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Inhibition of IκB kinase-β and IκB kinase-α by heterocyclic adamantyl arotinoids

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ABSTRACT

We recently reported on a series of retinoid-related molecules containing an adamantyl group, a.k.a. adamantyl arotinoids (AdArs), that showed significant cancer cell growth inhibitory activity and activated RXRα (NR2B1) in transient transfection assays while devoid of RAR transactivation capacity. We have now explored whether these AdArs could also bind and inhibit IKKβ, a known target that mediates the induction of apoptosis and cancer cell growth inhibition by related AdArs containing a chalcone functional group. In addition, we have prepared and evaluated novel AdArs that incorporate a central heterocyclic ring connecting the adamantyl-phenol and the carboxylic acid at the polar termini. Our results indicate that the majority of the RXRα activating compounds lacked IKKβ inhibitory activity. In contrast, the novel heterocyclic AdArs containing a thiazole or pyrazine ring linked to a benzoic acid motif were potent inhibitors of both IKKα and IKKβ, which in most cases paralleled significant growth inhibitory and apoptosis inducing activities.

1. Introduction

The adamantyl arotinoids (AdArs)[1,2] are included within the group of atypical retinoids or retinoid-related molecules (RRMs),[3–5] a name that reflects the fact that they exert their anticancer activities independently of the transactivation of the retinoid receptors (RARs, subtypes α, β, and γ; and RXRs, subtypes α, β, and γ).[6,7] RARs and RXRs are members of the nuclear hormone receptor superfamily of ligand-responsive transcription factors,[8] which mediate the multifarious actions of natural and synthetic retinoids in embryo and throughout life. Some AdArs, however, are known to bind to RARs, such as **1a** (6-[(3-adamant-1-yl)-4-hydroxy-phenyl]-2-naphthoic acid, CD437, also called AHPN), which is a RARγ agonist.[5] Other analogs of **1a**, such as **2a** (AHPC, Adarotene, which also binds RARγ and is a stronger apoptogenic agent than **1a**), 5-Cl-AHPN **1b** and 3-Cl-AHPC **2b** (see Fig. 1), lack RAR transactivation activity while preserving the induction of growth arrest and apoptotic activity in a variety of cancer cell lines.[9–11] Moreover, 3-Cl-AHPC **2b** binds the nuclear hormone receptor small heterodimer partner (SHP) and modulates SHP interaction with the Sin3A repressor.[12,13] While still unclear, the mechanism of RRM-mediated cell death, in particular the apoptosis induced by **1a**, appears to be largely dependent on cell type. Evidences for caspase-dependent and independent mechanisms[14–16] via the intrinsic[17,18] and extrinsic pathways[19] have been provided for these compounds.

In addition to SHP, RRMs with pro-apoptotic activity can target the IKK/NFκB signaling pathway via direct inhibition of IKKβ, which has been validated as a cancer target in vitro and in preclinical studies with very promising results, although clinical studies have not yet produced positive outcomes.[20,21] Thus, great efforts have been dedicated to develop IKK/NFκB inhibitors as potential therapies for the treatment of cancer and inflammatory diseases.[22–24] We initially found that MX781 **3** substantially inhibited IKK isolated from TNFα-stimulated HeLa cells, and displayed effective and consistent inhibition of IKK/NFκB activity in various cancer cell lines, thus confirming IKK as an AdAr target.[25] Furthermore, a number of chalcone containing analogs with an additional substituent *ortho* to the carbonyl group were prepared and found to elicit enhanced inhibition of recombinant IKKβ in vitro, which paralleled increased growth inhibitory and apoptosis inducing activities in cancer cells.[26] Most recently, substitution of the chalcone functionality by a heterocyclic group has demonstrated that AdArs can inhibit IKK and induce apoptosis independently of a potential Michael addition from a Cys residue to the α,β-unsaturated ketone.[27] Contrasting with the inhibition of IKK/NFκB signaling by MX781 **3** and its apoptogenic analogs observed by us, activation of NFκB by CD437 **1a** is necessary for the induction of apoptosis in prostate

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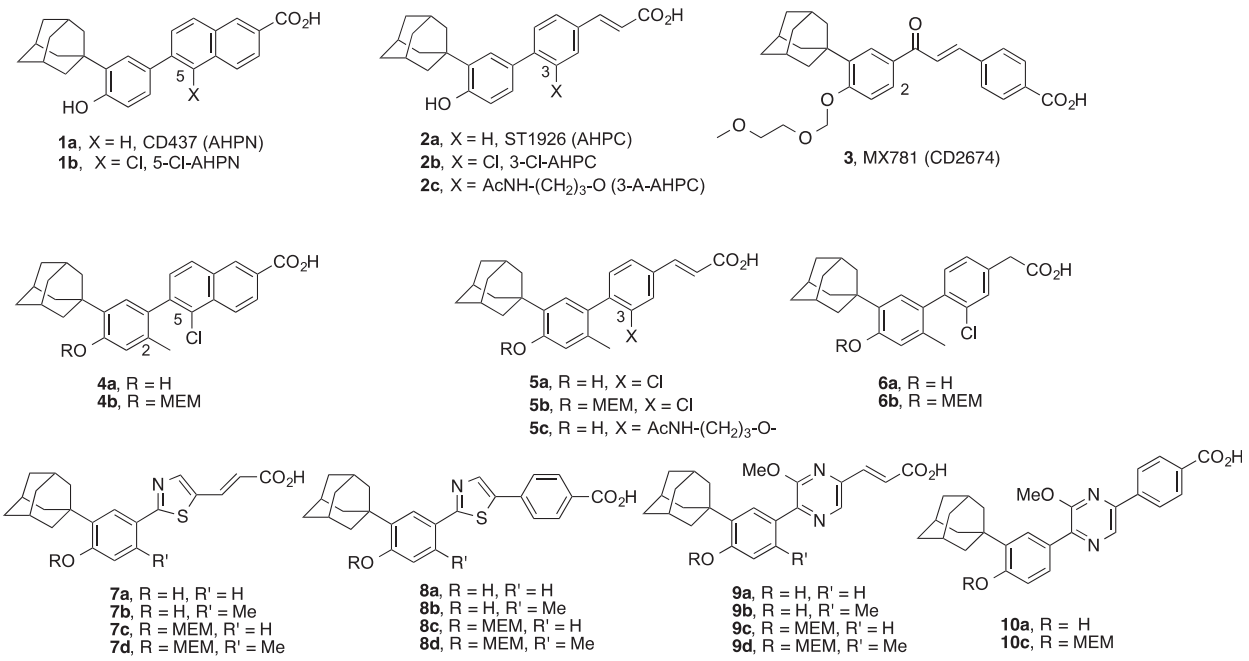


Figure 1. RRMs with adamantyl groups.

carcinoma cells.[28,29] Cinnamic acid derivative **2b** also activates IKKα and IKKβ in breast carcinoma and leukemia cancer cells.[28,30,31] The exact mechanism of IKK/NFκB activation by these AdArs is still undefined.[13,30,31]

In a previous study, we prepared a series of analogs of **2** that incorporate an additional Me substituent at the adamantyl-phenol end *ortho* to the biphenyl connection and naphthoic, cinnamic and phenylacetic acids as polar end groups (compounds **4**–**6**).[32] The compounds derived from cinnamic and naphthoic acid exhibited potent antiproliferative activities in several cancer cell lines, and this effect correlated in general with the induction of apoptosis as measured by caspase activation. However, the strong deviation of planarity of these AdArs due to the presence of the 2,2′-disubstituted biphenyl connection altered their binding profile from RAR to RXR. We were able to show that some of those analogs induced RXR activity as efficiently as 9-*cis*-retinoic acid in transient transfection assays, suggesting that RXR might be responsible for their observed tumor cell growth inhibitory effects.[32]

We now report on the activities of these analogues in the inhibition of IKKα, IKKβ and IKKε in vitro and found that none of the RXR ligands with the exception of the partial agonist **4b** inhibited IKKβ by >75%. In contrast, potent growth inhibitory activity was seen with **4a**, which correlated well with strong inhibition of both IKKα and IKKβ in the absence of RAR/RXR activity. We also profiled a novel series of AdArs (**7**–**10**) that incorporate a central heterocyclic ring that connects the adamantyl-phenol and the carboxylic acid at the polar termini. The MEM derivative of the phenol *ortho* to the adamantyl group was also included in order to reveal the role of this substituent that is present in the parent compound MX781 **3**, which is a potent inhibitor of IKK/NFκB signaling.[26,27] The new heterocyclic compounds elicited negligible RAR and RXR transactivation activity and only the thiazole **8b** functioned as strong RAR antagonist. Furthermore, the benzoic-linked thiazoles **8a**–**d** and methoxypyrazine **10a** elicited an even greater inhibitory activity against recombinant IKKβ in vitro than compound **3**, which in some cases (**8a** and **10a**) correlated with superior anticancer activity. In general, the presence of a MEM group reduced IKKβ inhibitory activity compared to the hydroxyl group-containing analog.

2. Synthesis

The synthesis of AdArs **4**-**6a**,**b** has been reported before.[32] An improved preparation of 3-acetamidopropyloxy-AHPC, 3-A-AHPC **2c**, an antagonist of **2a**, and its methyl analog **5c** has been developed, which differs from that of the original procedure in the order of steps for the formation of the bromocinnamic ester **15**,[11] and thus does not require protection/deprotection of the phenol. Bromination of 3-hydroxybenzaldehyde **11** was followed by the condensation of **12** with triethylphosphonoacetate and DBU[11] to afford **13** in 94% yield. The phenoxide of **13** (generated from treatment with K_2CO_3 in acetone) was treated with Boc-protected 3-bromopropanamine **14** to give **15** (94%). This step was followed by the Suzuki reaction with the previously described[11,32] boronic acids **16a**[11,32,33] and **16b**[32] to effect the coupling of the two fragments and provide the AdAr skeleton of **17a** and **17b**. These steps required optimization of the reaction conditions [$Pd(PPh_3)_4$, Na_2CO_3, dioxane, microwave irradiation, 100 °C, 30 min] and afforded the desired biphenyl compounds in excellent yields (89 and 93%, respectively). Sequential deprotection of the silyl ether (to **18a** and **18b**) and *tert*-butoxycarbonyl groups afforded the intermediate aminophenols, which were treated with acetic anhydride and pyridine to give the corresponding derivatives (**19a** and **19b**, respectively). Saponification of the esters in **19a** and **19b** produced the desired AdArs **2c** and **5c**, respectively.

For the preparation of the heterocyclic derivatives, we have chosen the dihalogenated heterocycles, namely dibromothiazole **20** (Scheme 2) and bromoiodopyrazine **26** (Scheme 3) as linchpin units to which the other substituents could be incorporated by exploiting the differential reactivity of the halogens in palladium-catalyzed cross-coupling reactions.[34,35] The premise that site-selective reactions of dibromothiazole **20** and bromoiodopyrazine **26** at the most electron-deficient positions are feasible has previously been reported.[36–39]

The synthesis of 2,5-dibromothiazole **20** and the selective Pd-catalyzed cross-coupling reaction at position C2 have been described,[40] but the functionalization of dibromothiazole by sequential halogen replacement reactions with different organometallics is unprecedented. For our purpose, the Suzuki coupling

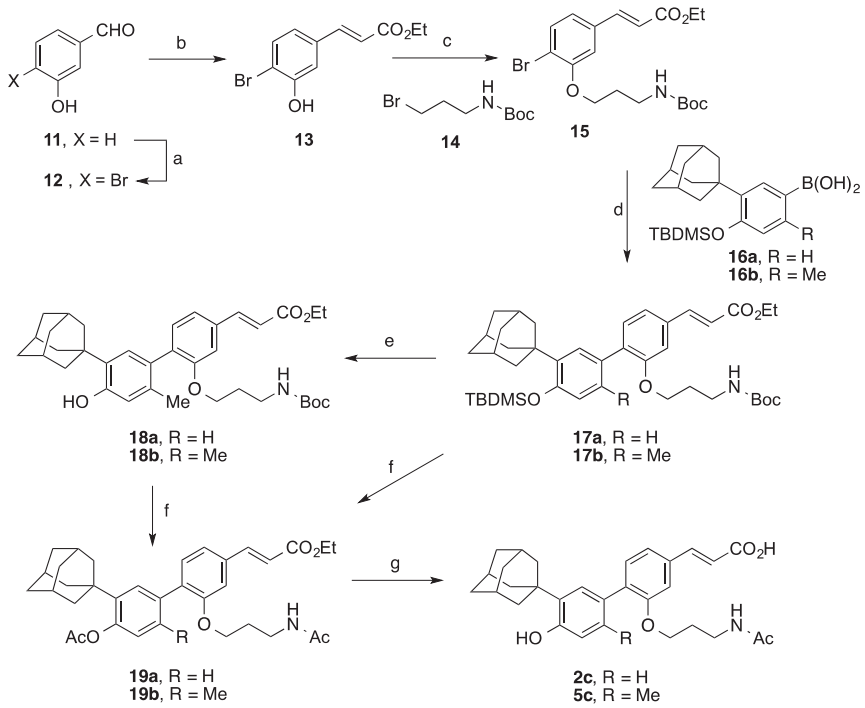
of 2,5-dibromothiazole **20** and aryl boronic acids **16a**[11,32,33] and **16b**[32] took place at 90 °C in the presence of $Pd(PPh_3)_4$ and aqueous Na_2CO_3.[38,39] Product **22a** was obtained in moderate yield (50%) and was accompanied by small amounts of the bis-coupled derivative **21a** (5%). The mixture of mono- and bis-coupled products of **16b** could not be separated and was used in the fluoride-induced deprotection to obtain **23b** (30%, two steps) and bis-coupled **21b** (5%, two steps). After deprotection of **22a** (Scheme 2), the adamantylphenols **23a** and **23b** were treated with NaH and MEMCl in THF at 0 °C to afford the MEM derivatives **23c** and **23d**, respectively. Only by using the Jeffery modification of the Heck reaction,[41] in the presence of *n*-Bu_4NCl and under strictly anhydrous conditions, could **23** efficiently react with methyl acrylate to produce the desired product (**24a–d**). Protection of phenols **24a–d** with MEMCl and hydrolysis ($LiOH{\cdot}H_2O$) of the esters afforded carboxylic acids **7a–d** (Scheme 2). Due to the electron-withdrawing nature of the methyl ester, the Suzuki coupling of bromothiazoles **23a–d** with 4-(methoxycarbonyl)phenylboronic acid to afford arotinoids **25a–d** required activation by microwave irradiation. Saponification ($LiOH{\cdot}H_2O$) afforded carboxylic acids **8a–d** in the yields shown in Scheme 2.

A similar synthetic approach was employed for the pyrazine derivatives (Scheme 3). The Suzuki coupling of dihalopyrazine **26** and arylboronic acids **16a** and **16b** (Scheme 1) afforded **27a** and **27b** in 76% and 30% yield, respectively. The Heck reaction of these bromopyrazines with methyl acrylate also caused the silyl group deprotection and produced **28a** and **28b** in 67% and 57% yield, respectively. In the case of **27a**, the starting pyrazine was partially recovered (19%) in deprotected form (compound **29a**, see below). Treatment of the phenols with MEMCl gave derivatives **28c** and **28d**, respectively, in good yields. Saponification of **28a–d** ($LiOH{\cdot}H_2O$) afforded carboxylic acids **9a–d** (Scheme 3). Fluoride-promoted deprotection of **27a** and **27b** gave rise to phenols **29a** and **29b**, which were converted into the MEM derivatives **29c** and **29d**, respectively, under the usual conditions. The coupling of these bromopyrazines with 4-(methoxycarbonyl)phenylboronic acid under the same Suzuki conditions was only successful for the non-methylated analogs **29a** and **29c**, and produced the final AdAr scaffold in moderate yields. However, similar treatment with analogs having a methyl group (**29b** and **29d**) led to their decomposition. Finally saponification of esters **30a** and **30c** afforded arotinoids **10a** and **10c**, respectively, in good yields (Scheme 3).

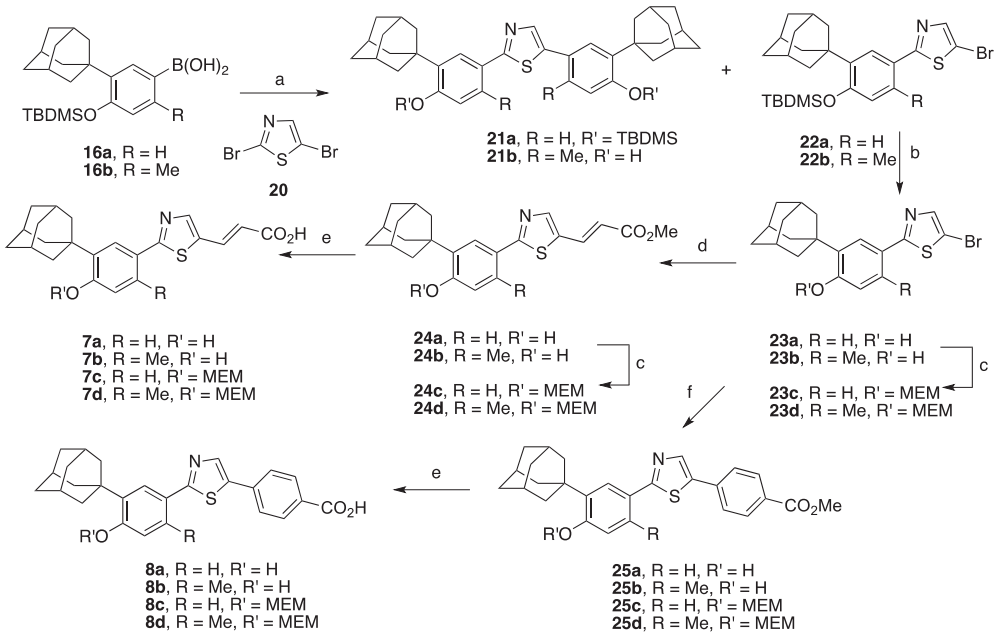
3. Biology

3.1. Inhibition of IKKβ and IKKα by the novel AdArs

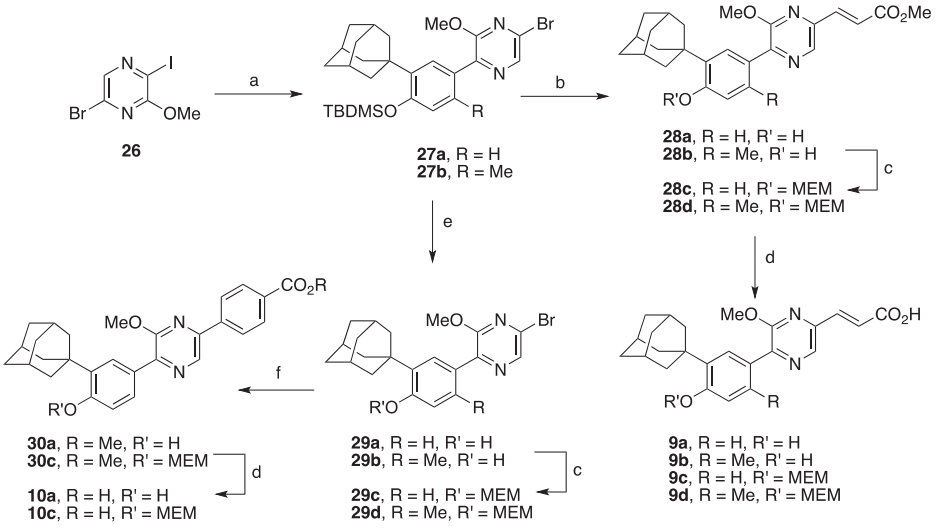
Following up on our previous reports that portrayed the inhibition of IKKβ by MX781 **3** and derivatives,[25–27] we evaluated the effect of AdArs on recombinant IKKs using a LANCE TR-FRET kinase assay. The naphthoic acid 2′-Me-5-Cl-AHPN **4a** was a strong inhibitor of both IKKα and IKKβ with an IC_{50} of 4.75 μM against IKKβ, about 2.5 times more potent than MX781 **3** (IC_{50} 11.83 μM) (Table 1). The presence of a MEM chain in compound **4b** substantially reduced the activity against IKKα, while preserving strong inhibition of IKKβ, although to a lesser extent as illustrated by the higher IC_{50} value (7.06 μM). The presence of the naphthoic acid ring was crucial, as compounds **5a**,**b**,**c** and **6a** were inactive whereas **6b** elicited partial activity. Among the heterocyclic compounds, the benzoic acid-linked thiazoles **8a–d** were the strongest inhibitors of IKKβ and IKKα, with the MEM chain and the Me substituent in **8d** marginally reducing IKKα activity. The Me substituent at the adamantyl-phenol end *ortho* to the biphenyl connection and the MEM substitution did not interfere with anti-IKKβ activity as all four analogs elicited similar IC_{50} values, between 3.37 μM (**8a**) and 5.16 μM (**8c**). In contrast, substitution of the benzoic acid by an acrylic acid in compounds **7a–d** severely affected IKK activity and partial activity was only detected with the methylated analog **7b**. Likewise, the methoxypyrazine containing AdAr **10a** was also a potent inhibitor of both IKKα and IKKβ, but addition of the MEM



Scheme 1. Reagents and reaction conditions: (a) Br_2, HOAc, 25 °C, 14 h, 31%; (b) triethylphosphonoacetate, DBU (3 equiv), CH_2Cl_2, 25 °C, 4 h, 72%; (c) K_2CO_3, acetone, 60 °C, 24 h, 94%; (d) $Pd(PPh_3)_4$, Na_2CO_3, DME, 100 °C, MW, 30 min (**17a**, 89%; **17b**, 93%); (e) TBAF, THF, 0 °C, 2.5 h, 18b, 98%. (f) (i) EtOH, HCl, 85 °C, 1 h, (ii) Ac_2O, Py, CH_2Cl_2, 25 °C, 20 h (**19a**, 58%; **19b**, 37%); (g) MeOH, Na_2CO_3, 70 °C, 3 h (**2c**, 53%; **5c**, 57%).



