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Synthesis and Pharmacological Characterization of Disila-AM80 (Disila-tamibarotene) and Disila-AM580, Silicon Analogues of the RARα-Selective Retinoid Agonists AM80 (Tamibarotene) and AM580

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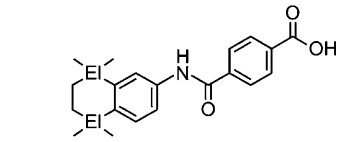
Dedicated to Professor Wolfdieter A. Schenk on the occasion of his 65th birthday

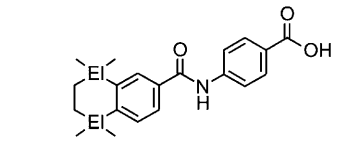
Introduction

Retinoic acid receptors, which act as heterodimers between either one of three RARs (RARα, β, γ) and RXRs (RXRα, β, γ), are exciting pharmacological targets for cancer and metabolic disease therapies.[1] Studies of the action of retinoic acid on acute promyelocytic leukemia have converted one of the worst leukemias to one that has a most favorable prognosis and might possibly be fully curable following recent advances in the field.[2] In addition, rexinoids are clinically used for the treatment of refractory T-cell leukemia, and novel treatment paradigms based on single-agent or combinatorial treatment are continuously being developed to exploit the enormous cytodifferentiation and apoptogenic potential of retinoids and rexinoids.[3] The medicinal-chemistry approaches taken in this context are attempts to increase ligand potency, functionality (agonist, mixed agonist/antagonist, neutral antagonist, or inverse agonist), and receptor selectivity.

In search of highly potent and receptor-selective retinoids, a series of silicon-containing RAR- and RXR-selective retinoid agonists has been synthesized and pharmacologically characterized in recent years.[4] As part of this research project, we have been interested in the biological properties of the silicon analogues of the RARα-selective retinoid agonists AM80 (tamibarotene, **1a**)[5] and AM580 (Ro-40-6055, **2a**),[5b–e,h,j,6] disila-AM80 (disila-tamibarotene, **1b**) and disila-AM580 (**2b**), respectively. In a series of earlier studies, the carbon/silicon switch (sila-substitution) strategy has been demonstrated to be a powerful tool for optimizing the pharmacodynamic and/or pharmacokinetic properties of drugs (for recent reviews on silicon-based drugs, see ref. [7]). In this context, disila-substitution of **1a** (→**1b**) and **2a** (→**2b**) was also very promising. Here we report on the synthesis of the silicon compounds **1b** and **2b** and the pharmacological characterization of the C/Si pairs **1a**/**1b** and **2a**/**2b**. These studies were performed as part of our systematic investigations on silicon-based drugs (for recent publications, see ref. [8]).



El = C: AM80 (Tamibarotene, **1a**)
El = Si: Disila-AM80 (Disila-tamibarotene, **1b**)



El = C: AM580 (**2a**)
El = Si: Disila-AM580 (**2b**)

Retinoids and rexinoids, as all other ligands of the nuclear receptor (NR) family,[9] act as ligand-regulated *trans*-acting transcription factors that bind to *cis*-acting DNA regulatory elements in the promoter regions of target genes. Conceptually, ligand binding does nothing more than modulate the communication functions of the receptor with the intracellular environment, which entails essentially receptor–protein and receptor–DNA or receptor–chromatin interactions. In this communication network, the receptor serves at the same time as intracellular sensor and regulator of cell/organ functions. Receptors are mediators of the information encoded in the chemical structure of a nuclear receptor ligand, as they interpret this information in the context of cellular identity and cell physiological status and convert it into a dynamic chain of receptor–protein and receptor–DNA interactions.[10] This interpretation is achieved by the allosteric effects that are exerted by a given (natural or synthetic) ligand on the cognate receptor, which result in two distinct events. The first event is the destabilization of the binding interface between the receptor and the corepressor complex (a complex that comprises among others epigenetically acting transcription-silencing histone deacetylases (HDACs)), which pre-exists on some promoters in the absence of ligands. Interestingly, some inverse agonists stabilize corepressor binding and thus act as superantagonists.[11,12] The second event is induced by the binding of an agonist to the

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receptor. In this case, the corepressor interface is destabilized, and a novel (but overlapping) surface is generated; this allows the recruitment of coactivator complexes. These complexes harbor histone acetylases (HATs), which have the opposite enzymatic activity of HDACs and allow for activated transcription.

