2 H, s, CH_2), 4.16–4.32 (2 H, m, CH_2N), 6.82 (2 H, d, *J* 8.6, H-PhOMe), 7.03 (1 H, dd, *J* 7.3 and 1.3, 3′-H), 7.14 (2 H, d, *J* 8.6, 2 × H-PhOMe), 7.24 (1 H, t, *J* 7.1, 4′-H), 7.34 (1 H, td, *J* 7.1 and 1.7, 5′-H), 7.40–7.45 (2 H, m, 4-H, 6′-H), 8.51 (1 H, d, *J* 1.7, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): −5.3 (2 × MeSi), 9.1 (CH_3), 9.2 (CH_3), 18.5 (CMe_3), 26.1 (3 × CH_3), 28.7 (2 × CH_3), 29.1 (CH_2), 29.6 (CH_2), 47.5 (CH_2N), 49.4 ($C(Et)_2$), 55.5 (OCH_3), 63.6 (CH_2OSi), 68.0 ($C(Me)_2$), 79.4 (CH_2), 114.3 (CH_{ar}), 115.3 (CH_{ar}), 124.0 (C_{ar}), 126.6 (CH_{ar}), 128.6 (CH_{ar}), 129.0 (CH_{ar}), 130.2 (CH_{ar}), 130.4 (C_{ar}), 131.2 (CH_{ar}), 136.6 (CH_{ar}), 137.2 (C_{ar}), 142.0 (C_{ar}), 144.0 (C_{ar}), 152.0 (C_{ar}), 159.2 (C_{ar}), 161.2 (CN); HRMS (DIC$^+$, *tert*-butane) calcd. for $C_{36}H_{52}N_3O_3Si$ [(M + H)$^+$] 602.3778, found 602.3780.

2-(2-(3-Amino-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridin-2-yl)phenyl)-2-ethylbutyl 2,2,2-trifluoroacetate (23). A solution of compound **22** (150 mg, 0.25 mmol) in TFA (1.5 ml) was stirred for 16 h at 25 °C. TFA was removed under vacuo and the residue was dissolved in CH_2Cl_2 (5 ml). Saturated $NaHCO_3$ (5 ml) was added and the separated aqueous phase was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 9 : 1) to give **23** (93 mg, 80%) as a yellow solid; mp-(degradation). ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.72 (6 H, t, *J* 7.4, 2 × CH_2CH_3), 1.41 (6 H, s, 2 × CH_3), 1.58–1.78 (4 H, m, 2 × CH_2CH_3), 3.59 (2 H, s, NH_2), 4.15 (2 H, s, CH_2), 4.30 (1 H, d, *J* 11.0, CH_2OCO), 4.38 (1 H, d, *J* 11.0, CH_2OCO), 7.08 (1 H, dd, *J* 7.5 and 1.3, 6-H), 7.33 (1 H, td, *J* 7.5 and 1.7, 5-H), 7.39–7.46 (2 H, m, 3-H, 4-H), 7.60 (1 H, d, *J* 1.8, 4′-H), 8.55 (1 H, d, *J* 1.8, 6′-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.6 (CH_3), 8.7 (CH_3), 27.6 (CH_2), 28.1 (CH_2), 28.7 (2 × CH_3), 46.9 ($C(Et)_2$), 67.9 ($C(Me)_2$), 70.7 (CH_2OCO), 79.7 (CH_2), 118.0 (q, J_{C-F} 285, CF_3), 121.4 (CH_{ar}), 124.1 (C_{ar}), 127.5 (CH_{ar}), 129.0 (CH_{ar}), 129.8 (CH_{ar}), 131.7 (CH_{ar}), 137.2 (C_{ar}), 138.4 (CH_{ar}), 140.5 (C_{ar}), 141.5 (C_{ar}), 150.7 (C_{ar}), 159.0 (d, J_{C-F} 41, CO), 161.1 (CN); ^{19}F NMR δ_F (138 MHz, $CDCl_3$): −75.5 (CF_3); *m/z* (ESI, acetonitrile) 464.1 [(M + H)$^+$].