Scheme 2. Reagents and reaction conditions: (a) **20**, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, 1,4-dioxane, 90 °C, 6 h (**22a**, 50%; **21a**, 5%); (b) *n*-Bu_4NF, THF, 0 °C, 3 h (**23a**, 91%; **23b**, 30% for the two steps, **21b**, 5%); (c) NaH, MEMCl, THF, 25 °C, 19 h (**23c**, 88%; **23d**, 66%; **24c**, 70%; **24d**, 78%); (d) Methyl acrylate, $Pd(OAc)_2$, PPh_3, *n*-Bu_4NCl, $NaHCO_3$, 4 Å molecular sieves, DMF, 70 °C, 17 h (**24a**, 68%; **24b**, 56%); (e) LiOH, THF/H_2O, 25 °C, 2 h (**7a**, 95%; **7b**, 76%; **7c**, 91%; **7d**, 92%; **8a**, 99%; **8b**, 77%; **8c**, 99%; **8d**, 94%); (f) 4-(methoxycarbonyl)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, DME, MW, 120 °C, 10 min (**25a**, 78%; **25b**, 53%; **25c**, 61%; **25d**, 61%).



Scheme 3. Reagents and reaction conditions: (a) boronic acids **16a**/**16b**, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, 1,4-dioxane, 50 °C, 12 h (**27a**, 76%; **27b**, 30%); (b) methyl acrylate, $Pd(OAc)_2$, PPh_3, *n*-Bu_4NCl, $NaHCO_3$, 4 Å MS, DMF, 70 °C, 17 h (**28a**, 67%; **28b**, 57%); (c) NaH, MEMCl, THF, 25 °C, 19 h (**28c**, 92%; **28d**, 87%; **29c**, 89%; **29d**, 99%); (d) LiOH, THF/H_2O, 25 °C, 2 h (**9a**, 73%; **9b**, 84%; **9c**, 62%; **9d**, 65%; **10a**, 99%; **10c**, 93%); (e) *n*-Bu_4NF, THF, 0 °C, 3 h (**29a**, 83%; **29b**, 63%); (f) 4-(methoxycarbonyl)phenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, 1,4-dioxane, 50 °C, 12 h (**30a**, 58%; **30c**, 66%).

chain in analog **10c** greatly impaired IKK activity. As observed with the thiazole containing AdArs, substitution of the benzoic acid by acrylic acid in the pyrazines (compounds **9a**–**d**) severely compromised IKK activity and only the methylated analogs **9b** and **9d** caused partial inhibition of recombinant IKKα.

Interestingly, none of the previously reported RXRα agonists (**4b**, **5a**, **5b**, and **6b**)[32] were strong inhibitors of IKK, with the exception of **4b** that inhibited IKKβ by 80% and **6b**, which partially inhibited both IKKα and IKKβ (<50%). On the other hand, the atypical IKK family member IKKε was not affected by any of the AdArs, and only compound **4a** elicited limited inhibition (41%). The cinnamic acid **2b** caused a partial inhibition of IKKα and IKKβ activity in vitro, which suggests that activation of IKK/NFκB signaling reported by others in breast cancer and leukemia cells[13,30,31] likely occurs upstream of the IKK complex.

3.2. Effect of AdArs on cancer cell growth

We have previously demonstrated that MX781 **3** inhibits cancer cell growth and induces apoptosis in an IKKβ-dependent manner.[25] This is further supported by our observations that several chalcone analogs of MX781 **3** with improved IKKα/IKKβ inhibitory activity

Table 1
Effect of AdArs on recombinant IKKs, Jurkat cell viability, and DEVDase activity

AdAr	% Inhibition of IKK activity[a]				Cell viability[b]		DEVDase[c]
	IKKα	IKKβ	IKKε	IC_{50} (μM) IKKβ	% Viability	IC_{50} (μM)	
2b	41.3 ± 3.8	40.6 ± 1.1	24.1 ± 6.9		6.6 ± 0.7		74.3 ± 16
2c	5.0 ± 4.9	0	14.4 ± 4.1		42.7 ± 8.6		6.1 ± 1.7
3	56.3 ± 4.4	43.9 ± 4.7	15.8 ± 5.6	11.83	28.5 ± 5.5	3.33	20.7 ± 7.8
4a	87.3 ± 5.5	96.4 ± 2.7	41.5 ± 14	4.75	7.7 ± 4.8	2.19	55.8 ± 8.0
4b	33.9 ± 3.2	79.2 ± 6.0	13.7 ± 5.2	7.06	33.1 ± 4.9	5.62	12.4 ± 2.0
5a	23.7 ± 4.5	4.9 ± 2.4	11.9 ± 9.5		34.1 ± 0.9	4.04	0.8 ± 0.9
5b	13.5 ± 2.9	4.3 ± 3.6	2.9 ± 4.8		83.7 ± 3.6		1.3 ± 1.2
5c	2.3 ± 4.0	0	5.2 ± 8.0		28.0 ± 4.0	2.61	6.3 ± 0.9
6a	26.9 ± 2.9	4.9 ± 5.6	8.5 ± 6.8		45.8 ± 1.7	3.98	1.8 ± 0.8
6b	42.3 ± 4.4	39.8 ± 9.5	0		86.8 ± 1.9		2.6 ± 0.5
7a	32.8 ± 3.6	5.0 ± 4.2	0		92.9 ± 4.3		0.6 ± 1.8
7b	46.6 ± 5.0	26.2 ± 1.6	0		92.3 ± 5.0		1.5 ± 0.8
7c	4.5 ± 5.8	1.9 ± 3.4	14.3 ± 7.6		102.9 ± 5.1		0.6 ± 0.3
7d	29.2 ± 1.6	12.2 ± 6.9	11.1 ± 4.0		96.1 ± 1.8		1.6 ± 1.2
8a	85.3 ± 2.2	94.1 ± 0.6	11.6 ± 4.7	3.37	6.0 ± 2.2	2.24	81.4 ± 8.6
8b	87.9 ± 9.5	95.0 ± 2.6	0	4.78	39.0 ± 9.9	4.40	12.1 ± 2.9
8c	82.9 ± 3.7	89.3 ± 3.5	25.3 ± 5.9	5.16	74.5 ± 4.0	5.43	9.8 ± 2.8
8d	73.3 ± 5.7	87.7 ± 3.9	17.0 ± 8.0	4.43	59.5 ± 0.9	5.71	4.9 ± 0.5
9a	17.9 ± 4.9	8.2 ± 4.2	7.8 ± 4.4		60.9 ± 2.4	5.01	3.1 ± 1.3
9b	50.1 ± 5.1	7.3 ± 5.8	6.7 ± 3.6		70.9 ± 5.1	5.38	2.6 ± 0.4
9c	4.2 ± 4.3	1.6 ± 3.9	9.4 ± 5.8		94.9 ± 4.2		0.2 ± 0.9
9d	45.7 ± 6.3	3.8 ± 3.3	5.9 ± 3.4		96.5 ± 4.0		0.3 ± 1.0
10a	78.5 ± 5.7	83.9 ± 3.5	26.1 ± 5.9	7.81	14.9 ± 7.2	3.13	42.6 ± 3.2
10c	23.8 ± 7.4	25.4 ± 5.5	18.8 ± 6.5		91.4 ± 4.2		2.5 ± 0.3

[a] The effect of 20 μM AdArs on the activity of recombinant IKKs was determined by LANCE Ultra-kinase assay at a concentration of ATP near the apparent K_m for each kinase. Values indicate the percentage of inhibition with respect to solvent control samples ± standard deviation obtained in 3–4 experiments performed in triplicate. IC_{50} values (in μM) were calculated over 8 point 1/2.5 serial dilution curve starting at 40 μM.

[b] Effect of AdArs on cancer cell proliferation. The percentage of cell viability was calculated in Jurkat T cells treated with 4 μM of the indicated AdArs for 24 h. Control cells were incubated with the same volume of solvent DMSO (0.1% v/v). Cell viability values below 60% identify cell-killing activity. The average ± standard deviation of three independent experiments performed with triplicate data points is shown. IC_{50} values (in μM) were calculated for active compounds over an 8 point dose response curve starting at 10 μM.

[c] A DEVDase fluorometric assay was used as a measure of apoptosis in Jurkat cells treated with 5 μM of the indicated AdArs for 4 h, as described in Section 5. The values indicate the fold induction of DEVDase activity with respect to control cells incubated in the presence of solvent DMSO. The average ± standard deviation of two independent experiments performed in triplicate is shown. Values of 2 or below are not significant as they are within the standard error of control samples.

elicited enhanced growth inhibition and apoptosis inducing activities in Jurkat T cells.[26,27] We therefore evaluated the effect of heterocyclic AdArs on the viability of Jurkat cells and DEVDase activity as measures of cell proliferation and apoptosis inducing activity, respectively. As shown in Table 1, the methylated analog of 5-Cl-AHPN, compound **4a**, and two heterocyclic AdArs, the thiazole **8a** and the pyrazine **10a**, elicited the greatest inhibition of Jurkat cell viability (>85%) and induction of apoptosis (>40 fold), similar to that observed with the apoptogenic compound 3-Cl-AHPC **2b** and considerably higher than MX781 **3**. The corresponding derivatives containing the MEM chain, which is characteristic of MX781 **3**, **4b** and **8c** produced a much diminished growth inhibition and pro-apoptotic effect, whereas **10c** was inactive in both assays. Likewise, the methylated compounds **8b** and **8d** also showed partial activity in Jurkat cells even though they elicited significant inhibition of recombinant IKKα and IKKβ in vitro. Although we found clear differences in cell viability and DEVDase activity among the various AdArs when tested at a single concentration, all active compounds exhibited similar IC_{50} values against Jurkat cells, with compounds **4a**, **8a**, and **10a** having the lowest IC_{50}s (2.19, 2.24, and 3.13 μM, respectively). This agrees with the strongest induction of DEVDase activity and robust inhibition of IKKs. While there is an overall good correlation between the effect of AdArs on IKK activity and Jurkat cell viability, the inhibition of IKKα/β observed with some thiazole analogs was not sufficient to trigger cell killing and optimal DEVDase activity (see compounds **8c** and **8d**), although they still inhibited cell proliferation. Furthermore, it is worth mentioning that compound **2c** and its methyl analog **5c** exhibited growth inhibition and weak but reproducible activation of caspases independently of IKKα/β inhibition. This effect could be a consequence of growth arrest, since **2c** has been reported to block the induction of apoptosis but not growth arrest by other AdArs.[11]

As reported by others, 3-Cl-AHPN **2b** elicited robust cell killing activity but limited inhibition of recombinant IKKα/β in vitro, which relates to the reported activation of IKK/NFκB signaling in breast cancer cells.[13,30,31] The RXR agonists **4b** and **5a** had substantial cancer cell killing activity, which appeared to be dependent (**4b**) or independent (**5a**) of the activation of caspases (Table 1). These results concur with our previous report on adamantyl rexinoids[32] and the small differences observed here could be due to different experimental conditions used in both studies.

3.3. RAR/RXR transactivation profile of AdArs

The RAR/RXR profile of compounds **4**, **5**, and **6** has already been reported, with compounds **4b**, **5a**,**b** and **6b** functioning as RXR agonists.[32] Of the novel heterocyclic compounds described here, none was able to induce significant RARα or RXRα-mediated transcriptional activity on their own, with the exception of the MEMO-linked thiazole **8c**, which induced weak transactivation of Gal4-RXRα (3-fold induction over solvent control or 21% of the maximum activity observed with the control rexinoid CD3254 **33**) (Table 2 and Fig. 2). In contrast, the 2-methylphenyl-thiazole **8b** inhibited luciferase activity of Gal4-RARα in the antagonistic mode (Table 2), and a subsequent dose response experiment revealed an IC_{50} of 1.277 μM. Similarly, the corresponding unmethylated positional isomer also functioned as an RARα antagonist in this system, with an IC_{50} value of 2.65 μM (data not shown).

Table 2
RAR/RXR transactivation profile of AdAr

Ligand	RAR profile		RXR profile		RXR-coactivator interaction[c]	
	Agonist[a]	Antagonist[b]	Agonist[a]	Antagonist[b]	D22	SRC-1
None	1	1.2 ± 0.2	1	7.1 ± 2.9	100 ± 4	148 ± 7
31, atRA	110.8 ± 12	100	n.t.	n.t.	n.t.	n.t.
32, UVI2024	1.3 ± 0.3	7.1 ± 2.9	n.t.	n.t.	n.t.	n.t.
33, CD3254	n.t.	n.t.	14.3 ± 3.4	100	416 ± 15	561 ± 12
34, UVI3003	n.t.	n.t.	1.0 ± 0.2	23.3 ± 2.4	−4 ± 4	−2 ± 3
4a	1.1 ± 0.2	90.0 ± 4.2	0.9 ± 0.1	69.9 ± 2.5	29 ± 3	53 ± 6
4b	1.1 ± 0.1	82.7 ± 5.9	9.8 ± 2.8	84.7 ± 5.4	159 ± 6	187 ± 7
5a	1.1 ± 0.2	67.1 ± 1.4	13.3 ± 1.9	96.2 ± 7.2	487 ± 36	373 ± 18
5b	1.8 ± 0.5	61.5 ± 6.2	19.0 ± 3.8	120.6 ± 11	654 ± 81	437 ± 16
5c	1.0 ± 0.4	70.0 ± 2.7	0.9 ± 0.1	73.6 ± 3.7	113 ± 4	152 ± 1
6a	1.4 ± 0.4	79.7 ± 5.2	1.4 ± 0.2	96.1 ± 5.0	28 ± 7	81 ± 24
6b	1.3 ± 0.4	74.1 ± 6.0	16.0 ± 4.4	96.3 ± 8.1	214 ± 12	422 ± 11
7a	1.1 ± 0.1	92.4 ± 5.0	1.7 ± 0.4	78.7 ± 2.6	156 ± 3	162 ± 5
7b	1.0 ± 0.1	87.3 ± 8.4	1.3 ± 0.2	85.7 ± 9.8	77 ± 3	82 ± 9
7c	1.0 ± 0.1	94.2 ± 7.8	0.9 ± 0.1	83.9 ± 6.1	127 ± 23	130 ± 8
7d	1.9 ± 2.0	75.3 ± 8.4	1.5 ± 0.2	91.7 ± 5.5	88 ± 3	133 ± 9
8a	4.6 ± 1.2	66.2 ± 2.4	0.9 ± 0.1	67.2 ± 6.6	94 ± 13	183 ± 17
8b	1.4 ± 0.1	33.2 ± 4.4	1.9 ± 0.5	91.7 ± 5.5	113 ± 1	117 ± 10
8c	1.2 ± 0.2	92.4 ± 9.4	3.1 ± 1.3	83.2 ± 5.9	133 ± 5	159 ± 5
8d	0.9 ± 0.1	61.6 ± 4.0	0.9 ± 0.2	91.4 ± 7.6	93 ± 9	115 ± 6
9a	1.1 ± 0.2	93.2 ± 5.0	1.7 ± 0.3	119.4 ± 4.8	92 ± 6	116 ± 4
9b	1.0 ± 0.3	89.0 ± 6.2	1.0 ± 0.1	89.4 ± 2.7	93 ± 3	106 ± 2
9c	1.1 ± 0.2	78.7 ± 5.4	0.9 ± 0.1	94.9 ± 4.4	119 ± 15	122 ± 7
9d	0.8 ± 0.1	99.5 ± 9.9	1.1 ± 0.1	86.3 ± 4.7	87 ± 3	106 ± 4
10a	1.9 ± 0.4	95.4 ± 12	1.0 ± 0.1	83.7 ± 7.7	102 ± 11	111 ± 16
10c	1.1 ± 0.3	108.7 ± 12	1.1 ± 0.1	87.7 ± 4.0	170 ± 9	172 ± 5

n.t.: not tested.

[a] Values indicate the fold induction of RARα or RXRα activity with respect to solvent control cells (non-stimulated). As positive control, RARα-transfected cells were treated with 1 μM atRA **31**, whereas RXRα-expressing cells were treated with 1 μM of the synthetic rexinoid CD3254 **33**. AdArs were used at 4 μM. The average ± standard deviation of two independent experiments with triplicate data points is shown.

[b] To determine the antagonist profile of AdAr analogs, RAR/RXR-expressing cells were incubated with 100 nM atRA **31**/CD3254 **33** in the presence of a 40 fold molar excess of the indicated AdArs. The values indicate the percentage of activity with respect to control cells stimulated with agonist ligand (atRA **31** or CD3254 **33**) in the absence of AdAr (100% activity). The percentage of activity of non-stimulated cells is also shown. As positive controls, RAR and RXR-transfected cells were treated with 1 μM of the well-known antagonists UVI2024 **32** and UVI3003 **34**, respectively. The average ± standard deviation of 2 or 3 experiments performed with triplicate data points is shown.

[c] Two separate TR-FRET-based homogeneous assays were used to measure the interaction of GST-RXRα-LBD with two different coactivator-derived peptides, D22 and SRC1. The value indicates the percentage of change compared to samples that contained no ligand (Delta F%, see experimental section for definition). The experiment was repeated twice with triplicate data points and the average data ± standard deviation (n = 6) is shown.

Although not as powerful as the inverse agonist UVI2024 **32** (IC_{50} 0.114 μM),[27] both thiazole containing AdArs were stronger antagonists of RARα than the parental compound MX781 **3** (IC_{50} 4.474 μM).

To confirm that the RXR transactivating AdArs are indeed able to directly bind to the RXR LBD, we performed cell free coactivator recruitment assays with purified recombinant GST-RXRα LBD and two coactivator derived peptides: the synthetic peptide D22 labeled with fluorescein and biotin-tagged SRC-1-676-700 peptide containing the second LXXLL motif. Concurring with the cell-based luciferase transactivation assays, compounds **5a** and **5b** induced a robust binding of RXRα LBD to both D22 and SRC-1 peptides, to a level comparable to that observed with the rexinoid agonist CD3254 **33**. The full agonist **6b**[32] also induced strong interactions with SRC-1 peptide, but behaved as a partial agonist with D22 peptide (see Table 2 and Fig. S1). As expected, the naphthoic acid derivative **4b** produced a modest increase of RXRα-peptide interactions above basal controls in the absence of ligand, which is in accordance with the partial agonist activity observed in transient transfection assays (see Table 2), as we have recently reported.[32] The heterocyclic AdArs induced no or very limited (<2 fold) recruitment of coactivator peptides by RXRα LBD.

The rexinoid antagonist UVI3003 **34**[42] completely inhibited RXRα-D22/SRC-1 interactions, even to the level of non-protein control (Table 2). Likewise, the adamantyl-phenol derivatives (lacking the MEM chain) of the two rexinoids **4b** and **6b**, **4a** and **6a** respectively, also inhibited the recruitment of both D22 and SRC-1 peptides by RXRα LBD significantly (Table 2 and Fig. S2),

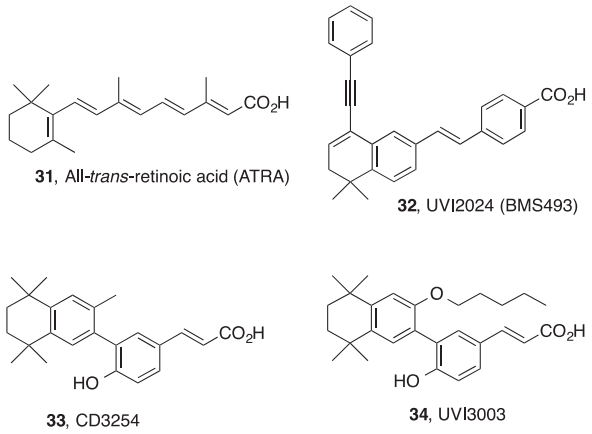


Figure 2. Structure of selected RAR and RXR modulators.

suggesting that **4a** and **6a** might function as weak inverse agonists. When used in combination with a low concentration of CD3254 agonist **33**, both **4a** and **6a** inhibited the interaction of RXRα LBD with D22 coactivator peptide stimulated by CD3254 (Fig. S2). Even though this effect was not comparable to that of UVI3003 **34** (25% inhibition by **4a** and **6a** versus complete inhibition of RXRα/D22 binding by UVI3003 **34**), it concurred with a weak but consistent effect elicited by **4a** in a cell based Gal4-RXRα transactivation assay in the antagonist mode (30% inhibition) (see Table 2).