A major breakthrough of the past few years is that we now recognize the enormous variety of communication processes that can be collectively or separately addressed by simply modifying the ligand structure, and we have begun to understand and pharmaceutically exploit the corresponding mechanisms. The basis of nuclear receptor communication is their ability to provide surfaces for interaction in an allosterically controlled ligand-dependent manner. Here we report on the observation that even subtle steric and/or electronic effects resulting from a twofold carbon/silicon exchange in the synthetic RAR subtype-selective agonists **1a** and **2a** can result in a difference in transactivation potential of up to one magnitude for the corresponding disila-analogues **1b** and **2b**, respectively, for two of the three RAR subtypes.

Results and Discussion

Syntheses

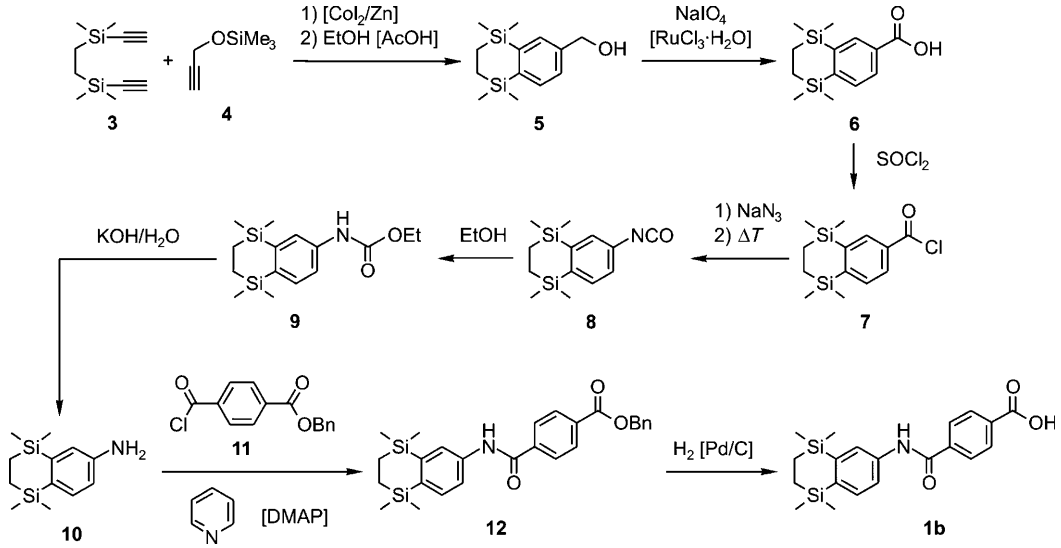
Disila-AM80 (disila-tamibarotene, **1b**) was synthesized in a multistep synthesis according to Scheme 1, starting from 1,2-bis-(ethynyldimethylsilyl)ethane (**3**). Diyne **3** was treated with 3-(trimethylsiloxy)propyne (**4**) in the presence of cobalt(II) iodide/zinc in acetonitrile, followed by treatment with ethanol/acetic acid to provide (5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (**5**; 41% yield). Oxidation of alcohol **5** with sodium periodate in the presence of ruthenium(III) chloride afforded 5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (**6**; 61% yield). Compound **6** was then treated with thionyl chloride to give 5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene-2-carbonyl chloride (**7**; 76% yield), which upon treatment with sodium azide and subsequent heating of the resulting azide provided 2-isocyanato-5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene (**8**; 74% yield). Treatment of **8** with ethanol afforded ethyl (5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (**9**; 97% yield), which upon treatment with potassium hydroxide in ethanol/water and subsequent acidification with hydrochloric acid afforded 5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-amine (**10**; 91% yield). Subsequent treatment of **10** with benzyl 4-(chlorocarbonyl)benzoate (**11**) in the presence of pyridine and 4-(dimethylamino)pyridine (DMAP) gave benzyl 4-{[(5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)amino]carbonyl}benzoate (**12**; 74% yield).[13] Compound **12** was then treated with hydrogen in the presence of palladium/carbon to finally provide **1b** (93% yield).

