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Synthesis and Evaluation of Imidazo[2,1-*b*]thiazoles as Iodide Efflux Inhibitors in Thyrocytes

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The Na^+/I^- symporter (NIS) mediates iodide uptake in the thyroid gland as well as in other NIS-expressing cells. This transport is the basis for an emerging approach to selective cancer cell destruction by using radioiodide after targeted NIS gene transfer. Therapeutic efficacy requires that radioiodide retention be maximized in tumor cells. A first generation of forty imidazo[2,1-*b*]thiazole derivatives as iodide efflux inhibitors is described along with the evaluation of their biological properties. Structure–activity relationship studies by using radioiodide uptake in rat thyroid-derived cells (FRTL5) revealed that the 5,6-dihydroimidazo[2,1-*b*]thiazole heterocycle is required for activity. Introduction of electron-donor substituents on the 3-biphenyl moiety led to the discovery of novel potent compounds. A compound was identified with enhanced potency compared to reference **1**. These molecules give the possibility to increase the cellular retention of radioiodide in NIS-expressing tumors, leading to higher absorbed doses and killing efficacy.

Introduction

The sodium iodide symporter (NIS) is responsible for the accumulation of iodide in thyroid follicular cells, which represents the first step in the biosynthesis of thyroid hormones T3 and T4.[1] The ability of NIS-expressing cells to take up iodide has provided the basis for selective cell destruction in benign and malignant thyroid disease by using radioiodide (^{131}I).[2] It was proposed to extend this strategy to extrathyroid cancer tissues that do not express functional NIS.[3,4] Many investigators have demonstrated that NIS gene transfer mediated by nonviral or viral vectors into a variety of cells confers increased radioiodine uptake and renders them susceptible to being killed by ^{131}I in vitro.[5–7] In recent years, a therapeutic effect of ^{131}I on animals bearing tumors expressing ectopic NIS has been reported, demonstrating the potential of tumor-specific NIS gene therapy coupled with internal radioiodine therapy as a very promising strategy for treatment of cancers, especially those with a poor prognosis.[8–10] Unfortunately, radioiodine retention within these non-thyroid NIS-expressing cells was low due to a rapid efflux of free radioiodide. Thus, new strategies to increase radioiodide entrapment and ensure efficient cytotoxic effects are awaited. Several approaches have been proposed to efficiently increase cellular iodide retention, one of which is to use small organic molecules. Retinoic acid in conjunction with dexamethasone was reported to induce a significant increase of iodide accumulation in breast cancer xenotransplants by stimulation of functional NIS protein expression.[11] The DNA-demethylating agent 5-azacytidine was shown to restore NIS mRNA expression and iodide uptake in three thyroid cancer cell lines.[12] 4,4′-Diisothiocyanatostilbene-2,2′-disulfonic acid (DIDS) was found to significantly increase intracellular radioiodide retention in thyroid cancer cells by reducing iodide efflux.[13] However, none of these agents has been shown to consistently enhance radioiodide uptake in human clinical studies.[5]

Recently, 3-biphenyl-4′-yl-5,6-dihydroimidazo[2,1-*b*]thiazole (compound **1** in Figure 1), which was identified by high-

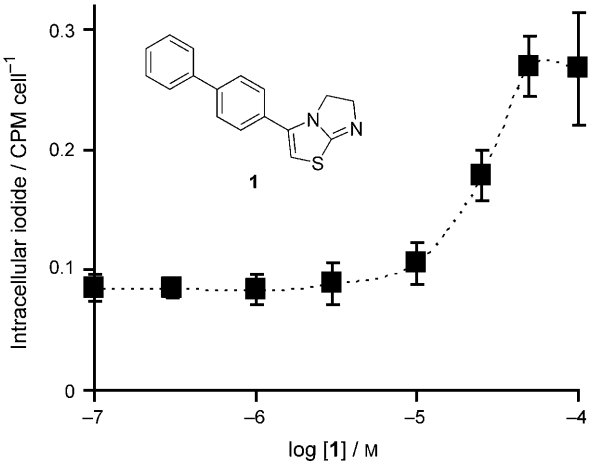

Figure 1. Concentration–response curve of compound **1**. FRTL5 cells in 96-well microplates were incubated at 20 °C for 120 min with **1** (10^{-7}–10^{-4} M) and $Na^{125}I$ (10 μM, 0.2 μCi per well). The cells were washed and radioactivity was determined after the addition of scintillation cocktail. Results are shown for one experiment, which is representative of three independent experiments with mean values ± standard deviation ($n=8$). $NaClO_4$-mediated inhibition of iodide uptake was tested as a control in each plate ($IC_{50}=2\times10^{-7}$ M, ±200%). CPM, counts per minute.