4. Discussion

Adamantyl arotinoids (AdArs) have been recognized as promising anticancer therapeutic agents due to their growth inhibitory and apoptosis inducing activities. Although originally derived from RARγ/β selective retinoid-related molecules, AdArs are often classified as atypical retinoids as they exert their cancer cell growth inhibitory and apoptogenic activities independently of RAR transactivation. While certain AdArs have been shown to target IKKβ as a likely mediator of their anticancer activity, others have been shown to function as RXR agonists. Yet, other AdArs have been reported by others to bind the nuclear receptor SHP while activating IKK/NFκB signaling in order to induce apoptosis.

Here we report on the IKK inhibitory activity of rexinoid AdArs and a novel series of heterocyclic containing AdArs with OH or OMEM substitutions at the adamantyl phenyl ring. None of the novel heterocyclic AdArs described has any significant RAR or RXR transactivating effect. Only the thiazole analog **8b** functioned as a RARα antagonist, whereas the unmethylated MEMO-linked thiazole **8c** produced a weak activation of RXR (~20% of control). We demonstrate that inhibition of IKK and activation of RXR do not overlap, but they both correlate with robust tumor cell growth inhibitory activity. Thus, compound **4a** was shown previously to exhibit strong antiproliferative activity but not RXR activity;[32] we now demonstrate that **4a** is the most potent inhibitor of Jurkat cell proliferation (IC_{50} 2.19 μM) coinciding with strong inhibition of IKKα and IKKβ (IC_{50} 4.75 μM), which suggests that inhibition of IKKβ might be responsible for the growth inhibitory activity of this AdAr. This contrasts with the limited or no anti-IKK activity found with rexinoid AdArs that show proven cancer cell growth inhibitory effects (**5a**,**b** and **6b**). One exception to this rule is the MEM analog of **4a**, naphthoic acid **4b**, which has strong growth inhibitory activity, functions as a partial RXR agonist, and also inhibits IKKβ with an IC_{50} of 7.06 μM.

Our present studies further confirm the rexinoid activity of these AdArs using a cell free biochemical assay in which we measure the interaction of recombinant GST-RXRα LBD with coactivator derived peptides. This assay proved more sensitive than cellular assays in detecting weak inverse agonists. As a result, we could demonstrate that removal of the MEM chain from the adamantyl phenol ring converts two of the rexinoid agonists (**4b** and **6b**) into weak RXRα inverse agonists (**4a** and **6a**). Compounds **4a** and **6a** elicited strong inhibition of RXR-peptide interaction in vitro, but had no effect on RXR-driven luciferase activity when used alone. When assayed in the antagonist mode (in the presence of suboptimal concentrations of a rexinoid agonist, CD3254 **33**)[42] we found that **4a** behaved as a weak antagonist in both cellular and biochemical assays, whereas **6a** was only active in the biochemical assay with D22 peptide. It is very likely that AdArs function in a coactivator specific fashion and therefore affect RXRα-driven transactivation in a cell type dependent manner.

In general, there is a good correlation between the inhibition of IKKβ activity and the inhibition of cancer cell viability, which in turn is associated with induction of apoptosis. Thus, a correlation analysis between the inhibition of IKKβ and inhibition of cell viability by the heterocyclic AdArs (**7**-**9**) and including the parent compound **3** as well as the naphtoic acid derivatives **4a** and **4b**, produced a correlation coefficient of 0.8039 with a *P* value of 0.0002 (data not shown). The strongest correlation is seen with **4a**, thiazole **8a**, and pyrazine **10a**. Thiazole **8a** displays the greatest inhibition of IKKβ (IC_{50} 3.37 μM) and the maximum induction of DEVDase activity (>80 fold stimulation), whereas pyrazine **10a** also elicits robust inhibition of IKKβ (IC_{50} 7.81 μM) and induction of apoptosis in terms of DEVDase activity (43 fold increase). To strengthen this correlation, substitution of the benzoic acid in compounds **8** and **10** by an acrylic acid (compounds **7** and **9**, respectively), greatly impaired both IKK inhibition and anticancer activity. Furthermore, while this correlation between the inhibition of IKK and cancer cell growth, and induction of apoptosis is reminiscent of the activity observed with chalcone containing AdArs,[26,27] inhibition of recombinant IKK in vitro does not always correlate with potent anticancer activity among the heterocyclic AdArs, in particular with those containing a MEM chain. Thus, addition of a Me group and/or a MEM chain into thiazole **8a** (compounds **8b**, **8c**, and **8d**) diminished growth inhibitory activity and greatly impaired apoptosis inducing capability in Jurkat cells without affecting the inhibition of IKKα/β. This reduced cellular activity could be the consequence of impaired cellular uptake, metabolism, and/or off target activities unrelated to cancer cell growth and apoptosis.

Other than IKK and RXR, the orphan receptor SHP has also been shown to be the target of AdArs, in particular 3-Cl-AHPC **2b** and analogs.[12,43] 3-Cl-AHPC **2b** has been reported by others to activate IKK/NFκB signaling pathway, an activity that seems necessary for the induction of apoptosis.[28] The mechanism of IKK/NFκB activation has not been delineated, but is in conflict with our observed modest but consistent inhibition of recombinant IKKα/β activity in our cell-free assay. This suggests that 3-Cl-AHPC **2b** has pleiotropic effects in a cellular environment, including but not limited to inhibition of protein phosphatases as possible mediators of IKK activation.

The recent resolution of the IKKβ crystal structure[44,45] will certainly have a positive impact in the future lead optimization efforts to improve the potency and selectivity of AdArs as IKK inhibitors. Until now, we have relied on the synthesis and evaluation of numerous compounds, including chalcones and heterocyclic AdArs in order to withdraw some structural requirements for optimal inhibition. Whereas our lead compound MX781 **3** had a chalcone functional group and a MEM chain in the adamantyl phenolic ring, the results presented here and elsewhere clearly demonstrate that eliminating the MEM chain has generally a beneficial effect on the overall IKK/growth inhibitory activity of the AdAr (compare compounds **4a** and **4b**). Moreover, the chalcone function is not critical for IKK inhibition by AdArs, as substitution by certain heterocyclic groups also improves activity (see for example thiazole **8a** and pyrazine **10a**). The inclusion of a heterocyclic thiazole or pyrazine group within the arotinoid structure could have advantages over classical arotinoids for the inhibition of protein kinases that we are trying to achieve with these AdARs. Thiazole and pyrazine ring systems are important structural elements found in kinase inhibitors, even in FDA approved drugs (i.e., dasatinib). Pyrazine is less basic than pyridine or pyrimidine, which are commonly found in ATP-competitive kinase inhibitors.

5. Experimental

5.1. General

Solvents were dried according to published methods and distilled before use. All other reagents were commercial compounds of the highest purity available. All reactions were carried out under argon atmosphere, and those not involving aqueous reagents were carried out in oven-dried glassware. Analytical thin layer chromatography (TLC) was performed on aluminium plates with Merck Kieselgel 60F254 and visualized by UV irradiation (254 nm) or by staining with a solution of phosphomolibdic acid. Flash column chromatography was carried out using Merck Kieselgel 60 (230–400 mesh) under pressure. Infrared spectra were obtained on JASCO FTIR 4200 spectrophotometer, from a thin film deposited onto a NaCl glass. ^1H NMR spectra were recorded in $CDCl_3$, CD_3OD,

CD_3CN and DMSO-d_6 at ambient temperature on a Bruker AMX-400 spectrometer at 400 MHz with residual protic solvent as the internal reference ($CDCl_3$, δ_H = 7.26 ppm; CD_3CN, δ_H = 1.94 ppm; CD_3OD, δ_H = 3.31 ppm; DMSO-d_6, δ_H = 2.50 ppm); chemical shifts (δ) are given in parts per million (ppm), and coupling constants (J) are given in Hertz (Hz). The proton spectra are reported as follows: *d* (multiplicity, coupling constant *J*, number of protons, assignment). ^{13}C NMR spectra were recorded in CD_3Cl_3, CD_3OD, DMSO-d_6 and CD_3CN at ambient temperature on the same spectrometer at 100 MHz, with the central peak of $CDCl_3$ (δ_c = 77.0 ppm), CD_3OD (δ_c = 49.0 ppm), DMSO-d_6 (δ_c = 39.4 ppm) or CD_3CN (δ_c = 118.3, 1.3 ppm) as the internal reference. The DEPT135 sequence was used to aid in the assignment of signals on the ^{13}C NMR spectra. Melting points were determined on a Stuart SMP10 apparatus. Elemental analyses were determined on a Carlo ErbaEA 1108 analyzer. MS experiments were performed on an APEX III FT-ICR MS (Bruker Daltonics, Billerica, MA), equipped with a 7T actively shielded magnet. Ions were generated using an Apollo API electrospray ionization (ESI) source (Bruker Daltonics, Billerica, MA), with a voltage between 1800 and 2200 V (to optimize ionisation efficiency) applied to the needle, and a counter voltage of 450 V applied to the capillary. Samples were prepared by adding a spray solution of 70:29.9:0.1 (v/v/v) methanol/water/formic acid to a solution of the sample at a v/v ratio of 1–5% to give the best signal-to-noise ratio. Data acquisition and data processing were performed using the XMASS software, version 6.1.2 (Bruker Daltonics). FAB experiments were performed on a VG AutoSpec instrument, using 3-nitrobenzylalcohol or glycerol as matrix.

5.2. General procedure for the Suzuki coupling

In a Schlenk flask, a solution containing the haloheterocycle (1 mmol), the boronic acid (1.3 mmol), methanol (5 mL) and a 2 M aqueous sodium carbonate solution (3.35 mmol) in benzene (25 mL) was deoxygenated by bubbling a stream of argon through it. $Pd(PPh_3)_4$ (0.14 mmol) was then added and the flask was evacuated and purged with argon. The reaction mixture was heated for the time indicated and the reaction was quenched with water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel as indicated.

5.3. General procedure for the microwave-assisted Suzuki coupling

In a reaction flask, a solution containing the haloheterocycle (1.0 mmol), the boronic acid (1.1 mmol) and a 2 M aqueous sodium carbonate solution (4.0 mmol) in DME (10 mL) was deoxygenated by bubbling a stream of argon through it. $Pd(PPh_3)_4$ (0.10 mmol) was then added and the flask was evacuated and purged with argon. The reaction mixture was heated in a microwave reactor for the time indicated and the reaction was quenched with water and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel as indicated.

5.4. General procedure for the deprotection of silyl ethers

Tetrabutylammonium fluoride (1.5 mmol) was added to a solution of the silyl ether (1 mmol) in THF (1 mL) at 0 °C. After the solution was stirred for 2 h at this temperature, water was added and the reaction was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel as indicated.

5.5. General procedure for the protection of phenols with MEMCl

Sodium hydride (60% as a dispersion in oil, 1.1 mmol) was added to a solution of the phenol (1.0 mmol) in THF (10 mL). After stirring for 30 min at room temperature, 2-methoxyethoxymethyl chloride (1.1 mmol) was added and the mixture was stirred at room temperature for 19 h. The reaction was quenched with water and extracted with EtOAc (3×). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography and crystallized as indicated.

5.6. General procedure for the Heck reaction

Tetrabutylammonium chloride (1.0 mmol) was added to a solution of sodium hydrogencarbonate (2.5 mmol) and 4 Å molecular sieves (0.4 g/mmol) in DMF (8 mL) and stirring was maintained for 15 min at room temperature. Then, a solution containing triphenylphosphine (0.08 mmol), methyl acrylate (2 mmol) and the haloheterocycle (1.0 mmol) in DMF (0.13 mL) was added via cannula. The mixture was stirred for 15 min and $Pd(OAc)_2$ (0.08 mmol) was added. After stirring the reaction mixture at 70 °C for 17 h, the solid was removed via filtration through Celite® and the solvent was evaporated in vacuo. The residue was treated with CH_2Cl_2 and washed with $NaHCO_3$ (3×). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel and crystallized as indicated.

5.7. General procedure for the hydrolysis of esters

Lithium hydroxide (15 mmol) was added to a solution of ester (1 mmol) in a 1:1 THF/H_2O (17 mL) mixture. The solution was stirred at room temperature for 2 h, neutralized with 10% HCl and extracted with EtOAc (4×). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the solvent was evaporated in vacuo. Crystallization of the residue provided the desired acid as indicated.

5.7.1. Ethyl (*E*)-3-[3-(adamant-1-yl)-(2-(3-(*tert*-butoxycarbonylamino)propoxy)-4-(*tert*-butyldimethylsilyloxy)biphenyl-4-yl]acrylate (17a)

According to the general procedure for the microwave-assisted Suzuki coupling, the reaction of **15**[11] (0.15 g, 0.35 mmol) and arylboronic acid **16a**[11] (0.017 g, 0.46 mmol) gave, after purification of column chromatography on silica gel (70:30 hexane/EtOAc), 0.12 g (55%) of a white solid identified as **17a**. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.74 (d, J = 16.0 Hz, 1H, H3), 7.30 (d, J = 8.4 Hz, 1H, ArH), 7.14 (d, J = 2.4 Hz, 1H, H2″ or H2′), 7.1 (d, J = 2.0 Hz, 1H, H2′ or H2″), 6.99 (dd, J = 8.0, 2.0 Hz, 1H, H6″ or H6′), 6.96 (dd, J = 8.4, 2.4 Hz, 1H, H6′ or H6″), 6.82 (d, J = 8.0 Hz, 1H, ArH), 6.34 (d, J = 16.0 Hz, 1H, ArCHC*H*), 4.75 (br, 1H, NH), 4.20 (q, J = 7.1 Hz, 2H, $COOCH_2CH_3$), 4.07 (t, J = 5.8 Hz, 2H, H2), 3.34 (q, J = 5.6 Hz, 2H, CH_2NHAc), 1.9–2.1 (m, 11H, 3 × $AdCH_2$ + -$OCH_2CH_2CH_2N$ + 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$), 1.44 (s, 9H, CO-*t*-Bu), 1.28 (t, J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.06 (s, 9H, $SiC(CH_3)$), 0.36 (s, 6H, 2 × $SiCH_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.9 (s), 157.7 (s), 156.0 (s), 154.1 (s), 144.4 (d), 139.0 (s), 136.3 (s), 133.6 (s), 133.5 (s), 131.5 (d), 131.4 (s), 129.4 (d), 127.5 (d), 119.0 (d), 118.7 (d), 116.7 (d), 111.8 (d), 66.0 (t, $ArOCH_2$), 60.3 (t, $COOCH_2CH_3$), 40.4 (t, 3 × $AdCH_2$), 38.0 (t, CH_2N), 37.1 (t, 3 × $AdCH_2$), 37.0 (s, AdC), 29.6 (t, $OCH_2CH_2CH_2N$), 29.0

(d, 3 × AdCH), 28.9 (q, 3 x, HNCOC(CH_3)$_3$), 26.4 (q, 3×, SiC(CH_3)$_3$), 18.9 (s, Si*C* + *C*OCH$_3$), 14.3 (q, COOCH$_2$*C*H$_3$), −3.4 (q, 2 × Si(CH_3)) ppm. IR (NaCl): *ν* 3380 (w, N–H), 2928 (s, C–H), 2906 (s, C–H), 2855 (s, C–H), 1713 (s, C=O), 1631 (m), 1602 (m), 1480 (s), 1259 (s), 1172 (s) cm^{-1}. MS (FAB$^+$): *m*/*z* (%) 689 (M$^+$, 100), 633 (18), 632 (10), 591 (18), 590 (41), 588 (20), 545 (34), 544 (76), 542 (36), 397 (20), 341 (32).

5.7.2. Ethyl (*E*)-3-[5-(adamant-1-yl)-2-(3-(*tert*-butoxycarbonylamino)propoxy)-4-(*tert*-butyldimethylsilyloxy)-2-methylbiphenyl-4-yl]acrylate (17b)

According to the general procedure for the microwave-assisted Suzuki coupling, the reaction of **15**[11] (0.15 g, 0.35 mmol) and arylboronic acid **16b**[32] (0.18 g, 0.46 mmol) gave, after purification of column chromatography on silica gel (85:15 hexane/EtOAc), 0.22 g (91%) of a white solid identified as **17b**. ^{1}H NMR (400.13 MHz, $CDCl_3$): *δ* 7.43 (d, *J* = 16.0 Hz, 1H, H3), 7.17 (d, *J* = 2.7 Hz, 1H, H3′), 7.16 (d, *J* = 8.5 Hz, 1H, H6′), 6.94 (dd, *J* = 8.5, 2.7 Hz, 1H, H5′), 6.87 (s, 1H, ArH), 6.66 (s,1H, ArH), 6.28 (d, *J* = 16.0 Hz, 1H, H2), 4.76 (br, 1H, NH), 4.16 (q, *J* = 7.2 Hz, 2H, COO*CH*$_2$CH$_3$), 4.07 (t, *J* = 6.0 Hz, 2H, ArOCH$_2$), 3.34 (t, *J* = 6.0 Hz, 2H, *CH*$_2$NH^{t}Boc), 1.9–2.1 (m, 14H, 3 × AdCH$_2$ + OCH$_2$*CH*$_2$CH$_2$N + 3 × AdCH + ArCH$_3$), 1.73 (s, 6H, 3 × AdCH$_2$), 1.44 (s, 9H, CO^{t}Bu), 1.25 (t, *J* = 7.2 Hz, 3H, COOCH$_2$*CH*$_3$), 1.06 (s, 9H, SiC(CH_3)$_3$), 0.37 (s, 3H, SiCH$_3$), 0.36 (s, 3H, SiCH$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): *δ* 166.9 (s), 157.7 (s), 156.0 (s), 153.9 (s), 143.6 (d), 136.6 (s), 136.2 (s), 134.2 (s), 134.1 (s), 132.1 (d), 130.9 (s), 129.6 (d), 120.5 (d), 118.7 (d), 116.4 (d), 111.1 (d), 79.2 (s, O*C*(CH$_3$)$_3$), 65.9 (t, OCH$_2$), 60.2 (q, COO*C*H$_2$CH$_3$), 40.5 (t, 3 × AdCH$_2$), 38.0 (t, CH$_2$N), 37.0 (t, 3 × AdCH$_2$), 36.5 (s, AdC), 29.6 (t, CH$_2$*C*H$_2$CH$_2$N), 29.0 (q or d, 3 × AdCH or SiC(*C*H$_3$)$_3$ or 3× C(*C*H$_3$)$_3$), 28.4 (q or d, 3 × C(*C*H$_3$)$_3$ or 3 × AdCH or SiC(*C*H$_3$)$_3$), 26.4 (q or d, SiC(*C*H$_3$)$_3$ or 3 × C(*C*H$_3$)$_3$ or 3 × AdCH), 19.7 (q, ArCH$_3$), 18.9 (s, Si*C*(CH$_3$)$_3$), 14.2 (q, COOCH$_2$*C*H$_3$), −3.4 (q, SiCH$_3$), −3.3 (q, SiCH$_3$) ppm. IR (NaCl): *ν* 3377 (m, N–H), 2959 (m, C–H), 2903 (m, C–H), 2853 (s, C–H), 1702 (s, C=O), 1505 (m), 1486 (m), 1454 (m), 1256 (s), 1230 (s), 1168 (s), 1019 (s), 872 (s), 837 (s), 782 (s), 731 (s) cm^{-1}. MS (FAB$^+$): *m*/*z* (%) 705 ([M+1]$^+$, 19), 704 (M$^+$, 100), 703 ([M-1]$^+$, 54), 648 (11), 647 (11), 646 (11), 605 (10), 604 (22), 604 (14), 559 (15), 558 (32). HRMS (FAB$^+$): calcd for $C_{42}H_{61}NO_6Si$, 703.4223; found, 703.4243.