Disila-AM580 (**2b**) was synthesized from **7** according to Scheme 2. Treatment of **7** with methyl 4-aminobenzoate (**13**) in the presence of pyridine and DMAP gave methyl 4-{[(5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]amino}benzoate (**14**; 94% yield), which upon treatment with potassium hydroxide in methanol/water and subsequent acidification with hydrochloric acid afforded **2b** (74% yield).

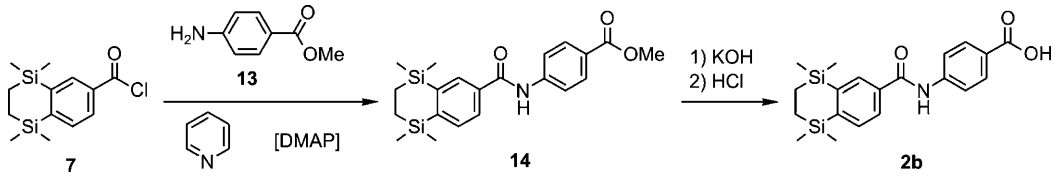
Compounds **1b**, **2b**, **5**, **6**, **9**, **10**, **12**, and **14** were isolated as colorless crystalline solids, whereas compounds **7** and **8** were obtained as colorless liquids. The identities of all these compounds were established by elemental analyses (C, H, N) and NMR studies (^{1}H, ^{13}C, ^{29}Si).

Pharmacological studies

To compare the in vivo transcription activation capacities of AM80 (**1a**) and disila-AM80 (**1b**), we used a cellular reporter system that has been described previously.[14] Briefly, two chi-



Scheme 1. Preparation of compound **1b**.



Scheme 2. Preparation of compound **2b**.

meric constructs, comprising 1) a chimeric receptor composed of the RAR ligand binding domain (GAL4-RARα, β, γ) and 2) a luciferase-based reporter gene driven by the GAL4 response element (17-mer-G-Luc) in front of the minimal β-globin promoter, have been stably introduced into HeLa cells. Exposing the three reporter cells to the C/Si analogues **1a** and **1b** yielded the dose–response curves shown in Figure 1. In the case of RARα, both compounds exhibited virtually identical profiles, with EC_{50} values of around 5 nM (Figure 1A). However, in the case of RARβ and even more pronounced for RARγ, there was a significant left-shift of the dose–response curves for **1b**, revealing that the binding of the silicon compound conferred a higher transactivation potential onto these receptors than the corresponding carbon analogue **1a** (Figure 1B and C). It is worth mentioning that the twofold sila-substitution in **1a** (→**1b**) resulted for RARγ in a tenfold increase of transcription induction from the cognate reporter.

AM580 (**2a**) is a derivative of AM80 (**1a**) that displays enhanced RARα selectivity and induces a transcriptional response superior to that seen with the potent pan-agonist TTNPB (Figure 2). As for AM80 (**1a**) and disila-AM80 (**1b**), there was no difference in the dose–response profile of RARα for AM580 (**2a**) and disila-AM580 (**2b**) (cf Figures 1A and 2A). Similar to the C/Si analogues **1a** and **1b**, the silicon compound **2b** activated transcription through RARβ and RARγ at lower concentration than the corresponding carbon analogue **2a** (Figure 2B and C).