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throughput screening was shown to strongly enhance iodide retention in NIS-expressing cells.[14] By using this compound, cell-trapped iodide was increased by a factor of 4–5 in rat thyroid-derived cells (FRTL5), and by a factor of 2–3 in human embryonic kidney cells (HEK293) that were permanently transfected with the human NIS cDNA. Isotopic flux experiments showed that compound **1** does not act by activating NIS function. It was shown that compound **1** inhibits the function of an unidentified anion channel or exchanger. To further explore the mode of action of **1**, photoreactive analogues were recently designed with which it will be possible to identify the target protein(s) responsible for iodide efflux in NIS-expressing cells.[15] However, agents that enhance radioiodide retention are expected to improve radioablation regardless of the mechanism of action. The advent of **1** as a powerful iodide-sequestering agent is particularly attractive because dihydroimidazothiazoles are small versatile structures and can easily be synthesized. However, concentration–response experiments showed that **1** has a maximal activity at a concentration of 50–100 μM and is inactive below 10 μM (Figure 1). Therefore, it is extremely important to explore this class of compounds not only to design more potent compounds, but also to define structure–activity relationships and to provide pharmacological tools for the study of iodide efflux mechanisms.

We have synthesized a series of 40 analogues (**2**–**41**, Table 1) of compound **1** containing structural modifications of the biphenyl (**2**–**30**) or imidazothiazole (**31**–**41**) moieties. We have further investigated the effects of these variations on radioiodide uptake in FRTL5 cells.

Results and Discussion

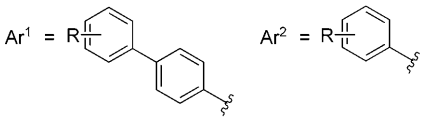
Chemistry

Variations of the biphenyl: The synthesis of compound **2** is depicted in Scheme 1. Commercially available 4-biphenylacetic acid was treated with *N*-bromosuccinimide and catalytic amounts of azobisisobutyronitrile in CH_2Cl_2 to afford the α-bromocarboxylic acid **43**. The α-bromoaldehyde **45** was obtained after esterification of **43** with trimethylsilyldiazomethane in a toluene/methanol solvent mixture, followed by reduction of ester **44** by reaction with diisobutylaluminium hydride. Compound **2** was finally obtained by using the Hantzsch thiazole synthesis by reacting 2-imidazolidinethione and haloaldehyde **45** in boiling ethanol.[16]

The preparation of compounds **3**–**20** was achieved by using Suzuki–Miyaura coupling reactions between key intermediate **21** and various commercially available arylboronic acids (Scheme 2).[17] Intermediate **21** was isolated as a hydroiodide salt after reacting 4-iodoacetophenone with 2-imidazolidinethione and iodine in boiling ethanol. For biological assays, **21** was isolated as the free base after liquid/liquid extraction work-up.

The synthesis of compounds **22**–**30** with various aryl groups in the 3-position of the dihydroimidazo[2,1-*b*]thiazole is depicted in Scheme 3. These compounds were prepared by using the Hantzsch thiazole synthesis from 2-imidazolidinethione

Table 1. Structure and biological evaluation of imidazo[2,1-*b*]thiazoles **1**–**41**.



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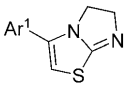
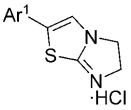
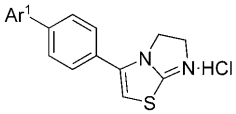
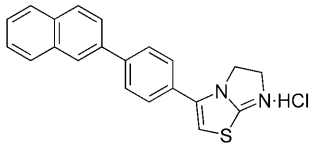
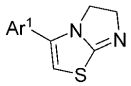
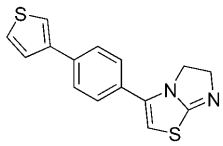
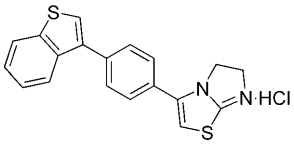
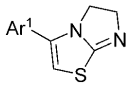
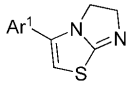
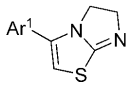
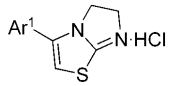
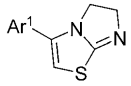
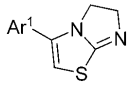
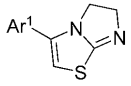
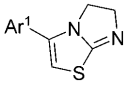
1		H	14	340
2		H	n.a.	n.a.
3		H	n.a.	n.a.
4			n.a.	n.a.
5		4-OPh	55	160
6			42	260
7			n.a.	n.a.
8		3,5-diCF_3	n.a.	n.a.
9		3-CF_3	n.a.	n.a.
10		2-CF_3	46	160
11		4-Me,5-NO_2	n.a.	n.a.
12		C(O)CH_3	67	120
13		3-Cl	n.a.	n.a.
14		3-NO_2	n.a.	n.a.
15		4-SMe	n.a.	n.a.