5.7.3. Ethyl (*E*)-3-(2-(3-acetamidopropoxy)-4-acetoxy-3-(adamant-1-yl)-biphenyl-4-yl)acrylate (19a)

To a mixture of **17a** (0.11 g, 0.19 mmol) in EtOH (3.2 mL) was added concentrated HCl (0.32 mL). This mixture was heated at 85 °C for 8 h and then concentrated. The residue containing the primary amine **18a** was sequentially treated with CH_2Cl_2 (4.6 mL), pyridine (0.24 mL, 3.01 mmol), and Ac_2O (0.08 mL, 0.82 mmol) and stirred overnight at room temperature before addiction of H_2O and extraction with EtOAc (3×). The organic layer was washed with H_2O, brine, dried (Na_2SO_4), the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (98:2 CH_2Cl_2/MeOH) to afford **19a** (0.04 g, 58%) as a white solid (mp 215 °C, CH_2Cl_2/MeOH/hexane). ^{1}H NMR (400.13 MHz, CD_3OD): *δ* 7.81 (d, *J* = 15.5 Hz, 1H, H3), 7.43 (d, *J* = 8.4 Hz, 1H, ArH), 7.38 (s, 1H, ArH), 7.32 (s, 1H, ArH), 7.25 (d, *J* = 8.4 Hz, 1H, ArH), 7.15 (d, *J* = 8.3 Hz, 1H, ArH), 7.08 (d, *J* = 8.3 Hz, 1H, ArH), 6.46 (d, *J* = 15.5 Hz, 1H, H2), 6.18 (br, 1H, NH), 4.32 (q, *J* = 7.1 Hz, 2H, COO*CH*$_2$CH$_3$), 4.20 (t, *J* = 5.8 Hz, 2H, ArO*CH*$_2$), 3.58 (q, *J* = 5.8 Hz, 2H, *CH*$_2$NHAc), 2.49 (s, 3H, Ac), 2.13 (br, 6H, 3 × AdCH$_2$), 2.11 (s, 6H, 3 × AdCH or COCH$_3$), 1.57 (m, 8H, 3 × AdCH$_2$ + OCH$_2$*CH*$_2$CH$_2$N), 1.40 (t, *J* = 7.1 Hz, 3H, COOCH$_2$*CH*$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): *δ* 170.4 (s), 169.5 (s), 166.6 (s), 158.0 (s), 148.5 (s), 143.8 (d), 140.5 (s), 136.7 (s), 135.5 (s), 133.7 (s), 131.6 (d), 129.4 (d), 127.7 (d), 124.0 (d), 119.5 (d), 116.5 (d), 111.9 (d), 66.2 (t, O*C*H$_2$), 60.4 (t, O*C*H$_2$), 41.1 (t, 3 × AdCH$_2$), 37.2 (t, *C*H$_2$N), 36.8 (t + s, 3 × AdCH$_2$ + AdC), 28.9 (t, OCH$_2$*C*H$_2$CH$_2$NHAc), 28.8 (d, 3 × AdCH), 23.2 (q), 21.8 (q), 14.3 (q, COOCH$_2$*C*H$_3$) ppm. IR (NaCl): *ν* 3293 (w, N–H), 2903 (m, C–H), 2849 (m, C–H), 1753 (m), 1705 (m, C=O), 1651 (m, C=O), 1633 (m, C=O), 1476 (m), 1367 (m), 1203 (s), 1173 (s), 1038 (m), 750 (s) cm^{-1}. EM (EI): *m*/*z* (%) 559 (M$^+$, 5), 418 (12), 135 (11), 100 (100). HRMS (EI): calcd for $C_{34}H_{41}NO_6$, 559.2934; found, 559.2928.

5.7.4. Ethyl (*E*)-3-[5-(adamant-1-yl)-2-(3-(*tert*-butoxycarbonylamino)propoxy)-4-hydroxy-2-methylbiphenyl-4-yl]acrylate (18b)

According to the general procedure for the cleavage of silyl ethers, compound **17b** (0.17 g, 0.25 mmol) was treated with a solution of TBAF (0.27 mL, 1 M in THF, 0.27 mmol) to afford, after purification by column chromatography on C_{18} silica gel (100% acetonitrile), 0.16 g (98%) of a yellow solid identified as **18b**. ^{1}H NMR (400.13 MHz, $CDCl_3$): *δ* 7.42 (d, *J* = 16.0 Hz, 1H, H3), 7.19 (d, *J* = 2.6 Hz, 1H, H3), 7.15 (d, *J* = 8.4 Hz, 1H, H6), 6.95 (dd, *J* = 8.4, 2.6 Hz, 1H, H5), 6.88 (s, 1H, H6′), 6.55 (s, 1H, H3′), 6.30 (d, *J* = 16.0 Hz, 1H, H2), 4.80 (s, 1H, NH or OH), 4.18 (q, *J* = 7.0 Hz, 2H, COO*CH*$_2$CH$_3$), 4.09 (t, *J* = 5.6 Hz, 2H, ArOCH$_2$), 3.30 −3.40 (m, 2H, *CH*$_2$NHBoc), 1.9–2.1 (m, 14 H, 3 × AdCH + ArCH$_3$ + 3 × AdCH$_2$ + OCH$_2$*CH*$_2$CH$_2$N), 1.76 (br, 6H, 2 × AdCH$_2$), 1.46 (s, 9H, C(CH$_3$)$_3$), 1.27 (t, *J* = 7.0 Hz, 3H, COOCH$_2$*CH*$_3$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): *δ* 166.9 (s), 157.8 (s), 156.0 (s), 153.8 (s), 143.5 (d), 136.0 (s), 134.8 (s), 134.3 (s), 133.5 (s), 132.1 (d), 131.3 (s), 129.4 (d), 118.8 (d), 118.3 (d), 116.4 (d), 111.1 (d), 79.4 (s, *C*(CH$_3$)$_3$), 65.9 (t, OCH$_2$), 60.3 (q, COO*C*H$_2$CH$_3$), 40.7 (t, 3 × AdCH$_2$), 38.0 (t, CH$_2$N), 37.1 (t, 3 × AdCH$_2$), 36.4 (s, AdC), 29.6 (t, CH$_2$*C*H$_2$CH$_2$N), 29.0 (d, 3 × AdCH or 3 × C(*C*H$_3$)$_3$), 28.4 (q or d, 3 × C(*C*H$_3$)$_3$ or 3 × AdCH), 19.4 (q, ArCH$_3$), 14.3 (q, COOCH$_2$*C*H$_3$) ppm. IR (NaCl): *ν* 3315 (m, N–H), 3400-3100 (br, O–H), 2976 (m, C–H), 2903 (m, C–H), 2849 (m, C–H), 1700 (s, C=O), 1683 (s, C=O), 1537 (m), 1395 (m), 1366 (m), 1315 (m), 1272 (m), 1227 (s), 1170 (s), 1040 (m), 858 (m), 727 (s) cm^{-1}. MS (EI): *m*/*z* (%) 589 (M$^+$, 86), 534 (10), 533 (30), 516 (32), 515 (84), 490 (13), 489 (39), 444 (13), 433 (25), 432 (79), 427 (10), 344 (21), 287 (13), 136 (12), 135 (100), 102 (86), 93 (12). HRMS (EI): calcd for $C_{36}H_{47}NO_6$, 589.3403; found, 589.3401.

5.7.5. Ethyl (*E*)-3-[4-acetoxy-(2-(3-acetamidopropoxy)-5-(adamant-1-yl)-2-methylbiphenyl-4-yl]acrylate (19b)

To a mixture of **18b** (0.16 g, 0.28 mmol) in EtOH (4.6 mL) was added concentrated HCl (0.46 mL). This mixture was heated at 85 °C for 1 h and then concentrated. The residue containing the primary amine was sequentially treated with CH_2Cl_2 (9.2 mL), pyridine (0.49 mL, 6.07 mmol) and Ac_2O (0.07 mL, 0.72 mmol) and stirred overnight at room temperature before addition of H_2O and extraction with EtOAc (3×), followed by washing with H_2O, brine and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was crystallized from CH_2Cl_2/MeOH/hexane afford the corresponding acid **19b** (0.06 g, 37%) as white solid (mp 215 °C, CH_2Cl_2/MeOH/hexane). ^{1}H NMR (400.13 MHz, CD_3OD): *δ* 7.41 (d, *J* = 16.0 Hz, 1H, H3), 7.27 (d, *J* = 2.4 Hz, 1H, H3′), 7.11 (d, *J* = 8.6 Hz, 1H, H6′), 7.00 (dd, *J* = 8.6, 2.4 Hz, 1H, H5′), 6.75 (s, 1H, H6′), 6.62 (s, 1H, H3′), 6.34 (d, *J* = 16.0 Hz, 1H, H2), 4.14 (q, *J* = 7.1 Hz, 2H, COO*CH*$_2$CH$_3$), 4.09 (t, *J* = 5.5 Hz, 2H, ArOCH$_2$), 3.38 (t, *J* = 6.7 Hz, 2H, *CH*$_2$NHAc), 2.12–2.14 (m, 9H, 3 × AdCH$_2$ + Ac), 1.9–2.0 (m, 11H, 3 × AdCH + ArCH$_3$ + Ac + OCH$_2$*CH*$_2$CH$_2$N), 1.77 (br, 6H, 3 × AdCH$_2$), 1.24 (t, *J* = 7.1 Hz, 3H, COOCH$_2$*CH*$_3$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): *δ* 173.5 (s), 168.8 (s), 160.0 (s), 145.3 (d), 137.9 (s), 135.5 (s), 135.3 (s), 134.1 (s), 133.3 (d), 131.2 (s), 130.0 (d), 119.3 (d), 118.8 (d), 117.9 (d), 112.2 (d), 66.8 (t, ArO*C*H$_2$), 61.6 (t, COO*C*H$_2$CH$_3$), 41.8 (t, 3 × AdCH$_2$), 38.3 (t, *C*H$_2$NHAc), 37.6 (t, 3 × AdCH$_2$), 37.7 (s, AdC), 30.7 (q, 2x Ac +NAc), 30.3 (t, OCH$_2$*C*H$_2$CH$_2$NHAc), 22.6 (d, 3 × AdCH), 19.8 (q, ArCH$_3$), 14.7

(q, $COOCH_2CH_3$) ppm. IR (NaCl): *ν* 3392 (m, N–H), 2975 (m, C–H), 2900 (s, C–H), 1746 (m, C=O), 1701 (s, C=O), 1650 (s, C=O), 1556 (s), 1540 (s), 1521 (s), 1493 (s), 1399 (s), 1234 (s), 1178 (s), 730 (s) cm^{-1}. MS (EI): *m*/*z* (%) 531 (18), 100 (100). HRMS (EI): calcd for $C_{35}H_{43}NO_6$, 573.3090; found, 573.3106.

5.7.6. (*E*)-3-[2-(3-Acetamidopropoxy)-3-(adamant-1-yl)-4-hydroxybiphenyl-4-yl]acrylic acid (2c)[11]

To a stirred suspension of compound **19a** (0.013 g, 0.023 mmol) in MeOH was treated with Na_2CO_3 (0.12 mL, 2 M in H_2O, 0.24 mmol). The mixture was stirred at 70 °C for 3 h, cooled down to room temperature, acidified (10% HCl), and extracted with EtOAc. The combined organic extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The residue was purified by crystallization (CH_2Cl_2/hexane) to afford 0.006 g (53%) of a white solid (mp: 215 °C) identified as **2c**.[11]

5.7.7. (*E*)-3-[2-(3-Acetamidopropoxy)-5-(adamant-1-yl)-4-hydroxy-2-methylbiphenyl-4-yl]acrylic acid (5c)

To a stirred suspension of compound **19b** (0.03 g, 0.05 mmol) in MeOH was treated with Na_2CO_3 (0.52 mL, 2 M in H_2O, 1.05 mmol). The mixture was stirred at 70 °C for 3 h, cooled down to room temperature, acidified (10% HCl), and extracted with EtOAc. The combined organic extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on silica gel (90:10 CH_2Cl_2/MeOH), to afford 0.015 g (57%) of a white solid identified as **5c**. ^{1}H NMR (400.13 MHz, CD_3OD): *δ* 7.36 (d, *J* = 16.0 Hz, 1H, H3), 7.26 (d, *J* = 2.5 Hz, 1H, H3), 7.06 (d, *J* = 8.5 Hz, 1H, H6), 6.97 (dd, *J* = 8.5, 2.5 Hz, 1H, H5), 6.75 (s, 1H, H6″), 6.60 (s, 1H, H3″), 6.34 (d, *J* = 16.0 Hz, 1H, H2), 4.08 (t, *J* = 6.1 Hz, 2H, $ArOCH_2$), 3.38 (t, *J* = 6.8 Hz, 2H, CH_2NHAc), 2.11 (s, 6H, 3 × $AdCH_2$), 1.8–2.0 (m, 5H, Ac or 3 × AdCH or $ArCH_3$ + -$ArOCH_2CH_2$), 1.94 (s, 3H, $ArCH_3$ or Ac or 3 × AdCH), 1.89 (s, 3H, 3 × AdCH or $ArCH_3$ or Ac), 1.76 (br, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): *δ* 172.0 (s, 2×), 158.0 (s), 155.4 (s), 143.2 (d), 136.3 (s), 134.2 (s), 134.0 (s), 133.4 (s), 131.8 (d), 129.9 (d), 128.3 (d, 2×), 117.3 (d), 116.1 (d), 110.7 (d), 65.4 (t, OCH_2), 40.3 (t, 3 × $AdCH_2$), 36.9 (t, 3 × $AdCH_2$), 36.2 (t, CH_2N), 36.1 (s, AdC), 29.2 (d, 3 × AdCH), 28.8 (t, OCH_2CH_2), 21.2 (q, $COCH_3$), 18.3 (q, $ArCH_3$). IR (NaCl): *ν* 3388 (m, NH), 3100-2950 (br, O–H), 2972 (s, C–H), 2902 (s, C–H), 1699 (s, C=O), 1650 (s, C=O), 1555 (s), 1539 (s), 1521 (s), 1512 (s), 1493 (s), 1455 (m), 1393 (m), 1051 (m) cm^{-1}. MS (EI): *m*/*z* (%) 503 ([M^+], 13), 135 (8), 101 (9), 100 ([$M-C_5H_{10}ON]^+$, 100). HRMS (EI): calcd for $C_{31}H_{37}NO_5$, 503.2672; found, 503.664.

5.7.8. 5-Bromo-2-[3-adamantan-1-yl-4-(*tert*-butyldimethylsilyloxy)phenyl]thiazole (22a)

Following the general procedure for the Suzuki reaction, 2,5-dibromothiazole **20** (0.70 g, 2.88 mmol) and boronic acid **16a**[11] (1.44 g, 3.74 mmol) were heated in benzene at 90 °C for 12 h. The residue was purified by column chromatography (SiO_2, 99:1 hexane/EtOAc), to give **22a** (0.72 g, 50%) as a white powder, mp 150–155 °C (hexane/$CHCl_3$), 0.11 g (5%) of disubstituted thiazole **21a** as a yellow solid, mp 237–238 °C (hexane/$CHCl_3$) and 0.05 g (8%) of starting material. Data for thiazole 22a. ^{1}H NMR (400.13 MHz, $CDCl_3$): *δ* 7.77 (d, *J* = 2.4 Hz, 1H, H2′), 7.66 (s, 1H, H4), 7.53 (dd, *J* = 8.4, 2.4 Hz, 1H, H6′), 6.83 (d, *J* = 8.4 Hz, 1H, H5′), 2.14 (s, 6H, 3 × $AdCH_2$), 2.09 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.37 (s, 6H, $Si(CH_3)_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): *δ* 170.3 (s), 157.0 (s), 144.4 (d), 140.4 (s), 125.7 (s), 125.6 (d), 124.8 (d), 119.4 (d), 106.9 (s), 40.2 (t, 3×), 37.0 (s), 36.9 (t, 3×), 28.9 (q, 3×), 26.4 (d, 3×), 19.0 (s), −3.4 (q, 2×) ppm. IR: *ν* 2905 (m, C–H), 2882 (m, C–H), 2845 (w, C–H), 1597 (w), 1475 (s), 1422 (w), 1272 (s), 1251 (s), 1132 (m), 921 (s), 837 (s), 818 (s), 788 (s), 727 (m) cm^{-1}. MS (ESI^+): *m*/*z* (%) 506 ([M+H]$^+$ [^{81}Br], 25), 504 ([M+H]$^+$ [^{79}Br], 26), 375 (34), 349 (30), 322 (25), 321 (100), 313 (19), 253 (35), 237 (28), 195 (63). HRMS (ESI^+): calcd for $C_{25}H_{35}{}^{81}BrNOSSi$ [M+H]$^+$ 506.1368 and $C_{25}H_{35}{}^{79}BrNOSSi$ [M+H]$^+$ 504.1386; found: 506.1392 and 504.1397. Elem. Anal. calcd for $C_{25}H_{34}BrNOSSi$: C, 59.91; H, 6.79; N, 2.78; found: C, 58.87; H, 6.28; N, 2.78. Data for thiazole **21a**. ^{1}H NMR (400.13 MHz, $CDCl_3$): *δ* 7.86 (s, 1H, ArH), 7.84 (s, 1H, ArH), 7.65 (d, *J* = 8.1 Hz, 1H, ArH), 7.43 (s, 1H, H4), 7.31 (d, *J* = 8.1 Hz, 1H, ArH), 6.84 (app. t, *J* = 7.1, 2H, H5′ + H5″), 2.18 (s, 6H, 3 × $AdCH_2$), 2.16 (s, 6H, 3 × $AdCH_2$), 2.11 (s, 6H, 6xAdCH), 1.80 (s, 12H, 6x$AdCH_2$), 1.07 (s, 18H, 2x$SiC(CH_3)_3$), 0.38 (s, 12H, 4 × $Si(CH_3)_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): *δ* 166.8 (s), 156.5 (s), 154.9 (s), 140.2 (s), 140.1 (s), 138.7 (s), 137.6 (d), 126.4 (s), 126.0 (d), 125.6 (d), 124.6 (d), 124.5 (d), 123.9 (s), 119.4 (d), 119.3 (d), 40.3 (t, 3×), 40.2 (t, 3×), 37.0 (t, 3×), 36.9 (s, 2×), 29.0 (d, 6×), 26.4 (q, 6×), 19.0 (s, 2×), −3.3 (q, 2×), −3.4 (q, 2×) ppm. IR: *ν* 2902 (m, C–H), 2850 (w, C–H), 1601 (w), 1486 (m), 1447 (w), 1391 (w), 1264 (s), 1122 (w), 920 (s), 866 (s), 837 (s), 815 (s), 788 (s), 742 (m) cm^{-1}. MS (ESI^+): *m*/*z* (%) 766 ([M+H]$^+$, 30), 566 (12), 484 (100), 433 (26), 396 (26), 391 (34), 379 (27), 365 (29), 363 (18), 359 (23), 358 (16), 343 (89), 341 (29), 317 (18), 247 (14). HRMS (ESI^+): calcd for $C_{47}H_{68}NO_2SSi_2$ [M+H]$^+$ 766.4504; found: 766.4500.

5.7.9. 5-Bromo-2-[3-adamantan-1-yl-6-methyl-4-(*tert*-butyldimethylsilyloxy)phenyl]thiazole (22b)

Following the general procedure for the microwave-assisted Suzuki reaction, 2,5-dibromothiazole **20** (0.22 g, 0.90 mmol) and boronic acid **16b**[32] (0.40 g, 1.0 mmol) were heated at 90 °C for 10 min. The residue was purified by column chromatography (SiO_2, 99:1 hexane/EtOAc), to give 0.27 g of a yellow oil (a mixture of mono- and disubstituted thiazole derivatives), which was used in the next step without further purification.

5.7.10. 2-(Adamantan-1-yl)-4-(5-bromothiazol-2-yl)phenol (23a)

In accordance with the general procedure for the cleavage of silyl ethers, ether **22a** (0.35 g, 0.69 mmol) gave, after purification by column chromatography (SiO_2, from 80:20 hexane/EtOAc to 100% EtOAc), 0.25 g (91%) of phenol **23a** as a white solid, mp 280–281 °C (hexane/CH_2Cl_3). ^{1}H NMR (400.13 MHz, DMSO-d_6): *δ* 10.02 (s, 1H, OH), 7.85 (s, 1H, H4′), 7.63 (d, *J* = 2.1 Hz, 1H, H3), 7.53 (dd, *J* = 2.1, 8.3 Hz, 1H, H5), 6.87 (d, *J* = 8.3 Hz, 1H, H6), 2.09 (s, 6H, 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.73 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): *δ* 169.6 (s), 158.7 (s), 144.6 (d), 136.2 (s), 125.0 (d), 124.2 (d), 123.5 (s), 116.9 (d), 106.1 (s), 39.5 (t, 3×), 36.4 (t, 3×), 36.2 (s), 28.2 (d, 3×) ppm. IR: *ν* 3500-3300 (br, O–H), 2898 (m, C–H), 2847 (m, C–H), 1595 (m), 1489 (m), 1412 (m), 1375 (m), 1271 (m), 1244 (s), 1125 (m), 999 (w), 816 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 392 ([M+H]$^+$ [^{81}Br], 100), 390 ([M+H]$^+$ [^{79}Br], 94), 349 (31), 321 (89), 279 (29), 253 (58). HRMS (ESI^+): calcd for $C_{19}H_{21}{}^{81}BrNOS$ [M+H]$^+$ 392.0502 and $C_{19}H_{21}{}^{79}BrNOS$ [M+H]$^+$, 390.0522; found: 392.0484 and 390.0508.