Taken together, disila-substitution of the RARα-selective synthetic retinoids AM80 (**1a**) and AM580 (**2a**) did not alter the induction of RARα-mediated transactivation in the presence of these ligands, which have been optimized for RARα binding and/or transactivation.[15] However, the carbon/silicon switch strongly affected RARβ- and RARγ-mediated transcription activation in the sense that the disila-analogues **1b** and **2b** displayed an up to tenfold higher activity at these receptors. This could be due to 1) an increased binding affinity of the silicon compounds **1b** and **2b** to these two receptors or 2) a differential allosteric effect of the carbon/silicon pairs **1a**/**1b** and **2a**/**2b** on RARβ and RARγ. According to this hypothesis, the carbon-based ligands **1a** and **2a** would suboptimally induce the formation of the coactivator binding surface or, alternatively, insufficiently destabilize the corepressor binding interface. Both these scenarios would result in a suboptimal transactivation potential of AM80 (**1a**) and AM580 (**2a**), while the affinity to the receptor might be identical to those of the disila-analogues **1b** and **2b**. Indeed, it is possible that the RARα selectivity of the carbon compounds **1a** and **2a** originates from a difference in their compromised abilities to generate optimal co-

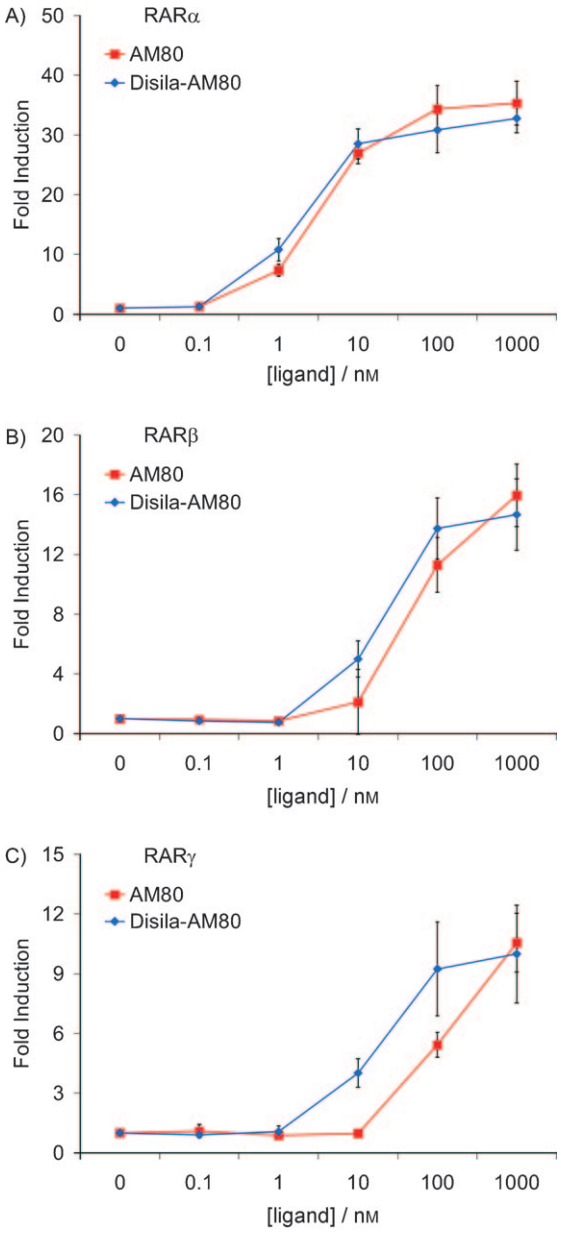


Figure 1. Dose–response curves of AM80 (**1a**) and disila-AM80 (**1b**) in RAR reporter cells. To compare the transactivation potential of **1a** and **1b**, reporter cells harboring a GAL4-RARα, GAL4-RARβ, or GAL4-RARγ chimera and a luciferase-based cognate reporter gene were exposed to increasing concentrations of compounds **1a** and **1b**, and their agonist activity at inducing transactivation was revealed by quantification of the induced luciferase activity. Note that, while RARα reporter cells show a virtually identical dose response, there is an up to tenfold left shift of the RARβ and RARγ activation profile for disila-AM80 (**1b**); this indicates a superior activity of the silicon compound for these receptors.