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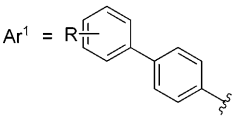
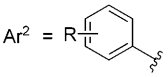
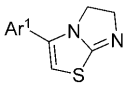
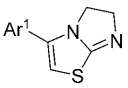
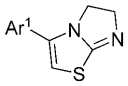
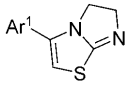
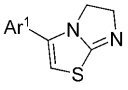
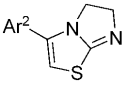
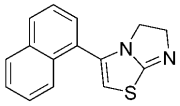
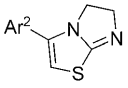
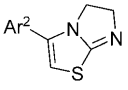
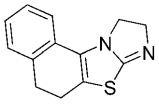
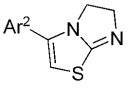
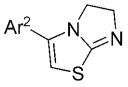
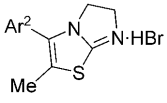
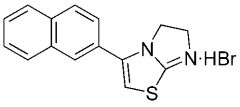
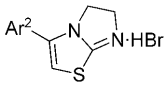
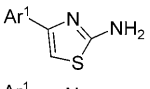
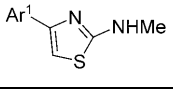
Ar^1 =  Ar^2 = 

Cmpd	Structure	R	EC_{150}[a] [μM]	% max[b]
16		4-OMe	n.a.	n.a.
17		4-OH	n.a.	n.a.
18		4-CH_2OH	32	240
19		4-NH_2	9	390
20		3-NH_2	36	210
21		4-I	n.a.	n.a.
22			n.a.	n.a.
23		3-OH	n.a.	n.a.
24		4-CO_2H	n.a.	n.a.
25			54	170
26		H	34	170
27		4-Br	74	120
28		4-Br	n.a.	n.a.
29			61	170
30		4-NO_2	42	120
31		H	n.a.	n.a.
32		H	n.a.	n.a.

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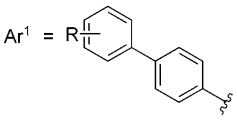
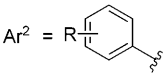
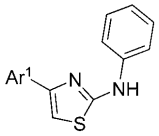
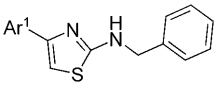
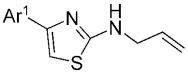
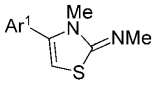
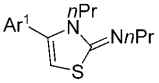
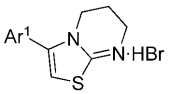
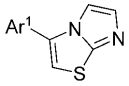
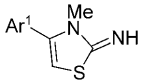
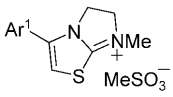
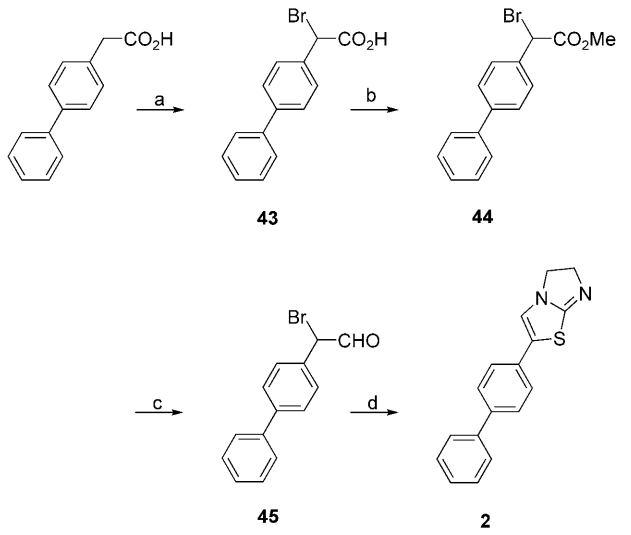
Ar^1 =  Ar^2 = 

Cmpd	Structure	R	EC_{150}[a] [μM]	% max[b]
33		H	n.a.	n.a.
34		H	n.a.	n.a.
35		H	n.a.	n.a.
36		H	n.a.	n.a.
37		H	n.a.	n.a.
38		H	n.a.	n.a.
39		H	n.a.	n.a.
40		H	n.a.	n.a.
41		H	n.a.	n.a.