5.7.11. 2-(Adamantan-1-yl)-4-(5-bromothiazol-2-yl)-5-methylphenol (23b)

In accordance with the general procedure for the cleavage of silyl ethers, the mixture obtained above gave, after purification by column chromatography (SiO_2, from 80:20 hexane/EtOAc to 100% EtOAc), 0.11 g (30%, two steps) of phenol **23b** as a white solid, mp 237–238 °C (hexane/CH_2Cl_2), and the disubstituted thiazole **21b** (0.03 g, 5% two steps) as a white solid, mp 237–238 °C. Data for **23b**: ^{1}H NMR (400.13 MHz, DMSO-d_6): *δ* 9.86 (s, 1H, OH), 7.91 (s, 1H, H4′), 7.44 (s, 1H, H3), 6.71 (s, 1H, H6), 2.40 (s, 3H, $ArCH_3$), 2.05 (s, 6H, 3 × $AdCH_2$), 2.02 (s, 3H, 3 × AdCH), 1.71 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): *δ*

169.3 (s), 157.7 (s), 144.1 (d), 134.5 (s), 133.9 (s), 127.8 (d), 122.7 (s), 119.2 (d), 106.9 (s), 39.8 (t, 3×), 36.5 (t, 3×), 35.9 (s), 28.3 (d, 3×), 20.7 (q) ppm. IR: *ν* 3500–3300 (br, O–H), 2900 (s, C–H), 2843 (m, C–H), 1606 (m), 1494 (m), 1444 (m), 1392 (s), 1244 (s), 1120 (s), 999 (m), 845 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 406 ($[M+H]^+$ [^{81}Br], 92), 404 ($[M+H]^+$ [^{79}Br], 100), 363 (16), 359 (8), 321 (9), 319 (66), 309 (9), 241 (11), 210 (13), 192 (7). HRMS (ESI^+): calcd for $C_{20}H_{23}{}^{81}BrNOS$ $[M+H]^+$ 406.0657 and $C_{20}H_{23}{}^{79}BrNOS$ $[M+H]^+$, 404.06782; found: 406.0655 and 404.0675. Data for thiazole **21b**. ^1H NMR (400.13 MHz, DMSO-d_6): δ 9.81 (s, 1H, OH), 9.61 (s, 1H, OH), 7.83 (s, 1H, H4), 7.62 (s, 1H), 7.18 (s, 1H), 6.82 (s, 2H; H5′ + H5″), 2.60 (s, 9H, 3 × $AdCH_2$ + $ArCH_3$), 2.57 (s, 3H, $ArCH_3$), 2.37 (s, 3H, 3 × AdCH), 2.2–2.1 (m, 6H, 3 × $AdCH_2$), 2.12 (s, 3H, 3 × AdCH), 1.81 (s, 12H, 6x$AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 166.2 (s), 157.0 (s), 156.1 (s), 140.1 (d), 137.0 (s), 134.2 (s), 133.9 (s), 133.7 (s), 133.6 (s), 128.4 (d), 127.8 (d), 123.3 (s), 120.4 (s), 119.2 (d), 118.6 (d), 39.9 (t, 3×), 39.8 (t, 3×), 36.6 (t, 3×), 35.9 (s), 35.8 (s), 28.3 (d, 6×), 20.9 (q), 20.2 (q) ppm. IR: *ν* 3500–3000 (br, O–H), 2900 (s, C–H), 2848 (m, C–H), 1602 (w), 1562 (w), 1494 (w), 1449 (w), 1393 (s), 1239 (s), 1120 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 566 ($[M+H]^+$, 100), 363 (8), 186 (13). HRMS (ESI^+): calcd for $C_{37}H_{44}NO_2S$ $[M+H]^+$ 566.3087; found: 566.3083.

5.7.12. 5-Bromo-2-[3-adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]phenyl]thiazole (23c)

According to the general procedure for the protection of phenols with MEMCl, **23a** (0.09 g, 0.23 mmol) gave, after purification by column chromatography (SiO_2, 85:15 hexane/EtOAc), compound **23c** (0.10 g, 88%) as a white solid, mp 125–126 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.78 (d, *J* = 2.3 Hz, 1H, H2′), 7.67 (s, 1H, H4), 7.61 (dd, *J* = 8.6, 2.3 Hz, 1H, H6′), 7.20 (d, *J* = 8.6 Hz, 1H, H5′), 5.37 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 2.13 (s, 6H, 3 × $AdCH_2$), 2.09 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$).ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.1 (s), 158.3 (s), 144.5 (d), 139.3 (s), 126.6 (s), 125.2 (d), 125.0 (d), 114.8 (d), 107.2 (s), 93.2 (t), 71.5 (t), 68.0 (t), 59.1 (q), 40.5 (t, 3×), 37.2 (s), 37.0 (t, 3×), 28.9 (d, 3×) ppm. IR: *ν* 2898 (m, C–H), 2849 (w, C–H), 1597 (w), 1472 (m), 1223 (m), 1096 (s), 980 (s), 846 (m), 814 (m) cm^{-1}. MS (ESI^+): *m*/*z* (%) 480 ($[M+H]^+$ [^{81}Br], 100), 478 ($[M+H]^+$ [^{79}Br], 99), 402 (7), 401 (10), 400 (41), 324 (4). HRMS (ESI^+): calcd for $C_{23}H_{29}{}^{81}BrNO_3S$ $[M+H]^+$ 480.1025, and $C_{23}H_{29}{}^{79}BrNO_3S$ 478.1046; found: 480.1020 and 478.1039.

5.7.13. 5-Bromo-2-[5-adamantan-1-yl-4-[(2-methoxy ethoxy)methoxy]-2-methylphenyl]thiazole (23d)

According to the general procedure for the protection of phenols with MEMCl, **23b** (0.04 g, 0.10 mmol) gave, after purification by column chromatography (SiO_2, 85:15 hexane/EtOAc), compound **23d** (0.03 g, 66%) as a colorless oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.73 (s, 1H, H6′), 7.55 (s, 1H, H4), 7.05 (s, 1H, H3′), 5.36 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 2.51 (s, 3H, $ArCH_3$), 2.10 (s, 6H, 3 × $AdCH_2$), 2.07 (s, 3H, 3 × AdCH), 1.77 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.7 (s), 157.3 (s), 143.8 (d), 136.5 (s), 135.3 (s), 128.5 (d), 125.7 (s), 117.2 (d), 108.0 (s), 93.1 (t), 71.5 (t), 67.9 (t), 59.0 (q), 40.6 (t, 3×), 37.0 (t, 3×), 36.8 (s), 28.9 (d, 3×), 21.0 (q) ppm. IR: *ν* 2900 (s, C–H), 2847 (m, C–H), 1604 (w), 1490 (m), 1450 (m), 1360 (m), 1242 (m), 1220 (m), 1097 (s), 1015 (s), 990 (s), 923 (m), 847 (m) cm^{-1}. MS (ESI^+): *m*/*z* (%) 494 ($[M+H]^+$ [^{81}Br], 100), 492 ($[M+H]^+$ [^{79}Br], 94), 418 (5), 416 (5). HRMS (ESI^+): calcd for $C_{24}H_{31}{}^{81}BrNO_3S$ $[M+H]^+$ 494.1182, and $C_{24}H_{31}{}^{79}BrNO_3S$ $[M+H]^+$ 492.1189; found: 494.1178 and 492.1199.

5.7.14. Methyl (*E*)-3-[2-(3-adamantan-1-yl-4-hydroxyphenyl) thiazol-5-yl]acrylate (24a)

Following the general procedure for the Heck reaction with methyl acrylate, bromide **23a** (0.09 g, 0.24 mmol) gave, after purification by column chromatography (SiO_2, 80:20 hexane/EtOAc), 0.06 g (68%) of ester **24a** as a yellow solid, mp 240–241 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, CD_3OD): δ 7.95 (s, 1H, H4′), 7.86 (d, *J* = 15.6 Hz, 1H, H3), 7.78 (d, *J* = 2.3 Hz, 1H, H2″), 7.63 (dd, *J* = 8.4, 2.3 Hz, 1H, H6″), 6.81 (d, *J* = 8.4 Hz, 1H, H5″), 6.26 (d, *J* = 15.6 Hz, 1H, H2), 3.78 (s, 3H, OCH_3), 2.20 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.83 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ 173.4 (s), 168.6 (s), 161.2 (s), 148.3 (d), 138.6 (s), 135.8 (d), 134.8 (s), 127.1 (d), 127.0 (d), 125.5 (s), 119.8 (d), 118.0 (d), 52.4 (q), 41.5 (t, 3×), 38.3 (t, 3×), 38.2 (s), 30.7 (d, 3×) ppm. IR: *ν* 2901 (m, C–H), 2877 (m, C–H), 2847 (m, C–H), 1720 (s, C=O), 1624 (m), 1600 (m), 1433 (m), 1359 (s), 1331 (m), 1269 (s), 1235 (s), 1167 (s), 1151 (s), 1120 (s), 959 (m), 819 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 396 ($[M+H]^+$, 100), 349 (6), 321 (8), 253 (6), 203 (7), 201 (8). HRMS (ESI^+): calcd for $C_{23}H_{26}NO_3S$ $[M+H]^+$ 396.1628; found: 396.1623.

5.7.15. Methyl (*E*)-3-[2-(5-adamantan-1-yl-4-hydroxy-2-methylphenyl)thiazol-5-yl]acrylate (24b)

Following the general procedure for the Heck reaction with methyl acrylate, bromide **23b** (0.10 g, 0.25 mmol) gave, after purification by column chromatography (SiO_2, 80:20 hexane/EtOAc), 0.06 g (56%) of ester **24b** as a yellow solid, mp 200–201 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.93 (s, 1H, H4′), 7.82 (d, *J* = 15.6 Hz, 1H, H3), 7.63 (s, 1H, H6″), 6.52 (s, 1H, H3″), 6.38 (s, 1H, OH), 6.22 (d, *J* = 15.6 Hz, 1H, H2), 3.82 (s, 3H, OCH_3), 2.44 (s, 3H, $ArCH_3$), 2.11 (s, 6H, 3 × $AdCH_2$), 2.07 (s, 3H, 3 × AdCH), 1.76 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.9 (s), 167.0 (s), 156.6 (s), 146.1 (d), 135.7 (s), 134.7 (s), 134.5 (d), 134.1 (s), 129.5 (d), 124.4 (s), 119.8 (d), 118.9 (d), 51.9 (q), 40.4 (t, 3×), 36.9 (t, 3×), 36.4 (s), 28.9 (d, 3×), 20.9 (q) ppm. IR: *ν* 3500–3200 (br, O–H), 2902 (m, C–H), 2847 (m, C–H), 1693 (s, C=O), 1622 (s), 1606 (m), 1453 (m), 1435 (m), 1383 (s), 1331 (s), 1175 (s), 1126 (m), 953 (s), 842 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 410 ($[M+H]^+$, 100), 210 (3), 143 (7). HRMS (ESI^+): calcd for $C_{24}H_{28}NO_3S$ $[M+H]^+$ 410.1784; found: 410.1779.

5.7.16. Methyl (*E*)-3-[2-(3-adamantan-1-yl-4-[(2-methoxy ethoxy)methoxy]phenyl)thiazol-5-yl]acrylate (24c)

According to the general procedure for the protection of the phenols with MEMCl, phenol **24a** (0.05 g, 0.13 mmol) gave, after purification by column chromatography (SiO_2, 80:20 hexane/EtOAc), compound **24c** (0.05 g, 70%) as a yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ 7.88 (s, 2H, H4′ + H2″), 7.79 (d, *J* = 15.6 Hz, 1H, H3), 7.72 (dd, *J* = 8.6, 2.2 Hz, 1H, H6″), 7.21 (d, *J* = 8.6 Hz, 1H, H5″), 6.19 (d, *J* = 15.6 Hz, 1H, H2), 5.38 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.6–3.5 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 2.15 (s, 6H, 3 × $AdCH_2$), 2.10 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.6 (s), 166.8 (s), 158.8 (s), 147.0 (d), 139.3 (s), 134.4 (d), 133.7 (s), 126.5 (s), 125.9 (d), 125.7 (d), 118.9 (d), 114.9 (d), 93.2 (t), 71.5 (t), 68.1 (t), 59.1 (q), 51.8 (q), 40.5 (t, 3×), 37.2 (s), 37.0 (t, 3×), 29.0 (d, 3×) ppm. IR: *ν* 2903 (s, C–H), 2849 (m, C–H), 1716 (s, C=O), 1623 (s), 1493 (w), 1424 (m), 1327 (m), 1224 (s), 1164 (s), 1102 (m), 982 (s) cm^{-1}. MS (ESI^+): *m*/*z* (%) 484 ($[M+H]^+$, 100), 321 (5). HRMS (ESI^+): calcd for $C_{27}H_{34}NO_5S$ $[M+H]^+$ 484.2152; found: 484.2136.

5.7.17. Methyl (*E*)-3-[2-(5-adamantan-1-yl-4-[(2-methoxy ethoxy)methoxy]-2-methylphenyl)thiazol-5-yl]acrylate (24d)

According to the general procedure for the protection of the phenols with MEMCl, phenol **24b** (0.03 g, 0.08 mmol) gave, after purification by column chromatography (SiO_2, 80:20

hexane/EtOAc), compound **24d** (0.03 g, 78%) as a yellow oil. ^{1}H NMR (400.13 MHz, $CDCl_3$) δ 7.93 (s, 1H, H4′), 7.81 (d, J = 15.6 Hz, 1H, H3), 7.69 (s, 1H, H6″), 7.06 (s, 1H, H3″), 6.21 (d, J = 15.6 Hz, 1H, H2), 5.37 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.6–3.5 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 2.58 (s, 3H, $ArCH_3$), 2.11 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × Ad), 1.77 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 170.3 (s), 166.8 (s), 157.6 (s), 146.3 (d), 136.6 (s), 135.9 (s), 134.4 (d), 134.2 (s), 128.9 (d), 125.6 (s), 118.9 (d), 117.3 (d), 93.0 (t), 71.5 (t), 68.0 (t), 59.0 (q), 51.8 (q), 40.6 (t, 3×), 37.0 (t, 3×), 36.8 (s), 28.9 (d, 3×), 21.4 (q) ppm. IR: ν 2902 (s, C–H), 2848 (m, C–H), 1718 (s, C=O), 1624 (s), 1503 (m), 1447 (m), 1432 (m), 1327 (m), 1217 (s), 1160 (s), 1122 (m), 1098 (m), 1016 (s), 989 (s), 847 (m), 752 (s) cm^{-1}.

5.7.18. (*E*)-3-[2-(3-Adamantan-1yl-4-hydroxyphenyl)thiazol-5-yl]acrylic acid (7a)

In accordance with the general procedure for the hydrolysis of esters, ester **24a** (0.01 g, 0.04 mmol) gave, after crystallization, 0.01 g (95%) of acid **7a** as a yellow solid, mp 284 °C (dec) (hexane/CH_2Cl_2). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 10.16 (s, 1H, OH), 8.11 (s, 1H, H4′), 7.78 (d, J = 15.6 Hz, 1H, H3), 7.72 (s, 1H, H2″), 7.63 (d, J = 7.6 Hz, 1H, H6″), 6.90 (d, J = 7.6 Hz, 1H, H5″), 6.16 (d, J = 15.6 Hz, 1H, H2), 3.4–3.2 (br, OH) 2.10 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.74 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 169.8 (s), 167.0 (s), 159.2 (s), 147.5 (d), 136.3 (s), 133.8 (d), 133.0 (s), 125.6 (d), 125.0 (d), 123.7 (s), 120.1 (d), 117.0 (d), 39.6 (t, 3×), 36.5 (t, 3×), 36.3 (s), 28.3 (d, 3×) ppm. IR: ν 3500–3000 (s, O–H), 2900 (m, C–H), 2848 (w, C–H), 1682 (m, C=O), 1619 (s), 1599 (s), 1385 (s), 1322 (m), 1251 (s), 1179 (s), 1149 (s), 1120 (s), 963 (s), 823 (s) cm^{-1}. MS (ESI$^+$): m/z (%) 382 ([M+H]$^+$, 100), 375 (20), 321 (27), 253 (53). HRMS (ESI$^+$): calcd for $C_{22}H_{24}NO_3S$ [M+H]$^+$ 382.1471; found: 382.1464. Elem. Anal. Calcd for $C_{22}H_{23}NO_3S$ ½[$(CH_3)_2SO$] C, 65.69; H, 6.32; N, 3.33; found: C, 65.73; H, 5.78; N, 2.94.

5.7.19. (*E*)-3-[2-(5-Adamantan-1-yl-4-hydroxy-2-methylphenyl) thiazol-5-yl]acrylic acid (7b)

In accordance with the general procedure for the hydrolysis of esters, ester **24b** (0.03 g, 0.07 mmol) gave, after crystallization, 0.02 g (76%) of acid **7b** as a yellow solid, mp 164–165 °C (hexane/CH_2Cl_2). ^{1}H NMR (400.13 MHz, CD_3OD): δ 7.96 (s, 1H, H4′), 7.82 (d, J = 15.6 Hz, 1H, H3), 7.53 (s, 1H, H6″), 6.65 (s, 1H, H3″), 6.21 (d, J = 15.6 Hz, 1H, H2), 2.46 (s, 3H, $ArCH_3$), 2.14 (s, 6H, 3 × $AdCH_2$), 2.04 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ 172.9 (s), 169.7 (s), 159.8 (s), 147.3 (d), 136.9 (s), 136.0 (s), 135.8 (d), 135.5 (s), 130.2 (d), 124.6 (s), 120.9 (d), 120.4 (d), 41.6 (t, 3×), 38.3 (t, 3×), 37.8 (s), 30.7 (d, 3×), 21.4 (q) ppm. IR: ν 3500–3000 (s, O–H), 2901 (s, C–H), 2848 (w, C–H), 1684 (s, C=O), 1606 (s), 1449 (m), 1382 (s), 1361 (m), 1222 (s), 1159 (s), 1125 (s), 964 (m), 851 (m), 754 (s) cm^{-1}. MS (ESI$^+$): m/z (%) 396 ([M+H]$^+$, 100), 326 (4), 148 (5), 143 (4). HRMS (ESI$^+$): calcd for $C_{23}H_{26}NO_3S$ [M+H]$^+$ 369.1628; found: 396.1624. Elem. Anal. Calcd for $C_{23}H_{25}NO_3S$ C, 69.84; H, 6.37; N, 3.54; found: C, 69.52; H, 6.15; N, 3.37.

5.7.20. (*E*)-3-[2-(3-Adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]phenyl)thiazol-5-yl]acrylic acid (7c)

In accordance with the general procedure for the hydrolysis of esters, ester **24c** (0.05 g, 0.10 mmol) gave, after crystallization, 0.04 g (91%) of acid **7c** as a yellow solid, mp 232–233 °C (hexane/CH_2Cl_2). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.93 (s, 1H, H4′), 7.9–7.8 (m, 2H, H3 + H2″), 7.74 (d, J = 8.4 Hz, 1H, H6″), 7.22 (d, J = 8.4 Hz, 1H, H5″), 6.19 (d, J = 15.5 Hz, 1H, H2), 5.39 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 2.15 (s, 6H, 3 × $AdCH_2$), 2.10 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.3 (s), 170.3 (s), 158.9 (s), 147.7 (d), 139.3 (s), 136.4 (d), 133.4 (s), 126.3 (s), 126.0 (d), 125.8 (d), 118.0 (d), 114.9 (d), 93.1 (t), 71.5 (t), 68.1 (t), 59.1 (q), 40.5 (t, 3×), 37.2 (s), 37.0 (t, 3×), 28.9 (d, 3×) ppm. IR: ν 2901 (s, C–H), 2848 (m, C–H), 1699 (s, C=O), 1616 (m), 1497 (m), 1271 (m), 1222 (s), 1147 (s), 1101 (s), 987 (s), 855 (m) cm^{-1}. MS (ESI$^+$): m/z (%) 470 ([M+H]$^+$, 100). HRMS (ESI$^+$): calcd for $C_{26}H_{32}NO_5S$ [M+H]$^+$ 470.1996; found: 470.1991. Elem. Anal. Calcd for $C_{26}H_{31}NO_5S$ ½H_2O C, 65.25; H, 6.74; N, 2.93; found: C, 65.55; H, 6.29; N, 2.69.

5.7.21. (*E*)-3-[2-(5-Adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]-2-methylphenyl)thiazol-5-yl]acrylic acid (7d)

In accordance with the general procedure for the hydrolysis of esters, ester **24d** (0.03 g, 0.06 mmol) gave, after crystallization, 0.02 g (92%) of acid **7d** as a yellow solid, mp 169–170 °C (hexane/CH_2Cl_2). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 7.99 (s, 1H, H4′), 7.90 (d, J = 15.6 Hz, 1H, H3), 7.70 (s, 1H, H6″), 7.07 (s, 1H, H3″), 6.22 (d, J = 15.6 Hz, 1H, H2), 5.38 (s, 2H, OCH_2O), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.42 (s, 3H, OCH_3), 2.57 (s, 3H, $ArCH_3$), 2.12 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 171.1 (s), 171.0 (s), 157.7 (s), 146.8 (d), 136.7 (s), 136.3 (d), 136.0 (s), 134.0 (s), 129.0 (d), 125.4 (s), 118.5 (d), 117.4 (d), 93.1 (t), 71.5 (t), 68.0 (t), 59.0 (q), 40.6 (t, 3×), 37.0 (t, 3×), 36.8 (s), 29.0 (d, 3×), 21.5 (q) ppm. IR: ν 2900 (s, C–H), 2850 (m, C–H), 1689 (s, C=O), 1618 (s), 1323 (m), 1268 (m), 1220 (s), 1100 (s), 1017 (s), 993 (s), 963 (m), 847 (m) cm^{-1}. MS (ESI$^+$): m/z (%) 484 ([M+H]$^+$, 100), 408 (4). HRMS (ESI$^+$): calcd for $C_{27}H_{34}NO_5S$ [M+H]$^+$ 484.2152; found: 484.2143. Elem. Anal. calcd for $C_{27}H_{33}NO_5S$: C, 67.05; H, 6.88; N, 2.90; found: C, 66.91; H, 6.48; N, 2.84.