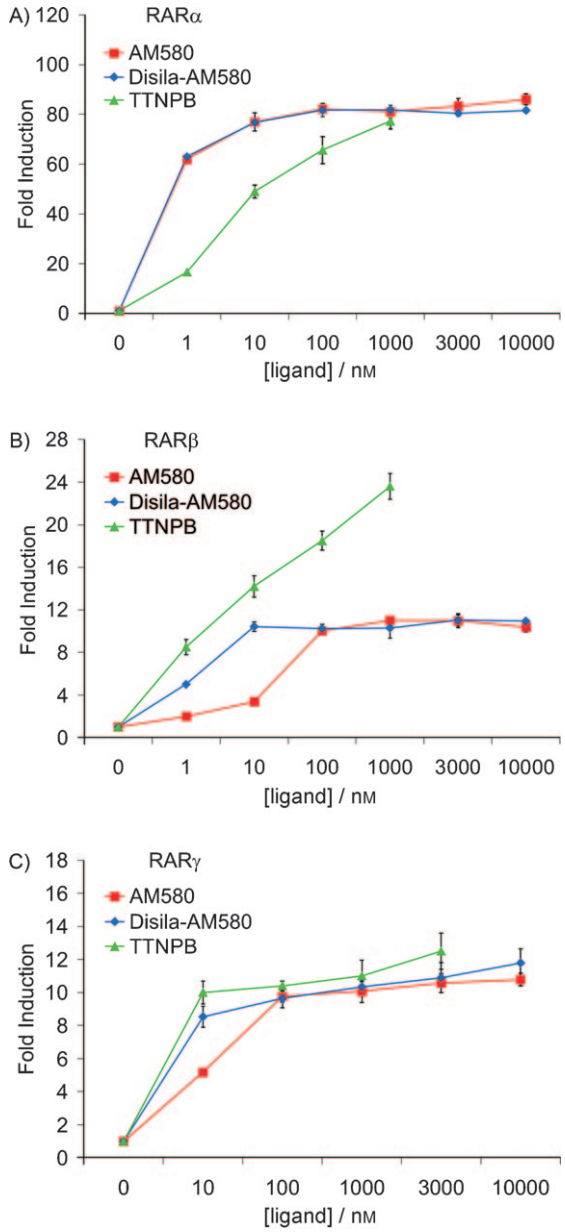


Figure 2. Dose–response curves of AM580 (**2a**) and disila-AM580 (**2b**) in RAR reporter cells. The dose–response curves were established analogously to those of **1a** and **1b** (see Figure 1). The activation profile of the potent synthetic pan-retinoid TTNPB is depicted for comparison.

activator binding surfaces for RARβ and RARγ rather than from distinct binding affinities to the three RARs. In such an allosteric model, facilitated release of the corepressor complex would equally well explain the increased activity of the disila-analogues **1b** and **2b**. In the case of the silicon compounds **1b** and **2b**, the subtle steric and/or electronic sila-substitution effects might possibly "correct" for the suboptimal allosteric effects and lead to a reconstitution of an optimal binding surface. These results present a proof-of-principle for the notion that the carbon/silicon switch strategy is an additional option in the chemistry toolbox for the fine-tuning of nuclear receptor ligands in order to obtain optimized functionality.

Experimental Section

Chemistry

General procedures: All syntheses were carried out under dry nitrogen. The organic solvents used were dried and purified according to standard procedures and stored under dry nitrogen. A Büchi GKR-50 apparatus was used for the bulb-to-bulb distillations. Melting points were determined with a Büchi Melting Point B-540 apparatus by using samples in open glass capillaries.

4-{[(5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)amino]carbonyl}benzoic acid (disila-AM80, disila-tamibarotene, 1b): Hydrogen gas was passed through a mixture of tetrahydrofuran (THF; 40 mL), palladium (50 mg; 10 wt.% (dry basis) on activated carbon, wet; Degussa, type E101 NE/W), and **12** (200 mg, 422 μmol) at 20 °C over a period of 3 h. The precipitate was filtered off and discarded, the solvent of the filtrate was removed under reduced pressure, and the residue was crystallized from warm acetonitrile (4 mL; slow cooling of the solution from 60 to 20 °C) to give **1b** in 93% yield as a colorless crystalline solid (151 mg, 394 μmol); m.p. 265 °C.