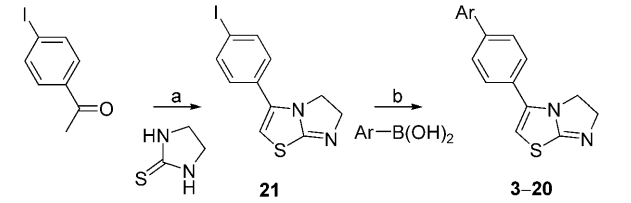
[a] EC_{150} is the concentration of compound required to increased iodide uptake halfway between minimal (100%) and maximal signals. [b] Maximum iodide entrapment at 100 μM (% max). Data are the means of three separate determinations. For reasons of clarity standard errors are not shown (< 10%). n.a. = not active.

and various 2-halocarbonyl compounds.[18] When the 2-halocarbonyl compound was not commercially available, the corresponding methylcarbonyl compound was used as the starting material. In this case, the 2-halocarbonyl compound was formed in situ by the addition of I_2 to the reaction mixture.

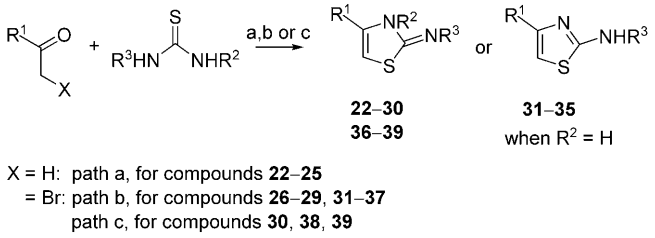
Variations at the dihydroimidazole ring: Compounds **31**–**39** were isolated after condensing 2′-bromo-4-phenylacetophenone with various thioureas by using the general Hantzsch thiazole synthesis (Scheme 3). In two particular cases (**38** and **39**), *p*-toluenesulfonic acid had to be added to the reaction mixture for the reaction to proceed. Concerning the regioselectivity of the cyclization reaction, it was reported that the Hantzsch synthesis starting from *N*-monosubstituted thioureas gives, without exception, aminothiazoles (the substituent is placed on the exocyclic nitrogen) rather than iminodihydro-



Scheme 1. *Reagents and conditions*. a) NBS, AIBN, CH_2Cl_2, reflux, 18 h; b) $TMSN_2$, toluene/MeOH, RT, 5 h; c) DIBAL-H, Et_2O, −78 °C, 4 h; d) 2-imidazolidinethione, EtOH, reflux, 16 h.



Scheme 2. *Reagents and conditions*. a) I_2, EtOH, reflux, 16 h; b) $Pd(PPh_3)_4$, K_3PO_4, DMF, 80 °C, 16 h.

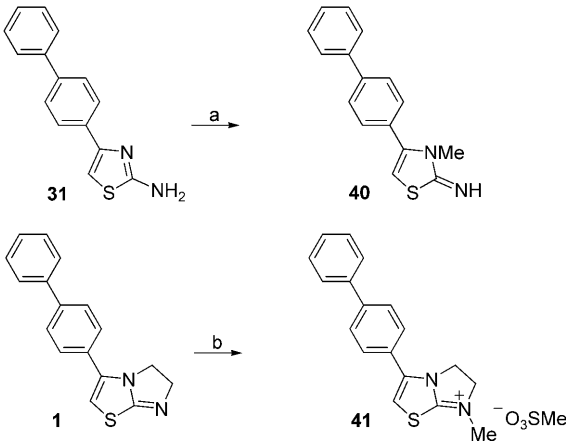


Scheme 3. *Reagents and conditions*. a) I_2, EtOH, reflux, 16 h; b) EtOH, reflux, 16 h; c) EtOH, APTS, reflux, 16 h.

thiazoles (the substituent is placed on the endocyclic thiazole nitrogen), as long as non-acidic conditions are used.[19] In the case of compounds **32**–**35**, ^{1}H NMR confirmed that *N*-monosubstituted aminothiazoles were obtained.