2-(2-(3-Amino-5-(4,5-dihydro-4,4-dimethyloxazol-2-yl)pyridin-2-yl)phenyl)-2-ethylbutan-1-ol (5a). To a solution of compound **23** (90 mg, 0.2 mmol) in H_2O–CH_3OH (1 : 2, 3.5 ml) was added K_2CO_3 (124 mg, 0.9 mmol). The mixture was stirred at 25 °C for 1 h and the solvents were removed under vacuo. The residue was purified by flash chromatography (DCM–Ac 8 : 2) to give **5a** (71 mg, 97%) as a pale yellow solid; mp 65 °C. IR ν_{max}/cm^{-1} 3316–3202, 1649; ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.63 (3 H, t, *J* 7.3, CH_2CH_3), 0.87 (3 H, t, *J* 7.3, CH_2CH_3), 1.28–1.38 (2 H, m, CH_2CH_3), 1.40 (6 H, s, 2 × CH_3), 1.65–1.85 (2 H, m, CH_2CH_3), 3.16 (1 H, d, *J* 12.2, CH_2OH), 3.40 (1 H, d, *J* 12.2, CH_2OH), 3.60 (2 H, s, NH_2), 4.14 (2 H, s, CH_2), 7.04 (1 H, dd, *J* 7.5 and 1.7, 6-H), 7.29 (1 H, td, *J* 7.5 and 1.1, 5-H), 7.41 (1 H, td, *J* 7.5 and 1.7, 4-H), 7.58 (1 H, dd, *J* 7.5 and 1.1, 3-H), 7.62 (1 H, d, *J* 1.8, 4′-H), 8.50 (1 H, d, *J* 1.8, 6′-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.7 (CH_3), 8.8 (CH_3), 27.5 (CH_2), 27.7 (CH_2), 28.7 (2 × CH_3), 48.8 ($C(Et)_2$), 67.7 (CH_2OH), 67.8 ($C(Me)_2$), 79.7 (CH_2), 121.6 (CH_{ar}), 124.3 (C_{ar}), 126.8 (CH_{ar}), 129.0 (CH_{ar}), 131.0 (CH_{ar}), 131.2 (CH_{ar}), 136.7 (C_{ar}), 138.2 (CH_{ar}), 140.4 (C_{ar}), 143.6 (C_{ar}), 151.4 (C_{ar}), 160.9 (CN); HRMS (DIC$^+$, *tert*-butane) calcd. for $C_{22}H_{30}N_3O_2$ [(M + H)$^+$] 367.2260, found 367.2256.

9,9-Diethyl-8,9-dihydro-3-(4,5-dihydro-4,4-dimethyloxazol-2-yl)-benzo[*f*]pyrido[3,2,*d*]oxazonin-6(5*H*)-one (*rac*-4a). Et_3N (162 µl, 1.16 mmol) was added to a stirred solution of compound **5a** (170 mg, 0.46 mmol) in THF (8.5 ml) at r.t. under N_2. The solution was allowed to cool to 0 °C and phosgene (251 µl of a 20% solution in toluene, 0.47 mmol) was added dropwise. The mixture was stirred at 25 °C for 1 h and saturated $NaHCO_3$ (8 ml) and EtOAc (10 ml) were added. The product was extracted with EtOAc (3 × 10 ml) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 8 : 2) to give *rac*-**4a** (152 mg, 84%) as a pale yellow solid; mp-(decomposition). IR ν_{max}/cm^{-1} 3311, 1743, 1651; ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.70 (3 H, t, *J* 7.2, CH_2CH_3), 0.92 (3 H, t, *J* 7.4, CH_2CH_3), 1.39 (6 H, s, 2 × CH_3), 1.40 (2 H, m, CH_2CH_3), 1.76 (1 H, m, CH_2CH_3), 1.90 (1 H, m, CH_2CH_3), 3.80 (1 H, d, *J* 10.7, CH_2OCO), 4.16 (2 H, s, CH_2), 4.21 (1 H, d, *J* 10.7, CH_2OCO), 6.60 (1 H, s, NH), 6.80 (1 H, dd, *J* 7.5 and 1.7, 3′-H), 7.24 (1 H, t, *J* 7.4, 4′-H), 7.40 (1 H, td, *J* 7.4 and 1.7, 5′-H), 7.50 (1 H, d, *J* 8.1, 6′-H), 7.97 (1 H, d, *J* 1.9, 4-H), 8.95 (1 H, d, *J* 1.9, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.3 (CH_3), 8.4 (CH_3), 24.7 (CH_2), 24.8 (CH_2), 28.7 (2 × CH_3), 48.5 ($C(Et)_2$), 68.3 ($C(Me)_2$), 73.6 (CH_2OCO), 79.8 (CH_2), 124.0 (C_{ar}), 127.0 (CH_{ar}), 128.4 (CH_{ar}), 129.7 (CH_{ar}), 131.3 (CH_{ar}), 132.4 (CH_{ar}), 133.7 (C_{ar}), 139.1 (C_{ar}), 141.7 (C_{ar}), 145.5 (CH_{ar}), 156.4 (C_{ar}), 160.1 (CN), 165.4 (CO); HRMS (IC$^+$, *tert*-butane) calcd. for $C_{23}H_{28}N_3O_3$ [(M + H)$^+$] 394.2131, found 394.2134.