4-{[(5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]amino}benzoic acid (disila-AM580, 2b): A mixture of methanol/water (3:1, *v/v*, 40 mL), potassium hydroxide (5.12 g, 91.3 mmol), and **14** (3.50 g, 8.80 mmol) was heated under reflux for 2 h. Most of the solvent was removed under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added, and the aqueous layer was adjusted to pH 1 by addition of hydrochloric acid (37 wt.%). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (2×50 mL), the combined organic extracts were dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was crystallized from boiling acetonitrile (25 mL; slow cooling of the solution to 20 °C) to give **2b** in 74% yield as a colorless crystalline solid (2.50 g, 6.52 mmol); m.p. 230 °C.

1,2-Bis(ethynyldimethylsilyl)ethane (3): This compound was synthesized according to ref. [4c].

3-(Trimethylsiloxy)propyne (4): This compound is commercially available.

(5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)methanol (5): Iodine (87.1 mg, 686 μmol) was added to a stirred suspension of zinc (202 mg, 3.09 mmol) in acetonitrile (150 mL), and the mixture was heated for 1 min until the yellow color disappeared. Subsequently, compounds **3** (6.00 g, 30.9 mmol) and **4** (5.54 g, 43.2 mmol), and a solution of cobalt(II) iodide in acetonitrile (0.1 M, 7.72 mL, 772 μmol of CoI_2) were added sequentially, and when the temperature of the reaction mixture rose above 40 °C (after ca. 5 min), it was cooled immediately in a water bath and stirred for 30 min. The precipitate was filtered off and discarded, and the solvent of the filtrate was removed under reduced pressure. The residue was dissolved in ethanol (100 mL)/acetic acid (1 mL), and the resulting solution was heated under reflux for 1 h. After the mixture had been cooled to 20 °C, a half-saturated aqueous solution of sodium chloride (100 mL) and ethyl acetate (100 mL) were added, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3×75 mL). The organic extracts were combined, washed with a saturated aqueous solution of sodium hydrogen sulfate (50 mL), and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 60×2.5 cm; silica gel (35–70 μm); eluent, *n*-hexane/ethyl acetate (9:1, *v/v*)). The relevant fractions (GC

analysis) were combined, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (120–140 °C/0.2 mbar) to afford **5** in 41% yield as a colorless crystalline solid (3.17 g, 12.7 mmol); m.p. 38–39 °C.

5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid (6): Ruthenium(III) chloride (56.3 mg, 270 μmol) was added at 20 °C in a single portion to a mixture of **5** (2.50 g, 9.98 mmol), sodium periodate (8.50 g, 39.7 mmol), acetonitrile (20 mL), ethyl acetate (20 mL), and water (30 mL). The reaction mixture was then cooled in a water bath (20 °C) and stirred for 2 h. The precipitate was filtered off and washed with ethyl acetate (3× 10 mL), the filtrate and the wash solutions were combined, the organic layer was separated, the aqueous layer was extracted with ethyl acetate (3×10 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the solid residue was recrystallized from boiling *n*-hexane (9 mL; slow cooling of the solution to 20 °C) to afford **6** in 61% yield as a colorless crystalline solid (1.62 g, 6.13 mmol); m.p. 142 °C.

5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene-2-carbonyl chloride (7): Thionyl chloride (27.0 g, 227 mmol) was added at 20 °C in a single portion to a stirred solution of **6** (4.00 g, 15.1 mmol) in dichloromethane (20 mL), and the mixture was then heated under reflux for 4 h. The solvent and the excess thionyl chloride were removed under reduced pressure, and the residue was fractionally distilled in vacuo (97–98 °C, 0.6 mbar) to give **7** in 76% yield as a colorless liquid (3.24 g, 11.5 mmol).