For the preparation of **40** and **41**, compounds **31** and **1** respectively were alkylated by using methyl methanesulfonate in boiling toluene (Scheme 4).

The identity of compounds **2**–**41** was verified by MS and ^{1}H NMR, and their purity was found to exceed 98% (reversed-phase HPLC).



Scheme 4. *Reagents and conditions*. a) $MeSO_3Me$, toluene, reflux, 18 h; b) $MeSO_3Me$, toluene, reflux, 4 h.

Biological results and discussion

Reference compound **1** was previously tested as the hydrobromide salt as well as the free base.[14] The biological activity of both samples was observed to be identical, showing that the use of salt forms has no influence on the outcome of the radioiodide uptake assay. However, it is extremely important that the tested samples are devoid of iodide because it will result in isotopic dilution during the assay. For this reason, compounds **2**–**41** were first assayed for iodide determination by using the Sandell–Kolthoff reaction.[20] The method uses the very specific catalytic effect of iodide on the reduction of the yellow-colored cerium ion (Ce^{4+}) to colorless Ce^{3+} by arsenious acid (As^{3+}). No trace of iodide was detected in the synthesized compound samples.

We then established the concentration–response curve of the newly synthesized compounds (**2**–**41**) for radioiodide uptake in FRTL5 cells. Potency was displayed as the EC_{150}, the concentration of compound required to increase iodide uptake halfway between minimal (100%) and maximal signals, and the percent maximum (%max) iodide entrapment that could be achieved at the highest tested concentration (i.e., 100 μM). The average standard error was calculated to be close to 10%. Thus, a compound was identified as active when %max exceeded 110%. The results show that 12 compounds (**5**, **6**, **10**, **12**, **18**–**20**, **25**–**27**, **29**, **30**) are able to significantly increase the level of cell-trapped iodide (Table 1 & Figure 2). The other 28 compounds were inactive.

A rapid review of the structure–activity relationship (SAR) showed that the 3-aryl-dihydroimidazo[2,1-*b*]thiazole is the basic structure for activity. Compounds with one phenyl group at C3 exhibited moderate activity (%max = 120 to 170% and EC_{150} = 34 to 74 μM, **25**–**27**, **30**) or were inactive (**21**, **23**, **24**, **28**). The addition of a second aromatic group to the 3-phenyl caused either a total loss of activity (**8**, **9**, **11**, **13**–**17**) or allowed maintenance of moderate to fairly good potency (EC_{150} = 9 to 67 μM and %max = 120 to 390%, **6**, **10**, **12**, **18**–**20**). In this series, compounds with electron-donating substituents on the biphenyl core (**18**–**20**) were more potent than compounds with electron-withdrawing substituents (**8**–**14**). The most inter-