5.7.22. Methyl 4-[2-(3-adamantan-1-yl-4-hydroxyphenyl) thiazol-5-yl]benzoate (25a)

Following the general procedure for the microwave-assisted Suzuki reaction, bromothiazole **23a** (0.02 g, 0.05 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.01 g, 0.08 mmol) were heated at 120 °C for 10 min. The residue was purified by column chromatography (SiO_2, 70:30 hexane/EtOAc), to give **25a** (0.02 g, 78%) as a yellow solid, mp >300 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 10.06 (s, 1H, OH), 8.36 (s, 1H, H4′), 8.00 (s, 2H, H2 + H6), 7.84 (s, 2H, H3 + H5), 7.73 (s, 1H, H2″), 7.64 (d, J = 7.1 Hz, 1H, H6″), 6.90 (d, J = 7.1, 1H, H5″), 3.87 (s, 3H, OCH_3), 2.12 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.74 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 168.4 (s), 165.7 (s), 158.8 (s), 141.2 (d), 136.3 (s), 135.6 (s), 135.5 (s), 130.1 (d, 2×), 128.6 (s), 126.1 (d, 2×), 125.2 (d), 124.7 (d), 123.9 (s), 117.0 (d), 52.2 (q), 36.5 (t, 3×), 36.3 (t, 3×), 28.3 (d, 3×) ppm. IR: ν 3600–3000 (br, O–H), 2900 (m, C–H), 2878 (m, C–H), 1701 (s, C=O), 1601 (s), 1392 (s), 1287 (s), 1271 (s), 1183 (s), 1111 (m), 1005 (s), 824 (s), 767 (s) cm^{-1}. MS (ESI$^+$): m/z (%) 446 ([M+H]$^+$, 100), 210 (9), 192 (9). HRMS (ESI$^+$): calcd for $C_{27}H_{28}NO_3S$ [M+H]$^+$ 446.1784; found: 446.1782. Elem. Anal. Calcd for $C_{27}H_{27}NO_3S$ C, 67.05; H, 6.88; N, 2.90; found: C, 66.91; H, 6.48; N, 2.84.

5.7.23. Methyl 4-[2-(5-adamantan-1-yl-4-hydroxy-2-methylphenyl)thiazol-5-yl]benzoate (25b)

Following the general procedure for the microwave-assisted Suzuki reaction, bromothiazole **23b** (0.04 g, 0.10 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.03 g, 0.15 mmol) were heated at 120 °C for 10 min. The residue was purified by column chromatography (SiO_2, 70:30 hexane/EtOAc), to give **25b** (0.02 g, 53%) as a yellow solid, mp 210–215 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.88 (s, 1H, OH), 8.39 (s, 1H, H4′), 7.99 (d, J = 8.4 Hz, 2H, H2 + H6), 7.83 (d, J = 8.4 Hz, 2H, H3 + H5), 7.60 (s, 1H, H6″), 6.75 (s, 1H, H3″), 3.87 (s, 3H, OCH_3), 2.51 (s, 3H,

$ArCH_3$), 2.09 (s, 6H, 3 × $AdCH_2$), 2.04 (s, 3H, 3 × AdCH), 1.73 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 168.3 (s), 165.7 (s), 157.7 (s), 140.6 (d), 136.0 (s), 135.6 (s), 134.7 (s), 133.9 (s), 130.0 (d, 2×), 128.6 (s), 128.1 (d), 126.2 (d, 2×), 122.9 (s), 119.4 (d), 52.2 (q), 39.9 (t, 3×), 36.6 (t, 3×), 35.9 (s), 28.4 (d, 3×), 21.1 (q) ppm. IR: ν 3300–3000 (br, O–H), 2902 (m, C–H), 2881 (m, C–H), 1708 (s, C=O), 1603 (m), 1435 (m), 1402 (m), 1278 (s), 1248 (m), 1183 (m), 1107 (m), 1021 (s), 1001 (s), 765 (s) cm^{-1}. MS (ESI^+): m/z (%) 460 ($[M+H]^+$, 100), 397 (14), 379 (18), 359 (16), 327 (16), 326 (55), 319 (33). HRMS (ESI^+): calcd for $C_{28}H_{30}NO_3S$ $[M+H]^+$ 460.1941; found: 460.1937.

5.7.24. Methyl 4-[2-(3-adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]phenyl)thiazol-5-yl]benzoate (25c)

Following the general procedure for the microwave-assisted Suzuki reaction, bromothiazole **23c** (0.03 g, 0.06 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.02 g, 0.09 mmol) were heated at 120 °C for 10 min. The residue was purified by column chromatography (SiO_2, 75:25 hexane/EtOAc), to give **25c** (0.02 g, 61%) as a yellow solid, mp 157–158 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.07 (s, 1H, H4′), 8.06 (d, J = 8.2 Hz, 2H, H2 + H6), 7.89 (d, J = 1.8 Hz, 1H, H2″), 7.74 (dd, J = 8.5, 1.8 Hz, 1H, H6″), 7.66 (d, J = 8.2 Hz, 2H, H3 + H5), 7.22 (d, J = 8.5 Hz, 1H, H5″), 5.38 (s, 2H, OCH_2O), 3.94 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 2.16 (s, 6H, 3 × $AdCH_2$), 2.10 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 169.0 (s), 166.5 (s), 158.4 (s), 140.2 (d), 139.2 (s), 136.9 (s), 136.0 (s), 130.4 (d, 2×), 129.3 (s), 126.8 (s), 126.1 (d, 2×), 125.4 (d), 125.3 (d), 114.9 (d), 93.2 (t), 71.5 (t), 68.0 (t), 59.1 (q), 52.2 (q), 40.5 (t, 3×), 37.2 (s), 37.0 (t, 3×), 29.0 (d, 3×) ppm. IR: ν 2874 (m, C–H), 2846 (w, C–H), 1717 (s, C=O), 1603 (m), 1434 (m), 1385 (m), 1275 (s), 1220 (m), 1184 (m), 1106 (s), 1071 (m), 979 (s), 836 (s) cm^{-1}. MS (ESI^+): m/z (%) 534 ($[M+H]^+$, 100). HRMS (ESI^+): calcd for $C_{31}H_{36}NO_5S$ $[M+H]^+$ 534.2309; found: 534.2296.

5.7.25. Methyl 4-[2-(5-adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]-1-methylphenyl)thiazol-5-yl]benzoate (25d)

Following the general procedure for the microwave-assisted Suzuki reaction, bromothiazole **23d** (0.03 g, 0.06 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.02 g, 0.09 mmol) were heated at 120 °C for 10 min. The residue was purified by column chromatography (SiO_2, 80:20 hexane/EtOAc and SiO_2-C_{18}, 5:95 CH_2Cl_2/CH_3CN), to give **25d** (0.02 g, 61%) as a yellow solid, mp 116–117 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.12 (s, 1H, H4′), 8.07 (d, J = 8.6 Hz, 2H, H2 + H6), 7.69 (s, 1H, H6″), 7.67 (d, J = 8.6 Hz, 2H, H3 + H5), 7.08 (s, 1H, H3″), 5.38 (s, 2H, OCH_2O), 3.94 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.42 (s, 3H, OCH_3), 2.60 (s, 3H, $ArCH_3$), 2.13 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 168.6 (s), 166.6 (s), 157.3 (s), 139.6 (d), 137.5 (s), 136.5 (s), 136.0 (s), 135.5 (s), 130.4 (d, 2×), 129.3 (s), 128.7 (d), 126.2 (d, 2×), 125.9 (s), 117.3 (d), 93.1 (t), 71.5 (t), 68.0 (t), 59.1 (q), 52.2 (q), 40.7 (t, 3×), 37.0 (t, 3×), 36.8 (s), 29.0 (d, 3×), 21.3 (q) ppm. IR: ν 2899 (m, C–H), 2848 (w, C–H), 1713 (s, C=O), 1603 (m), 1444 (m), 1271 (s), 1239 (m), 1161 (s), 1110 (s), 1018 (m), 979 (s), 848 (s), 770 (s) cm^{-1}. MS (ESI^+): m/z (%) 548 ($[M+H]^+$, 100). HRMS (ESI^+): calcd for $C_{32}H_{38}NO_5S$ $[M+H]^+$ 548.2465; found: 548.2452.

5.7.26. 4-[2-(3-Adamantan-1-yl-4-hydroxyphenyl)thiazol-5-yl] benzoic acid (8a)

According to the general procedure for the hydrolysis of esters, **25a** (0.01 g, 0.02 mmol) gave, after crystallization, acid **8a** (0.09 g, 99%) as a yellow solid, mp >310 °C (hexane/$CHCl_3$). ^1H NMR (400.12 MHz, DMSO-d_6): δ 10.06 (s, 1H, OH), 8.35 (s, 1H, H4′), 7.99 (d, J = 8.2 Hz, 2H, H2 + H6), 7.82 (d, J = 8.2 Hz, 2H, H3 + H5), 7.74 (d, J = 1.4 Hz, 1H, H2″), 7.64 (dd, J = 8.3, 1.4 Hz, 1H, H6″), 6.90 (d, J = 8.3 Hz, 1H, H5″), 2.11 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.74 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 168.2 (s), 166.8 (s), 158.8 (s), 141.0 (d), 136.3 (s), 135.7 (s), 135.2 (s), 130.2 (d, 2×), 129.8 (s), 126.1 (d, 2×), 125.2 (d), 124.7 (d), 123.9 (s), 117.0 (d), 39.7 (t, 3×), 36.5 (t, 3×), 36.3 (s), 28.3 (d, 3×) ppm. IR: ν 3582 (w, O–H), 3400–2800 (br, O–H), 2898 (m, C–H), 2877 (m, C–H), 2849 (m, C–H), 1681 (s, C=O), 1604 (s), 1425 (m), 1391 (s), 1297 (s), 1250 (m), 1187 (m), 1100 (m), 817 (m), 766 (m) cm^{-1}. MS (ESI^+): m/z (%) 432 ($[M+H]^+$, 100). HRMS (ESI^+): calcd for $C_{26}H_{26}NO_3S$ $[M+H]^+$ 432.1628; found: 432.1624. Elem. Anal. calcd for $C_{26}H_{25}NO_3S \cdot 1/2H_2O$ C, 70.88; H, 5.95; N, 3.18; found: C, 71.19; H, 5.44; N, 3.29.

5.7.27. 4-[2-(5-Adamantan-1-yl-4-hydroxy-2-methylphenyl) thiazol-5-yl]benzoic acid (8b)

According to the general procedure for the hydrolysis of esters, **25b** (0.02 g, 0.05 mmol) gave, after crystallization, acid **8b** (0.02 g, 77%) as a yellow solid, mp >300 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, DMSO-d_6): δ 9.87 (s, 1H, OH), 8.39 (s, 1H, H4′), 7.99 (d, J = 8.3 Hz, 2H, H2 + H6), 7.83 (d, J = 8.2 Hz, 2H, H3 + H5), 7.59 (s, 1H, H6″), 6.75 (s, 1H, H3″), 2.50 (s, 3H, $ArCH_3$), 2.09 (s, 6H, 3 × $AdCH_2$), 2.04 (s, 3H, 3 × AdCH), 1.73 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 168.1 (s), 166.8 (s), 157.6 (s), 140.4 (d), 136.2 (s), 135.2 (s), 134.7 (s), 133.9 (s), 130.2 (d, 2×), 129.8 (s), 128.1 (d), 126.1 (d, 2×), 122.9 (s), 119.4 (d), 39.9 (t, 3×), 36.6 (t, 3×), 35.9 (s), 28.3 (d, 3×), 21.1 (q) ppm. IR: ν 3400–3000 (br, O–H), 2902 (m, C–H), 2874 (m, C–H), 2849 (m, C–H), 1697 (s, C=O), 1605 (s), 1388 (s), 1259 (s), 1234 (s), 1180 (m), 1124 (m), 1020 (m), 976 (s), 850 (s), 773 (s) cm^{-1}. MS (ESI^+): m/z (%) 446 ($[M+H]^+$, 100), 373 (11), 331 (29), 327 (19), 326 (91). HRMS (ESI^+): calcd for $C_{27}H_{28}NO_3S$ $[M+H]^+$ 446.1784; found: 446.1785. Calcd for $C_{27}H_{27}NO_3S \cdot 1/5H_2O$ C, 64.91; H, 6.66; N, 2.80; found: C, 65.35; H, 6.29; N, 2.69.

5.7.28. 4-[2-(3-Adamantan-1-yl-4-[(2-methoxyethoxy)methoxy] phenyl)thiazol-5-yl]benzoic acid (8c)

According to the general procedure for the hydrolysis of esters, **25c** (0.01 g, 0.02 mmol) gave, after crystallization, acid **8c** (0.09 g, 99%) as a white solid, mp 275 −276 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, DMSO-d_6): δ 8.40 (s, 1H, H4′), 8.00 (d, J = 8.5 Hz, 2H, H2 + H6), 7.84 (d, J = 8.5 Hz, 2H, H3 + H5), 7.83 (d, J = 2.3 Hz, 1H, H2″), 7.78 (dd, J = 8.6, 2.3 Hz, 1H, H6″), 7.19 (d, J = 8.6 Hz, 1H, H5″), 5.39 (s, 2H, OCH_2O), 3.8–3.7 (m, 2H, OCH_2), 3.5–3.4 (m, 2H, OCH_2), 3.24 (s, 3H, OCH_3), 2.12 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.76 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): 167.5 (s), 166.8 (s), 157.8 (s), 141.2 (d), 138.4 (s), 136.5 (s), 135.0 (s), 130.2 (d, 2×), 130.0 (s), 126.2 (d, 2×), 125.9 (s), 125.3 (d), 124.5 (d), 114.9 (d), 92.9 (t), 71.0 (t), 68.0 (t), 58.1 (q), 39.9 (t, 3×), 36.7 (s), 36.4 (t, 3×), 28.3 (d, 3×) ppm. IR: ν 2902 (m, C–H), 2848 (w, C–H), 1690 (w, C=O), 1585 (m), 1546 (s), 1415 (s), 1223 (s), 1101 (s), 983 (s), 849 (m), 785 (s) cm^{-1}. MS (ESI^+): m/z (%) 559 ($[M+K+H]^+$, 82), 520 ($[M+H]^+$, 100), 459 (16), 455 (9), 445 (9), 415 (17), 401 (9), 371 (8), 210 (21). HRMS (ESI^+): calcd for $C_{30}H_{34}NO_5S$ $[M+H]^+$ 520.2152; found: 520.2145. Calcd for $C_{30}H_{33}NO_5S \cdot 1/2$ $[(CH_3)_2SO]$ C, 66.64; H, 5.51; N, 2.51; found: C, 66.12; H, 5.51; N, 2.62.

5.7.29. 4-[2-(5-Adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]-2-methylphenyl)thiazol-5-yl]benzoic acid (8d)

According to the general procedure for the hydrolysis of esters, **25d** (0.02 g, 0.03 mmol) gave, after crystallization, acid **8d** (0.01 g, 94%) as a yellow solid, mp 235–236 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, DMSO-d_6): δ 8.43 (s, 1H, H4′), 7.99 (d, J = 8.4 Hz, 2H, H2 + H6), 7.84 (d, J = 8.4 Hz, 2H, H3 + H5), 7.66 (s, 1H, H6″),

7.04 (s, 1H, H3″), 5.37 (s, 2H, OCH_2O), 3.8–3.7 (m, 2H, OCH_2), 3.5–3.4 (m, 2H, OCH_2), 3.25 (s, 3H, OCH_3), 2.56 (s, 3H, $ArCH_3$), 2.08 (s, 6H, 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.74 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 167.4 (s), 166.8 (s), 156.7 (s), 140.5 (d), 136.9 (s), 135.8 (s), 135.0 (s, 2×), 130.2 (d, 2×), 130.0 (s), 127.9 (d), 126.2 (d, 2×), 124.9 (s), 117.3 (d), 92.8 (t), 71.0 (t), 68.0 (t), 58.1 (q), 38.1 (t, 3×), 36.5 (t, 3×), 36.3 (s), 28.4 (d, 3×), 21.3 (q) ppm. IR: ν 3500–3200 (br, OH), 2900 (m, C–H), 2879 (m, C–H), 2849 (m, C–H), 1683 (s, C=O), 1604 (s), 1441 (m), 1426 (m), 1299 (m), 1225 (m), 1099 (s), 1016 (s), 984 (s), 845 (m), 767 (s) cm^{-1}. MS (ESI^+): m/z (%) 534 ($[M+H]^+$, 100), 319 (6), 210 (4). HRMS (ESI^+) calcd for $C_{31}H_{36}NO_5S$ $[M+H]^+$ 534.2309; found: 534.2303. Elem. Anal. calcd for $C_{31}H_{35}NO_5S$: C, 69.77; H, 6.61; N, 2.62; found: C, 69.52; H, 6.26; N, 2.59.

5.7.30. 5-Bromo-2-[3-adamantan-1-yl-4-(*tert*-butyldimethylsilyloxy)phenyl]-3-methoxypyrazine (27a)

Following the general procedure for the Suzuki reaction, pyrazine **26** (0.50 g, 1.59 mmol) and boronic acid **16a**[11] (0.80 g, 2.07 mmol) were heated in benzene at 50 °C for 12 h. The residue was purified by column chromatography (C_{18}-SiO_2, 100% CH_3CN) and crystallized, to give **27a** (0.64 g, 76%) as a white powder, mp 143–144 °C (hexane/$CHCl_3$). ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.28 (s, 1H, H6), 7.94 (d, J = 2.3 Hz, 1H, H2′), 7.78 (dd, J = 8.5, 2.3 Hz, 1H, H6′), 6.86 (d, J = 8.5 Hz, 1H, H5′), 4.06 (s, 3H, OCH_3), 2.15 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$), 1.05 (s, 9H, $SiC(CH_3)_3$), 0.37 (s, 6H, $Si(CH_3)_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.6 (s), 156.1 (s), 141.7 (s), 139.4 (s), 137.6 (d), 132.6 (s), 128.3 (d), 127.3 (d), 126.7 (s), 118.7 (d), 54.5 (q), 40.2 (t, 3×), 37.0 (t, 3×), 36.9 (s), 28.9 (q, 3×), 26.3 (d, 3×), 18.9 (s), –3.5 (q, 2×) ppm. IR: ν 2904 (s, C–H), 2853 (m, C–H), 1600 (m), 1522 (w), 1492 (m), 1419 (m), 1357 (s), 1248 (s), 1144 (s), 900 (s) cm^{-1}. MS (ESI^+): m/z (%) 531 ($[M+H]^+$ [^{81}Br], 35), 530 ($[M]^+$ [^{81}Br], 97), 529 ($[M+H]^+$ [^{79}Br], 34), 528 ($[M]^+$ [^{79}Br], 94), 473 ($[M-{}^tBu]^+$, 100), 353 (16), 351 (34), 349 (20), 135 (93), 73 (20). HRMS (ESI^+): calcd for $C_{27}H_{37}{}^{81}BrN_2O_2Si$ $[M]^+$ 530.1787 and $C_{27}H_{37}{}^{79}BrN_2O_2Si$ $[M]^+$ 528.1808; found: 530.1786 and 528.1791.