2-Isocyanato-5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalene (8): Sodium azide (506 mg, 7.78 mmol) was added at 0 °C in a single portion to a stirred solution of **7** (2.00 g, 7.07 mmol) in acetone (20 mL), and the reaction mixture was stirred at 0 °C for 1 h and then at 20 °C for a further 16 h. The resulting solid was filtered off and discarded, the solvent of the filtrate was removed under reduced pressure, the solid residue was dissolved in toluene (30 mL), and the resulting solution was heated under reflux for 3.5 h. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (120–140 °C/0.2 mbar) to give **8** in 74% yield as a colorless liquid (1.36 g, 5.20 mmol).

Ethyl (5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)carbamate (9): A solution of **8** (1.00 g, 3.82 mmol) in toluene (5 mL) was added dropwise over a period of 15 min to a boiling solution of ethanol (3 mL) in toluene (25 mL), and the reaction mixture was stirred under reflux for a further 4 h. The solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (135–145 °C, 0.2 mbar) to give **9** in 97% yield as a colorless crystalline solid (1.14 g, 3.71 mmol); m.p. 106 °C.

5,5,8,8-Tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-amine (10): A mixture of **9** (5.00 g, 16.3 mmol), potassium hydroxide (9.12 g, 163 mmol), and ethanol/water (3:1, *v*/*v*, 35 mL) was heated under reflux for 2 h. The solvent was removed under reduced pressure, ethyl acetate (100 mL) and water (50 mL) were added to the oily residue, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by bulb-to-bulb distillation (108 °C, 0.06 mbar) to give **10** in 91% yield (3.52 g, 14.9 mmol) as a colorless crystalline solid; m.p. 134 °C.

Benzyl 4-(chlorocarbonyl)benzoate (11): This compound was synthesized according to ref. [16].

Benzyl 4-{[(5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)amino]carbonyl}benzoate (12): A solution of **11** (880 mg, 3.20 mmol) in THF (10 mL) was added dropwise at 20 °C over a period of 5 min to a stirred solution of **10** (754 mg, 3.20 mmol), pyridine (278 mg, 3.51 mmol), and 4-(dimethylamino)-pyridine (20.0 mg, 164 μmol) in THF (20 mL), and the mixture was stirred at 20 °C for 12 h. Diethyl ether (40 mL) and water (10 mL) were added to the reaction mixture, the organic phase was separated and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The solid residue was recrystallized from ethyl acetate (20 mL; slow cooling of the solution to −20 °C) to give **12** in 74% yield as a colorless crystalline solid (1.12 g, 2.36 mmol); m.p. 173 °C.

Methyl 4-aminobenzoate (13): This compound is commercially available.

Methyl 4-{[(5,5,8,8-tetramethyl-5,8-disila-5,6,7,8-tetrahydronaphthalen-2-yl)carbonyl]amino}benzoate (14): Compound **7** (1.00 g, 3.53 mmol) was added at 20 °C in a single portion to a stirred solution of **13** (973 mg, 6.44 mmol) and 4-(dimethylamino)pyridine (21.6 mg, 177 μmol) in pyridine (20 mL), and the mixture was then stirred at 60 °C for 5 h. The solvent was removed under reduced pressure, and a half-saturated aqueous sodium chloride solution (30 mL) and ethyl acetate (50 mL) were added to the residue. The organic layer was separated, the aqueous layer was extracted with ethyl acetate (3×50 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (column dimensions, 40× 4 cm; silica gel (35–70 μm); eluent, *n*-hexane/ethyl acetate/triethylamine (7:3:1, *v*/*v*/*v*)). The relevant fractions (GC analysis) were combined, the solvent was removed under reduced pressure, and the solid residue was recrystallized from boiling methanol (45 mL; slow cooling of the solution to 20 °C). The solid was isolated by decantation of the solvent, washed with *n*-pentane (2×4 mL), and dried in vacuo (0.001 mbar, 20 °C, 4 h) to give **14** in 94% yield as a colorless crystalline solid (1.32 g, 3.32 mmol); m.p. 200 °C.

Pharmacological studies: All assays involving reporter cell lines were performed according to ref. [14].

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