9,9-Diethyl-8,9-dihydro-3-(ethoxycarboxy)benzo[*f*]pyrido[3,2,*d*]-oxazonin-6(5*H*)-one (*rac*-4b). A solution of compound *rac*-**4a** (26 mg, 0.07 mmol) in EtOH–conc. H_2SO_4 (9 : 1, 2 ml) was refluxed for 5 h. After cooling at 25 °C, saturated $NaHCO_3$ was added to pH = 8–9 and the product was extracted with CH_2Cl_2 (3 × 5 ml). The combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo. The residue was purified by flash chromatography (DCM–Ac 9.5 : 0.5) to give *rac*-**4b** (5 mg, 20%) as a pale yellow oil. IR ν_{max}/cm^{-1} 3274, 1727; ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.71 (3 H, t, *J* 7.3, CH_2CH_3), 0.94 (3 H, t, *J* 7.3, CH_2CH_3), 1.44 (5 H, m, CH_2CH_3, $COOCH_2CH_3$), 1.75 (1 H, m, CH_2CH_3), 1.90 (1 H, m, CH_2CH_3), 3.82 (1 H, d, *J* 10.9, CH_2OCO), 4.25 (1 H, d, *J* 10.9, CH_2OCO), 4.45 (2 H, q, *J* 7.1, $COOCH_2CH_3$), 6.08 (1 H, s, NH), 6.80 (1 H, dd, *J* 7.5 and 1.5, 3′-H), 7.26 (1 H, m, 4′-H), 7.43 (1 H, td, *J* 7.0 and 1.5, 5′-H), 7.54 (1 H, d, *J* 7.7, 6′-H), 8.05 (1 H, d, *J* 1.9, 4-H), 9.07 (1 H, d, *J* 1.9, 6-H); ^{13}C NMR δ_C (75 MHz, $CDCl_3$): 8.4 (CH_3), 8.5 (CH_3), 14.7 (CH_{3Et}), 24.9 (2 × CH_2), 48.6 ($C(Et)_2$), 62.1 (CH_{2Et}), 73.8 (CH_2OCO), 126.0 (C_{ar}), 127.1 (CH_{ar}), 128.5 (CH_{ar}), 129.8 (CH_{ar}), 131.1 (CH_{ar}), 133.7 (CH_{ar}), 133.8 (C_{ar}), 139.0 (C_{ar}), 141.6 (C_{ar}), 147.2 (CH_{ar}), 156.1 (C_{ar}), 165.2 (CO), 167.2 (CO); HRMS (IC$^+$, *tert*-butane) calcd. for $C_{21}H_{25}N_2O_4$ [(M + H)$^+$] 369.1814, found 369.1794.

3-Carboxy-9,9-diethyl-8,9-dihydrobenzo[*f*]pyrido[3,2,*d*]oxazonin-6(5*H*)-one (*rac*-4c). A stirred solution of compound *rac*-**4a** (15 mg, 0.04 mmol) in H_2SO_4 (1.8 N, 2 ml) was refluxed for 5 h. The mixture was allowed to cool to r.t. and saturated $NaHCO_3$

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was added to pH = 8–9. The aqueous phase was washed with (1 × 5 ml) and HCl (4 N) was added to pH 4. The separated aqueous phase was extracted with CH_2Cl_2 (3 × 5 ml) and the combined organic extract was dried ($MgSO_4$), filtered and concentrated under vacuo to give *rac*-**4c** (2 mg, 15%) as a pale yellow solid; mp-(decomposition). IR ν_{max}/cm^{-1} 3500–3000, 1722, 1599; ^1H NMR δ_H (300 MHz, $CDCl_3$): 0.72 (3 H, t, *J* 7.3, CH_2CH_3), 0.95 (3 H, t, *J* 7.3, CH_2CH_3), 1.45 (2 H, m, CH_2CH_3), 1.77 (1H, m, CH_2CH_3), 1.93 (1 H, m, CH_2CH_3), 3.84 (1 H, d, *J* 10.9, CH_2OCO), 4.27 (1 H, d, *J* 10.8, CH_2OCO), 6.80 (2 H, m, NH, 3′H), 7.26 (1 H, m, Ph), 7.44 (1 H, t, *J* 7.3, Ph), 7.54 (1 H, d, *J* 8.0, 6′-H), 8.08 (1 H, s, 4-H), 9.09 (1 H, s, 6-H); ^{13}C NMR δ_C (75 MHz, CD_3CD_2OD): 8.3 (CH_3), 8.5 (CH_3), 24.9 (CH_2), 25.2 (CH_2), 49.2 ($C(Et)_2$), 73.6 (CH_2OCO), 127.2 (CH_{ar}), 128.8 (CH_{ar}), 130.1 (CH_{ar}), 132.2 (CH_{ar}), 134.3 (CH_{ar}), 135.8 (C_{ar}), 140.1 (C_{ar}), 142.7 (2 × C_{ar}), 146.4 (CH_{ar}), 157.2 (C_{ar}), 165.9 (CN), 169.4 (CO); HRMS (IC^-, *tert*-butane) calcd. for $C_{19}H_{19}N_2O_4$ [$(M–H)^+$] 339.1345, found 339.1355.

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