5.7.31. 5-Bromo-2-[5-adamantan-1-yl-2-methyl-4-(*tert*-butyldimethylsilyloxy)phenyl]-3-methoxypyrazine (27b)

Following the general procedure for the Suzuki reaction, pyrazine **26** (0.36 g, 1.15 mmol) and boronic acid **16b**[32] (0.51 g, 1.26 mmol) were heated in benzene at 50 °C for 12 h. The residue was purified by column chromatography (SiO_2, 97:3 hexane/EtOAc and C_{18}-SiO_2, 95:5 CH_3CN/CH_2Cl_2), to give **27b** (0.18 g, 30%) as a foam. ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.32 (s, 1H, H6), 7.20 (s, 1H, H6′), 6.70 (s, 1H, H3′), 4.00 (s, 3H, OCH_3), 2.13 (s, 3H, $ArCH_3$), 2.11 (s, 6H, 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.76 (s, 6H, 3 × $AdCH_2$), 1.07 (s, 9H, $OSiC(CH_3)_3$), 0.38 (s, 6H, $OSi(CH_3)_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.3 (s), 155.3 (s), 143.9 (s), 137.4 (d), 137.0 (s), 134.9 (s), 134.0 (s), 128.9 (d), 126.5 (s), 120.9 (d), 54.6 (q), 40.4 (t, 3×), 37.0 (t, 3×), 36.6 (s), 29.0 (d, 3×), 26.4 (q, 3×), 19.3 (q), 18.9 (s), –3.4 (q, 2×) ppm. IR: ν 2900 (m, C–H), 2850 (m, C–H), 1605 (w), 1525 (w), 1497 (w), 1456 (m), 1420 (m), 1357 (s), 1251 (s), 1155 (s), 900 (s), 837 (s), 782 (s) cm^{-1}. MS (ESI^+): m/z (%) 545 ($[M+H]^+$ [^{81}Br], 100), 543 ($[M+H]^+$ [^{79}Br], 97), 279 (7). HRMS (ESI^+): calcd for $C_{28}H_{40}{}^{81}BrN_2O_2Si$ $[M+H]^+$ 545.2016 and $C_{28}H_{40}{}^{79}BrN_2O_2Si$ $[M+H]^+$ 543.2037; found: 545.2010 and 543.2030.

5.7.32. Methyl (*E*)-3-[5-(3-adamantan-1-yl-4-hydroxyphenyl)-6-methoxypyrazin-2-yl]acrylate (28a)

Following the general procedure for the Heck reaction, bromide **27a** (0.50 g, 0.95 mmol) gave, after purification by column chromatography (SiO_2, 70:30 hexane/EtOAc) and crystallization, 0.27 g (67%) of ester **28a** as a yellow solid, mp 245–246 °C (hexane/MeOH/THF) and 75 mg (19%) of deprotected starting pyrazine **29a** as a yellowish solid, mp 203–204 °C (hexane/MeOH/THF). Data for methyl (*E*)-3-[5-(3-adamantan-1-yl-4-hydroxyphenyl)-6-methoxypyrazin-2-yl]acrylate (**28a**). ^1H NMR (400.13 MHz, DMSO-d_6): δ 9.88 (br, 1H), 8.48 (s, 1H, H3′), 7.98 (d, J = 2.1 Hz, 1H, H2″), 7.86 (dd, J = 8.5, 2.1 Hz, 1H, H6″), 7.68 (d, J = 15.5 Hz, 1H, H3), 6.89 (d, J = 15.5 Hz, 1H, H2), 6.87 (d, J = 8.5 Hz, 1H, H5″), 4.02 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 2.10 (s, 6H, 3 × $AdCH_2$), 2.04 (s, 3H, 3 × AdCH), 1.73 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 166.1 (s), 158.1 (s), 156.2 (s), 144.0 (s), 140.8 (s), 139.9 (d), 137.3 (d), 135.2 (s), 128.0 (d), 127.7 (d), 125.4 (s), 121.0 (d), 115.9 (d), 53.4 (q), 51.6 (q), 39.8 (t, 3×), 36.5 (t, 3×), 36.3 (s), 28.3 (d, 3×) ppm. IR: ν 3300–3100 (br, O–H), 2900 (m, C–H), 2847 (w, C–H), 1712 (s, C=O), 1645 (w), 1532 (w), 1602 (w), 1449 (m), 1370 (s), 1162 (s), 1122 (m), 972 (m) cm^{-1}. MS (FAB^+): m/z (%) 421 ($[M+H]^+$, 100), 420 ($[M]^+$, 70), 419 (15), 307 (25), 289 (14), 155 (26), 154 (83). HRMS (FAB^+): calcd for $C_{25}H_{28}N_2O_4$ $[M]^+$, 420.2049; found: 420.2050. Data for 5-bromo-2-[3-adamantan-1-yl-4-hydroxyphenyl]-3-methoxypyrazine **29a**. ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.28 (s, 1H, H6), 7.93 (d, J = 2.0 Hz, 1H, H2′), 7.76 (dd, J = 8.3, 2.1 Hz, 1H, H6′), 6.68 (d, J = 8.3 Hz, 1H, H5′), 5.36 (br. s, OH), 4.06 (s, 3H, OCH_3), 2.16 (s, 6H, 3 × $AdCH_2$), 2.09 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 156.8 (s), 156.0 (s), 141.7 (s), 137.5 (d), 136.4 (s), 132.8 (s), 128.4 (d), 127.8 (d), 127.0 (s), 116.6 (d), 54.7 (q), 40.4 (t, 3×), 37.0 (t, 3×), 36.9 (s), 29.0 (d, 3×) ppm. IR: ν 3400–3100 (br, O–H), 2902 (w, C–H), 2882 (w, C–H), 2847 (w), 1599 (m), 1461 (m), 1409 (s), 1357 (s), 1284 (m), 1225 (s), 1177 (s), 1146 (s), 912 (s), 875 (m), 823 (m), 753 (s), 732 (s) cm^{-1}. MS (ESI^+): m/z (%) 417 ($[M+H]^+$[^{81}Br], 100), 415 ($[M+H]^+$[^{79}Br], 95), 359 (10), 279 (4), 201 (24). HRMS (ESI^+): calcd for $C_{21}H_{24}{}^{81}BrN_2O_2$ $[M+H]^+$ 417.0998 and $C_{21}H_{24}{}^{79}BrN_2O_2$ $[M+H]^+$ 415.1016; found: 417.1000 and 415.1030. Elem. Anal. calcd for $C_{21}H_{24}$ BrN_2O_2: C, 60.73; H, 5.58; N, 6.71; found: C, 60.84; H, 5.60; N, 6.71.

5.7.33. Methyl (*E*)-3-[5-(5-adamantan-1-yl-4-hydroxy-2-methylphenyl)-6-methoxypyrazin-2-yl]acrylate (28b)

Following the general procedure for the Heck reaction, bromide **27b** (0.09 g, 0.17 mmol) gave, after purification by column chromatography (SiO_2, 70:30 hexane/EtOAc), 0.04 g (57%) of ester **28b** as a yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.25 (s, 1H, H3′), 7.68 (d, J = 15.4 Hz, 1H, H3), 7.22 (s, 1H, H6″), 7.04 (d, J = 15.4 Hz, 1H, H2), 6.49 (s, 1H, H3″), 4.00 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.11 (s, 9H, $ArCH_3$ + 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.1 (s), 157.6 (s), 155.5 (s), 147.5 (s), 142.9 (s), 139.8 (d), 136.5 (d), 135.6 (s), 133.9 (s), 129.0 (d), 127.1 (s), 122.6 (d), 118.6 (d), 53.7 (q), 51.9 (q), 40.5 (t, 3×), 37.0 (t, 3×), 36.4 (s), 29.0 (d, 3×), 19.1 (q) ppm. IR: ν 3600–3100 (br, O–H), 2908 (s, C–H), 2852 (m, C–H), 1720 (s, C=O), 1448 (s), 1365 (s), 1328 (s), 1227 (m), 1185 (m), 1142 (m), 756 (m) cm^{-1}. MS (ESI^+): m/z (%) 435 ($[M+H]^+$, 100). HRMS (ESI^+): calcd for $C_{26}H_{31}N_2O_4$ $[M+H]^+$ 435.2278; found: 435.2268.

5.7.34. Methyl (*E*)-3-[5-(3-adamantan-1-yl-4-[(2-methoxyethoxy)methoxy]phenyl)-6-methoxypyrazin-2-yl]acrylate (28c)

According to the general procedure for the protection of the phenols with MEMCl, phenol **28a** (0.29 g, 0.70 mmol) gave, after purification by column chromatography (SiO_2, 70:30 hexane/EtOAc), compound **28c** (0.32 g, 92%) as a white solid, mp 145–146 °C (hexane/MeOH/THF). ^1H NMR (400.13 MHz, DMSO-d_6): δ 8.54 (s, 1H, H3′), 8.02 (s, 1H, H2″), 7.96 (d, J = 8.6 Hz, 1H, ArH), 7.72 (d, J = 15.6 Hz, 1H, H3), 7.14 (d, J = 8.6 Hz, 1H, ArH), 6.94 (d, J = 15.6 Hz, 1H, H2), 5.38 (s, 2H, OCH_2O), 4.04 (s, 3H, OCH_3), 3.79 (t, J = 3.9 Hz, 2H, $O(CH_2)_2O$), 3.76 (s, 3H, OCH_3), 3.51 (t, J = 3.9 Hz, 2H, $O(CH_2)_2O$), 3.24 (s, 3H, OCH_3), 2.10 (s, 6H, 3 × $AdCH_2$), 2.06

(s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 166.1 (s), 157.1 (s), 156.4 (s), 143.6 (s), 141.5 (s), 139.9 (d), 137.4 (d), 137.3 (s), 128.2 (d), 127.6 (s), 127.5 (d), 121.6 (d), 113.7 (d), 92.8 (t), 70.9 (t), 67.9 (t), 58.0 (q), 53.6 (q), 51.7 (q), 40.1 (t, 3×), 36.6 (t, 3×), 36.4 (s), 28.3 (d, 3×) ppm. IR: ν 2899 (w, C–H), 2850 (w, C–H), 1721 (w, C═O), 1641 (m), 1600 (w), 1522 (w), 1443 (w), 1361 (m), 1224 (m), 1158 (m), 1112 (s), 979 (s) cm^{-1}. MS (FAB^+): m/z (%) 509 ($[M+H]^+$, 100), 508 ($[M]^+$, 46), 433 (12), 307 (11), 155 (15), 154 (46). HRMS (FAB^+): calcd for $C_{29}H_{37}N_2O_6$ $[M+H]^+$, 509.2652; found: 509.2660.

5.7.35. Methyl (*E*)-3-[5-(5-adamantan-1-yl-4-[(2-methoxy ethoxy)methoxy]-2-methylphenyl)-6-methoxypyrazin-2-yl] acrylate (28d)

According to the general procedure for the protection of the phenols with MEMCl, phenol **28b** (0.02 g, 0.05 mmol) gave, after purification by column chromatography (SiO_2, 70:30 hexane/EtOAc), compound **28d** (0.02 g, 87%) as a yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ 8.26 (s, 1H, H3′), 7.67 (d, J = 15.3 Hz, 1H, H3), 7.23 (s, 1H, H6″), 7.06 (s, 1H, H3″), 7.04 (d, J = 15.3 Hz, 1H, H2), 5.35 (s, 2H, OCH_2O), 4.00 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.6–3.5 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 2.18 (s, 3H, $ArCH_3$), 2.10 (s, 6H, 3 × $AdCH_2$), 2.04 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 167.0 (s), 157.5 (s), 157.1 (s), 147.5 (s), 142.9 (s), 139.8 (d), 136.7 (d), 135.9 (s), 135.8 (s), 128.5 (d), 128.3 (s), 122.6 (d), 116.3 (d), 93.2 (t), 71.6 (t), 67.8 (t), 59.0 (q), 53.7 (q), 51.9 (q), 40.7 (t, 3×), 37.1 (t, 3×), 36.8 (s), 29.0 (d, 3×), 19.5 (q) ppm. IR: ν 2921 (s, C–H), 2853 (m, C–H), 1722 (s, C═O), 1449 (s), 1362 (s), 1323 (m), 1229 (m), 1162 (m), 1015 (m), 981 (m) cm^{-1}. MS (ESI^+): m/z (%) 523 ($[M+H]^+$, 100), 435 (3). HRMS (ESI^+): calcd for $C_{30}H_{39}N_2O_6$ $[M+H]^+$ 523.2803; found: 523.2787.

5.7.36. (*E*)-3-[5-(3-Adamantan-1-yl-4-hydroxyphenyl)-6-meth oxypyrazin-2-yl]acrylic acid (9a)

In accordance with the general procedure for the hydrolysis of esters, ester **28a** (0.18 g, 0.42 mmol) gave, after crystallization, acrylic acid **9a** (0.12 g, 73%) as a yellow solid, mp 256–257 °C (hexane/THF). ^1H NMR (400.13 MHz, CD_3OD): δ 8.23 (s, 1H, H3′), 7.97 (d, J = 1.8 Hz, 1H, H2″), 7.80 (dd, J = 8.4, 1.8 Hz, 1H, H6″), 7.64 (d, J = 15.4 Hz, 1H, H3), 6.93 (d, J = 15.4 Hz, 1H, H2), 6.78 (d, J = 8.4 Hz, 1H, H5″), 4.08 (s, 3H, OCH_3), 2.20 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.82 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ 169.9 (s), 159.7 (s), 158.4 (s), 146.5 (s), 143.3 (s), 141.1 (d), 137.8 (d), 137.2 (s), 129.5 (d), 129.4 (d), 127.3 (s), 123.7 (d), 116.9 (d), 54.1 (q), 41.5 (t, 3×), 38.3 (t, 3×), 38.1 (s), 30.6 (d, 3×) ppm. IR: ν 3500–3100 (br, O–H), 2900 (m, C–H), 2848 (w, C–H), 1683 (s, C═O), 1632 (w), 1601 (w), 1524 (w), 1444 (m), 1359 (s), 1298 (m), 1227 (s), 1177 (m), 1125 (m), 973 (w) cm^{-1}. MS (FAB^+): m/z (%) 407 ($[M+H]^+$, 100), 406 ($[M]^+$, 69). HRMS (FAB^+): calcd for $C_{24}H_{27}N_2O_4$ $[M+H]^+$, 407.1971; found: 407.1966. Purity: 96% (RP HPLC, gradient from 50:50 to 0:100 H_2O/CH_3CN, 1 mL/min).

5.7.37. (*E*)-3-[5-(5-Adamantan-1-yl-4-hydroxy-2-methylphenyl) -6-methoxypyrazin-2-yl]acrylic acid (9b)

In accordance with the general procedure for the hydrolysis of esters, ester **28b** (0.02 g, 0.05 mmol) gave, after crystallization, acrylic acid **9b** (0.017 g, 84%) as a yellow solid, mp 168–169 °C (hexane/CH_2Cl_2). ^1H NMR (400.13 MHz, CD_3OD): δ 8.27 (s, 1H, H3′), 7.69 (d, J = 15.5 Hz, 1H, H3), 7.07 (s, 1H, H6″), 7.01 (d, J = 15.5 Hz, 1H, H2), 6.63 (s, 1H, H3″), 4.01 (s, 3H, OCH_3), 2.15 (s, 6H, 3 × $AdCH_2$), 2.07 (s, 3H, $ArCH_3$), 2.03 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 6x$AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ 169.8 (s), 159.4 (s), 158.6 (s), 149.3 (s), 145.1 (s), 141.0 (d), 137.2 (d), 136.7 (s), 135.0 (s), 129.6 (d), 127.3 (s), 124.8 (d), 119.0 (d), 54.3 (q), 41.7 (t, 3×), 38.4 (t, 3×), 37.8 (s), 30.7 (d, 3×), 19.4 (q) ppm. IR: ν 3500–2800 (br, O–H), 2904 (s, C–H), 2851 (m, C–H), 1692 (s, C═O), 1449 (s), 1364 (s), 1235 (m), 1184 (m), 1142 (m) cm^{-1}. MS (ESI^+): m/z (%) 421 ($[M+H]^+$, 100), 394 (4), 359 (6), 201 (26). HRMS (ESI^+): calcd for $C_{25}H_{29}N_2O_4$ $[M+H]^+$ 421.2122; found: 421.2114. Purity: 98% (RP HPLC, gradient from 50:50 to 0:100 H_2O/CH_3CN, 1 mL/min).

5.7.38. (*E*)-3-(5-(3-Adamantan-1-yl-4-[(2-methoxy ethoxy)methoxy]phenyl)-6-methoxypyrazin-2-yl)acrylic acid (9c)

In accordance with the general procedure for the hydrolysis of esters, ester **28c** (0.18 g, 0.36 mmol) gave, after crystallization, acrylic acid **9c** (0.11 g, 62%) as a yellow solid, mp 215–216 °C (hexane/THF). ^1H NMR (400.13 MHz, DMSO-d_6): δ 8.51 (s, 1H, H3′), 8.02 (s, 1H, H2″), 7.96 (d, J = 8.6 Hz, 1H, ArH), 7.63 (d, J = 15.5 Hz, 1H, H3), 7.13 (d, J = 8.6 Hz, 1H, ArH), 6.87 (d, J = 15.5 Hz, 1H, H2), 5.38 (s, 2H, OCH_2O), 4.03 (s, 3H, OCH_3), 3.79 (t, J = 4.4 Hz, 2H, $O(CH_2)_2O$), 3.51 (t, J = 4.4 Hz, 2H, $O(CH_2)_2O$), 3.24 (s, 3H, $O(CH_2)_2$-OCH_3), 2.10 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 167.0 (s), 157.1 (s), 156.4 (s), 143.3 (s), 141.8 (s), 139.2 (d), 137.3 (s), 137.2 (d), 128.1 (d), 127.6 (s), 127.5 (d), 123.2 (d), 113.7 (d), 92.7 (t), 70.9 (t), 67.9 (t), 58.0 (q), 53.5 (q), 40.1 (t, 3×), 36.6 (t, 3×), 36.4 (s), 28.3 (d, 3×) ppm. IR: ν 3100–2800 (br, O–H), 1682 (s, C═O), 1630 (w), 1598 (w), 1523 (w), 1443 (w), 1361 (m), 1300 (m), 1223 (m), 1115 (s), 979 (s) cm^{-1}. MS (FAB^+): m/z (%) 495 ($[M+H]^+$, 100), 494 ($[M]^+$, 43), 419 ($[M - OCH_2CH_2OCH_3]^+$, 14), 176 (12). HRMS (FAB^+): calcd for $C_{28}H_{35}N_2O_6$ $[M+H]^+$, 495.2495; found: 495.2502. Purity: 98% (RP HPLC, gradient from 50:50 to 0:100 H_2O/CH_3CN, 1 mL/min).

5.7.39. (*E*)-3-[5-(5-Adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]-2-methylphenyl)-6-methoxypyrazin-2-yl]acrylic acid (9d)

In accordance with the general procedure for the hydrolysis of esters, ester **28d** (0.02 g, 0.04 mmol) gave, after crystallization, acrylic acid **9d** (0.015 g, 65%) as a yellow solid, mp 107–108 °C (hexane/CH_2Cl_2). ^1H NMR (400.13 MHz, CD_3OD): δ 8.28 (s, 1H, H3′), 7.62 (d, J = 16.0 Hz, 1H, H3), 7.15 (s, 1H, H6″), 7.05 (s, 1H, H3″), 7.05 (d, J = 16.0 Hz, 1H, H2), 5.36 (s, 2H, OCH_2O), 4.02 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.37 (s, 3H, OCH_3), 2.14 (s, 6H, 3 × $AdCH_2$), 2.13 (s, 3H, $ArCH_3$), 2.05 (s, 3H, 3 × AdCH), 1.81 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, CD_3OD): δ 170.9 (s), 159.3 (s), 158.4 (s), 148.3 (s), 145.9 (s), 139.6 (d, 2×), 137.1 (d+2s, 3×), 129.7 (s), 129.5 (d), 117.4 (d), 94.6 (t), 73.0 (t), 69.3 (t), 59.3 (q), 54.3 (q), 42.1 (t, 3×), 38.3 (t, 3×), 38.1 (s), 30.7 (d, 3×), 19.7 (q) ppm. IR: ν 3500–2800 (br, O–H), 2904 (s, C–H), 2851 (m, C–H), 1699 (m, C═O), 1642 (w), 1449 (m), 1361 (s), 1234 (s), 1182 (s), 1139 (m), 1017 (s), 980 (m) cm^{-1}. MS (ESI^+): m/z (%) 509 ($[M+H]^+$, 100), 421 (8), 201 (10). HRMS (ESI^+): calcd for $C_{29}H_{37}N_2O_6$ $[M+H]^+$ 509.2646; found: 509.2659.

5.7.40. 5-Bromo-2-[3-adamantan-1-yl-4-phenol]-3-methoxy pyrazine (29a)

In accordance with the general procedure for the cleavage of the silyl ethers, ether **27a** (0.23 g, 0.44 mmol) gave, after purification by column chromatography (SiO_2, from 90:10 hexane/EtOAc), 0.14 g (83%) of phenol **29a** as a yellow solid, mp 203–204 °C ($CHCl_3$/hexane). Spectroscopic data matched those showed above.

5.7.41. 5-Bromo-2-[5-adamantan-1-yl-4-hydroxy-2-meth ylphenyl]-3-methoxypyrazine (29b)

In accordance with the general procedure for the cleavage of the silyl ethers, ether **27b** (0.08 g, 0.15 mmol) gave, after purification

by column chromatography (SiO_2, from 90:10 hexane/EtOAc), 0.04 g (63%) of phenol **29b** as a yellow oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.31 (s, 1H, H4), 7.16 (s, 1H, H6′), 6.47 (s, 1H, H3′), 3.98 (s, 3H, OCH_3), 2.09 (s, 6H, 3 × $AdCH_2$), 2.07 (s, 3H, $ArCH_3$), 2.04 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.4 (s), 155.4 (s), 143.8 (s), 137.2 (d), 135.3 (s), 134.2 (s), 134.0 (s), 128.8 (d), 126.3 (s), 118.5 (d), 54.6 (q), 40.4 (t, 3×), 37.0 (t, 3×), 36.4 (s), 29.0 (d, 3×), 19.0 (q) ppm. IR: ν 3400–3100 (br, O–H), 2906 (s, C–H), 2852 (s, C–H), 1609 (m), 1526 (m), 1456 (s), 1401 (s), 1364 (s), 1225 (s), 1155 (s), 1008 (m), 894 (s), 757 (s) cm^{-1}. MS (ESI^+): m/z (%) 431 ($[M+H]^+[^{81}Br]$, 100), 429 ($[M+H]^+[^{79}Br]$, 100). HRMS (ESI^+): calcd for $C_{22}H_{26}{}^{81}BrN_2O_2$ $[M+H]^+$ 431.1153 and $C_{22}H_{26}{}^{79}BrN_2O_2$ $[M+H]^+$ 429.1172; found: 431.1142 and 429.1168.

5.7.42. 5-Bromo-2-[3-adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]phenyl]-3-methoxypyrazine (29c)

According to the general procedure for the protection of the phenols with MEMCl, phenol **29a** (0.04 g, 0.10 mmol) gave, after purification by column chromatography (SiO_2, 80:20 hexane/EtOAc), compound **29c** (0.04 g, 89%) as a yellow solid, mp 93–94 °C (hexane/EtOAc). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.29 (s, 1H, H6), 7.94 (d, J = 2.2 Hz, 1H, H2′), 7.86 (dd, J = 8.6, 2.2 Hz, 1H, H6′), 7.22 (d, J = 8.6 Hz, 1H, H5′), 5.38 (s, 2H, OCH_2O), 4.05 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.40 (s, 3H, OCH_3), 2.15 (s, 6H, 3 × $AdCH_2$), 2.08 (s, 3H, 3 × AdCH), 1.78 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.6 (s), 156.7 (s), 141.6 (s), 138.4 (s), 137.6 (d), 132.9 (s), 127.9 (d), 127.8 (d), 127.7 (s), 114.0 (d), 93.1 (t), 71.5 (t), 67.9 (t), 59.0 (q), 54.6 (q), 40.5 (t, 3×), 37.2 (s), 37.0 (t, 3×), 29.0 (d, 3×) ppm. IR: ν 2906 (m, C–H), 2885 (m, C–H), 1599 (w), 1520 (m), 1456 (m), 1418 (m), 1356 (s), 1219 (s), 1146 (s), 1100 (s), 1004 (s), 909 (s), 830 (m) cm^{-1}. MS (ESI^+): m/z (%) 505 ($[M+H]^+[^{81}Br]$, 96), 503 ($[M+H]^+[^{79}Br]$, 100), 430 (7), 429 (24), 427 (27), 209 (8), 192 (7). HRMS (ESI^+): calcd for $C_{25}H_{32}{}^{81}BrN_2O_4$ $[M+H]^+$ 505.1525 and $C_{25}H_{32}{}^{79}BrN_2O_4$ $[M+H]^+$ 503.1540; found: 505.1513 and 503.1534. Elem. Anal. calcd for $C_{25}H_{31}BrN_2O_4$: C, 59.64; H, 6.21; N, 5.56; found: C, 59.10; H, 5.84; N, 5.41.

5.7.43. 5-Bromo-2-[5-adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]-2-methylphenyl]-3-methoxypyrazine (29d)

According to the general procedure for the protection of the phenols with MEMCl, phenol **29b** (0.02 g, 0.05 mmol) gave, after purification by column chromatography (SiO_2, 95:5 hexane/EtOAc), compound **29d** (0.023 g, 99%) as a colourless oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.32 (s, 1H, H6), 7.18 (s, 1H, H6′), 7.05 (s, 1H, H3′), 5.35 (s, 2H, OCH_2O), 3.99 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 2.15 (s, 3H, $ArCH_3$), 2.09 (s, 6H, 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 157.3 (s), 157.0 (s), 143.8 (s), 137.5 (d), 136.0 (s), 135.6 (s), 134.3 (s), 128.4 (d), 127.5 (s), 116.3 (d), 93.2 (t), 71.6 (t), 67.8 (t), 59.0 (q), 54.6 (q), 40.7 (t, 3×), 37.1 (t, 3×), 36.8 (s), 29.0 (d, 3×), 19.4 (q) ppm. IR: ν 2904 (s, C–H), 2852 (m, C–H), 1526 (m), 1455 (m), 1421 (m), 1361 (s), 1232 (m), 1155 (s), 1100 (m), 1012 (s), 890 (m) cm^{-1}. MS (ESI^+): m/z (%) 519 ($[M+H]^+[^{81}Br]$, 100), 517 ($[M+H]^+[^{79}Br]$, 97), 476 (7), 431 (4), 429 (4). HRMS (ESI^+): calcd for $C_{26}H_{34}{}^{81}BrN_2O_4$ $[M+H]^+$ 519.1676 and $C_{26}H_{34}{}^{79}BrN_2O_4$ $[M+H]^+$ 517.1696; found: 519.1656 and 517.1686.

5.7.44. Methyl 4-[5-(3-adamantan-1-yl-4-hydroxyphenyl)-6-methoxypyrazin-2-yl]benzoate (30a)

Following the general procedure for the Suzuki reaction, bromopyrazine **29a** (0.04 g, 0.10 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.03 g, 0.14 mmol) were heated in 1,4-dioxane at 120 °C for 12 h. The residue was purified by column chromatography (SiO_2, 80:20 hexane/EtOAc), to give **30a** (0.03 g, 58%) as a yellow powder, mp 269–270 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.80 (s, 1H, OH), 8.92 (s, 1H, H3′), 8.28 (d, J = 8.5 Hz, 2H, H2 + H6), 8.07 (d, J = 8.5 Hz, 2H, H3 + H5), 8.01 (d, J = 2.0 Hz, 1H, H2″), 7.87 (dd, J = 8.4, 2.1 Hz, 1H, H6″), 6.87 (d, J = 8.4 Hz, 1H, H5″), 4.09 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.12 (s, 6H, 3 × $AdCH_2$), 2.05 (s, 3H, 3 × AdCH), 1.74 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 165.9 (s), 157.8 (s), 156.1 (s), 143.4 (s), 141.8 (s), 140.1 (s), 135.3 (s), 133.2 (d), 129.9 (s), 129.7 (d, 2×), 127.8 (d), 127.6 (d), 126.4 (d, 2×), 125.6 (s), 116.0 (d), 53.5 (q), 52.2 (q), 39.9 (t, 3×), 36.6 (t, 3×), 36.3 (s), 28.4 (d, 3×) ppm. IR: ν 3300–3000 (br, O–H), 2899 (m, C–H), 2846 (m, C–H), 1723 (s, C=O), 1599 (m), 1449 (m), 1434 (m), 1409 (s), 1368 (s), 1270 (s), 1220 (s), 1190 (s), 1110 (s), 771 (m) cm^{-1}. MS (ESI^+): m/z (%) 471 ($[M+H]^+$, 79), 379 (14), 369 (19), 355 (17), 353 (100), 317 (21), 279 (21), 275 (52), 259 (12), 210 (33). HRMS (ESI^+): calcd for $C_{29}H_{31}N_2O_4$ $[M+H]^+$ 471.2278; found: 471.2274.

5.7.45. Methyl 4-[5-(3-adamantan-1-yl-4-[(2-methoxyethoxy)methoxy]phenyl)-6-methoxypyrazin-2-yl]benzoate (30c)

Following the general procedure for the Suzuki reaction, bromopyrazine **29c** (0.05 g, 0.10 mmol) and 4-(methoxycarbonyl)phenylboronic acid (0.03 g, 0.14 mmol) were heated in 1,4-dioxane at 120 °C for 12 h. The residue was purified by column chromatography (SiO_2, from 85:15 to 75:25 hexane/EtOAc), to give **30c** (0.03 g, 66%) as a yellow powder, mp 125–126 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 8.74 (s, 1H, H3′), 8.15 (s, 4H, H2 + H3 + H5 + H6), 8.07 (d, J = 2.2 Hz, 1H, H2″), 7.98 (dd, J = 8.6, 2.2 Hz, 1H, H6″), 7.24 (d, J = 8.6 Hz, 1H, H5″), 5.39 (s, 2H, OCH_2O), 4.14 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.9–3.8 (m, 2H, OCH_2), 3.6–3.5 (m, 2H, OCH_2), 3.41 (s, 3H, OCH_3), 2.18 (s, 6H, 3 × $AdCH_2$), 2.10 (s, 3H, 3 × AdCH), 1.79 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ 166.7 (s), 157.5 (s), 156.9 (s), 144.9 (s), 142.4 (s), 140.5 (s), 138.3 (s), 133.0 (d), 130.5 (s), 130.0 (d, 2×), 128.5 (s), 128.1 (d), 128.0 (d), 126.3 (d, 2×), 114.0 (d), 93.1 (t), 71.5 (t), 67.9 (t), 59.0 (q), 53.6 (q), 52.2 (q), 40.6 (t, 3×), 37.2 (s), 37.0 (t, 3×), 29.0 (d, 3×) ppm. IR: ν 2898 (m, C–H), 2852 (w, C–H), 1719 (s, C=O), 1603 (w), 1444 (m), 1360 (m), 1269 (s), 1114 (s), 1028 (m), 984 (s), 820 (m) cm^{-1}. MS (ESI^+): m/z (%) 559 ($[M+H]^+$, 100). HRMS (ESI^+): calcd for $C_{33}H_{39}N_2O_6$ $[M+H]^+$ 559.2803; found: 559.2791. Elem. Anal. Calcd for $C_{33}H_{38}N_2O_6$ C, 70.95; H, 6.86; N, 5.01; found: C, 71.08; H, 6.38; N, 4.99.

5.7.46. 4-(5-(3-Adamantan-4-hydroxyphenyl)pyrazin-2-yl)benzoic Acid (10a)

In accordance with the general procedure for the hydrolysis of esters, ester **30a** (0.01 g, 0.02 mmol) gave, after crystallization, acid **10a** (0.09 g, 99%) as a white solid, mp 301–302 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 9.82 (s, 1H, OH), 8.94 (s, 1H, H3′), 8.29 (d, J = 7.0 Hz, 2H, H2+H6), 8.07 (d, J = 7.0 Hz, 2H, H3 + H5), 8.01 (s, 1H, H2″), 7.88 (d, J = 7.8 Hz, 1H, H6″), 6.88 (d, J = 7.8 Hz, 1H, H5″), 4.11 (s, 3H, OCH_3), 2.13 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 167.0 (s), 157.7 (s), 156.2 (s), 143.7 (s, 2×), 141.7 (s), 139.7 (s), 135.3 (s), 133.1 (d), 129.9 (d, 2×), 127.8 (d), 127.5 (d), 126.3 (d, 2×), 125.6 (s), 116.0 (d), 53.6 (q), 39.9 (t, 3×), 36.6 (t, 3×), 36.4 (s), 28.4 (d, 3×) ppm. IR: ν 3531 (m, OH), 3300–2700 (br, O–H), 2902 (s, C–H), 2848 (m, C–H), 1677 (s, C=O), 1604 (m), 1529 (m), 1426 (m), 1409 (s), 1359 (s), 1290 (s), 1215 (s), 1118 (s), 862 (s), 841 (s), 776 (s) cm^{-1}. MS (ESI^+): m/z (%) 457 ($[M+H]^+$, 100), 359 (5), 348 (4). HRMS (ESI^+): calcd for $C_{28}H_{29}N_2O_4$ $[M+H]^+$ 457.2122; found: 457.2117.

5.7.47. 4-[5-(3-Adamantan-1-yl-4-[(2-methoxyethoxy) methoxy]phenyl)6-methoxypyrazin-2-yl]benzoic acid (10c)

In accordance with the general procedure for the hydrolysis of esters, ester **30c** (0.03 g, 0.06 mmol) gave, after crystallization, acid **10c** (0.03 g, 93%) as a yellow solid, mp 252–253 °C (hexane/$CHCl_3$). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 8.95 (s, 1H, H3′), 8.28 (d, J = 8.4 Hz, 2H, H4+H6), 8.07 (d, J = 8.4 Hz, 2H, H3 + H5), 8.04 (d, J = 2.1 Hz, 1H, H2″), 7.97 (dd, J = 8.8, 2.0 Hz 1H, H6″), 7.14 (d, J = 8.8 Hz, 1H, H5″), 5.37 (s, 2H, OCH_2O), 4.10 (s, 3H, OCH_3), 3.8–3.7 (m, 2H, OCH_2), 3.5–3.4 (m, 2H, OCH_2), 3.25 (s, 3H, OCH_3), 2.11 (s, 6H, 3 × $AdCH_2$), 2.06 (s, 3H, 3 × AdCH), 1.75 (s, 6H, 3 × $AdCH_2$) ppm. ^{13}C NMR (100.62 MHz, DMSO-d_6): δ 167.0 (s), 156.9 (s), 156.3 (s), 144.3 (s), 141.2 (s), 139.6 (s), 137.4 (s), 133.2 (d), 131.4 (s), 129.9 (d, 2×), 127.9 (d), 127.8 (s), 127.4 (d), 126.4 (d, 2×), 113.8 (d), 92.8 (t), 71.0 (t), 67.9 (t), 58.1 (q), 53.6 (q), 40.2 (t, 3×), 36.7 (s), 36.5 (t, 3×), 28.4 (d, 3×) ppm. IR: ν 3500–3000 (br, O–H), 2900 (m, C–H), 2848 (m, C–H), 1681 (m, C=O), 1603 (w), 1442 (m), 1361 (m), 1301 (m), 1215 (m), 1116 (s), 1026 (m), 972 (s), 821 (m) cm^{-1}. MS (ESI^+): m/z (%) 545 ($[M+H]^+$, 100), 413 (30), 245 (40). HRMS (ESI^+): calcd for $C_{32}H_{37}N_2O_6$ $[M+H]^+$ 545.2646; found: 545.2641. Elem. Anal. calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14; found: C, 70.46; H, 6.68; N, 5.00.

5.8. Biology

5.8.1. Kinase assays

Kinase activity was measured using a LANCE Ultra time-resolved fluorescence resonance energy transfer (TR-FRET) assay and purified recombinant IKKs (Carna Biosciences). Kinases were diluted in kinase buffer (50 mM Hepes pH 7.4, 10 mM $MgCl_2$, 1 mM EGTA, 2 mM DTT, and 0.01% Tween-20) to a final concentration of 4 nM (IKKα), 1 nM (IKKβ), or 2 nM (IKKε). 50 nM Ulight-Iκϖ Bα and Ulight-rpS6 (Perkin Elmer) were used as peptide substrates for IKKα/β and IKKε, respectively. All assays were performed with an ATP concentration close to the apparent K_m for each enzyme (1.25 μM for IKKα/β and 5 μM for IKKε). After 1 h (IKKβ) or 2 h incubation (IKKα/ε) at room temperature, the reaction was stopped by addition of 20 mM EDTA in LANCE detection buffer, containing 2 nM Europium-labelled phospho-specific antibody (Perkin Elmer). Two hours later, the TR-FRET signals at 615 and 665 nm were measured upon excitation at 340 nm with a 50 μs delay in a Victor V multilabel reader. LANCE counts were normalized following Perkin Elmer's instructions. IC_{50} values for active compounds were determined using a 8 point titration experiment and GraphPrism software.

5.8.2. Cell proliferation assay

A luminescence based CellTiter-GLO assay (Promega) was used to determine the ATP levels as a measure of cell viability. Jurkat cells were grown in RPMI supplemented with 10% heat inactivated FBS. Cells were seeded the day before treatment in medium containing 0.5% FBS in a 384 well CulturPlate (Perkin Elmer) at a density of 10,000 cells per well (400,000 cells/mL). Cells were treated with increasing concentrations of the compounds in triplicate points. Control cells were treated with the same amount of solvent, DMSO, up to 0.1% v/v. After 24 h of treatment, a CellTiter-GLO assay was carried out following the manufacturer's instructions. A parallel CellTiter-GLO assay was performed at time 0 to determine cell growth and distinguish between inhibition of cell growth (cytostatic effect) versus induction of cell killing (cytotoxic effect).

5.8.3. DEVDase assay

Jurkat cells (20,000 per well) were seeded in 0.5% FBS-RPMI in a 384 well black OptiPlate. Following a 4 h incubation with 5 μM of test compounds, cells were lysed for 15 min (25 mM PIPES pH 7, 25 mM KCl, 5 mM EGTA, 1 mM DTT, 10 μM cytochalasin B, 0.5% NP-40, and a mixture of protease inhibitors consisting of 1 mM PMSF, 1 μg/mL leupeptine, and 1 μg/mL aprotinin) and DEVDase activity was measured following addition of an equal volume of 2× caspase buffer (50 mM HEPES pH 7.4, 100 mM NaCl, 1 mM EDTA, 5 mM DTT, 0.1% CHAPS and 10% sucrose) containing 100 μM of Ac-DEVD-AFC (Assay Biotechnology) essentially as described.[27] The emission at 510 nm was measured upon excitation at 390 nm every two minutes continuously for 1 h in a Victor 2 multilabel reader set at 37 °C and the slope of the linear part of the plot was calculated as a measure of DEVDase activity. The activity in untreated cells was measured as basal activity.

5.8.4. RAR/RXR transactivation assay

Gal4-RARα or Gal4-RXRα were transfected into HEK-293-luciferase reporter cells that express the luciferase gene under the control of 5 copies of an UAS element. HEK-293-luc cells were seeded in 96 well plates (30,000 cells per well) the day before transfection. Cells were transfected following a standard calcium phosphate DNA precipitation protocol using 10 ng Gal4-RARα or Gal4-RXRα vector together with 2 ng of β-galactosidase expression vector (50 ng total amount of DNA per well). Expression vectors have been described elsewhere.[27] Sixteen hours after transfection, cells were washed with PBS, replenished with fresh medium supplemented with 5% charcoal-treated FBS, and left to recover for 2 h prior to stimulation with 4 μM of the test compounds. As control, cells were stimulated with 1 μM atRA (Gal4-RARα), 1 μM CD3254 (Gal4-RXRα), or solvent (0.1% v/v DMSO) for basal activity. Cells were harvested 6 h (RARα) or 24 h (RXRα) after ligand stimulation and luciferase and β-galactosidase activities were measured using a Dual-Light chemiluminiscence assay system (Applied Biosystems) following the manufacturer's instructions. Normalized luciferase/β-galactosidase ratio was used to calculate the ligand-dependent RAR/RXR transactivation activity as fold induction over control non-stimulated cells. In a separate experiment, we tested the ability of compounds to function as RAR/RXR antagonists by stimulating cells with 0.1 μM atRA or 0.1 μM CD3254 in the absence or in the presence of 4 μM of the AdArs. Luciferase activity was normalized by β-galactosidase activity following background subtraction, and all activities were represented as percentage of control cells stimulated in the presence of atRA or CD3254.

5.8.5. RXR LBD-coactivator peptide recruitment assay

We used two different TR-FRET-based homogeneous assays to evaluate the interactions of recombinant GST-RXRα LBD with fluorescein labeled D22 coactivator peptide (Fl-LPYEGSL**LLKLL**RAP-VEEV) (Life Technologies) and with biotinylated SRC-1-676-700 peptide (CPSSHSSLTERHKI**LHRLL**QEGSPS-K-biotin) (AnaSpec). In both assays, 5 nM GST-RXRα LBD (Life Technologies) was incubated at room temperature with 150 nM coactivator peptide in a 20 μl final volume of binding buffer (25 mM Hepes pH 7.4 100 mM $NaCl_2$, 0.025% BSA, 5% glycerol, 0.005% Tween-20 and 2.5 mM DTT). Increasing concentrations of ligand or solvent control (⩽1% DMSO v/v) were included as indicated. For detection, 2 nM Terbium labeled anti-GST antibody (Life Technologies) was included in the Fl-D22 reaction and the TR-FRET signal was measured at 495 nm and 520 nm after 4 h of incubation at RT. The 520/495 ratio was calculated for each sample as a direct measure of RXRα-D22 interaction. Alternatively, 2 nM Eu-W1024-labeled anti-GST antibody (Perkin Elmer) together with 37.5 nM (4:1 biotin/streptavidin ratio) streptavidin conjugated SureLight-allophycocyanin (Perkin Elmer) were included in the binding reaction with biotin-SRC-1 peptide. The TR-FRET signal at 615 nm and 665 nm were measured after 4 h of incubation and the 665/615 ratio was used as RXRα-SRC-1 binding. To compare the results from different experiments, the percentage of change (Delta F%)

with respect to negative control samples containing no GST-RXRα was used as defined by CisBio:

$$\text{Delta F}\% = \frac{\text{Ratio of sample} - \text{ratio of negative control}}{\text{Ratio of negative control}} \times 100$$

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2014.01.006.

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