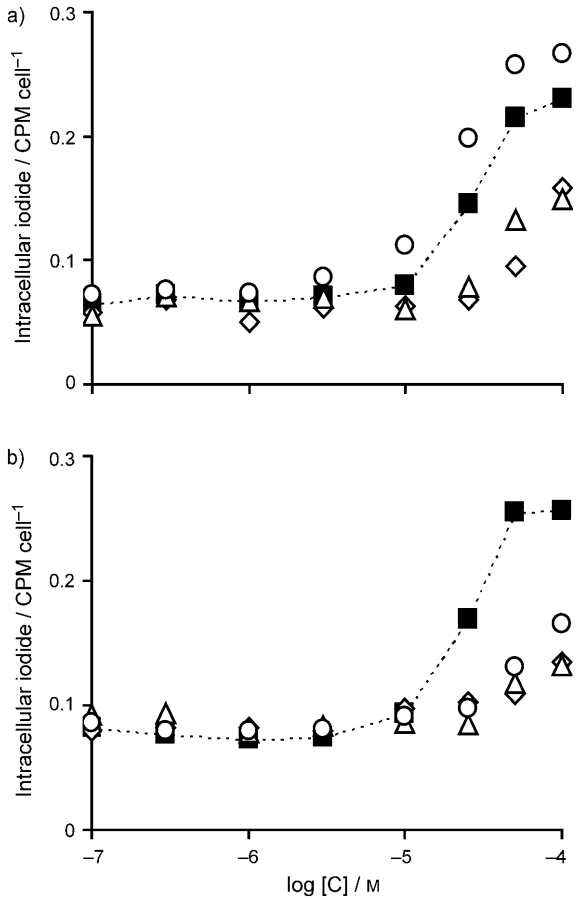


Figure 2. Concentration–response curve of six active compounds. FRTL5 cells were incubated at 20 °C for 120 min with compounds (10^{-7}–10^{-4} M) and $Na^{125}I$ (10 μM, 0.2 μCi per well). The cells were washed, and the radioactivity was determined after the addition of scintillation cocktail. Results are shown for one experiment, which is representative of three independent experiments. Standard errors ($n=3$) were in the range 2–11% from mean values. $NaClO_4$-mediated inhibition of iodide uptake was tested as a control in each plate ($IC_{50}=2\times10^{-7}$ M, ±200%). a) **1** (■), **6** (◇), **18** (△), **19**(○); b) **1** (■), **20** (○), **25** (◇), **29** (△). CPM, counts per minute.

esting result came from the 4-amino compound **19**, which displayed improved potency for iodide entrapment ($EC_{150}=9$ μM, %max = 390%) compared with reference compound **1** ($EC_{150}=14$ μM, %max = 340%). Notably, whereas the sequestering potency of **1** was close to background at 10 μM (110%), the 4-amino isomer **19** was significantly more potent at the same concentration (160%, see Figure 2). The 3-amino isomer **20** ($EC_{150}=36$ μM, %max = 210%) was less potent than **19**; this shows the importance of the orientation of the amino group on the second phenyl ring. The presence of additional aromatic groups on the biphenyl moiety (**3**–**5**) caused a partial or total loss of activity. Only the phenoxy derivative **5** retained moderate potency ($EC_{150}=55$ μM, %max = 160%), confirming that electron-donating substituents on the second aromatic group generally provide more potent molecules. Only a small loss of activity was observed when the second aryl group was replaced by a thiophenyl ($EC_{150}=42$ μM, %max = 260%, **6**), thus opening up possibilities for the preparation of second-generation libraries containing various heterocyclic moieties at this position. However, the benzo[*b*]thiophene derivative **7** was inactive, as were compounds **15**–**17** with electron-donating substituents. This result might be in contradiction with previous observations and suggests that electron-rich aromatic groups are important for compound activity. We believe that this behavior is caused by the poor solubility we observed for these particular compounds in aqueous media. The anchoring position of a naphthyl group in the 3-position of the dihydroimidazothiazole also affected the activity. Whereas the 2-naphthyl compound **29** caused a weak but significant enhancement of iodide entrapment ($EC_{150}=61$ μM, %max = 170%), the 1-naphthyl compound **22** was inactive. Varying the position of the biphenyl group on the dihydroimidazothiazole had a remarkable effect on potency. When the biphenyl was introduced at the C2 position (**2**), instead of C3 (**1**), we observed a complete loss of activity.

The dihydroimidazothiazole core was also examined. Interestingly, when the dihydroimidazole ring was modified to the saturated imidazo derivative **39**, potency was lost. The same was observed with compound **38** with a ring-expanded structure, as well as for aminothiazoles **31**–**35**, and mono- and di-alkyliminodihydrothiazoles **36**, **37**, and **40**. Taken together, these results show that the dihydroimidazothiazole moiety is essential for activity. The pK_a of compound **1** was measured as 7.9 by acid–base titration; this indicates that **1** is protonated in the assay media (pH 7.2). Hence, the question is raised whether the protonated form is necessary for the molecular recognition of **1** by its target. The *N*-methyl iminium **41** with a positive charge blocked at the 7-position was prepared and tested. We observed that this compound was inactive at concentrations up to 200 μM. However, the ionizable site is important for activity considering that it significantly increases drug solubility.

The anion channel blocker DIDS was reported to reduce iodide efflux and simultaneously increase the cellular retention of iodide in thyroid-derived cells.[13] We tested DIDS at three doses: 10 μM, 200 μM and 1 mM by using our experimental procedure. The results indicated that DIDS failed to increase iodide retention at the two lower doses (10 and 200 μM). In agreement with reported data,[13a,14] the anion channel blocker displayed a weak but significant effect at 1 mM in FRTL5 cells, with the intracellular radioactivity increased by 30–40% after incubation for two hours (not shown). Compounds from the dihydroimidazothiazole family produced much better biological activity as represented by compounds **1** and **19**, which increased intracellular iodide by 340% and 390%, respectively at 50 μM (Table 1).

To confirm the activity of the newly synthesized compounds, we tested their action on iodide efflux by using the isotopic dilution method. We believe this technique to be more suitable than simply rinsing the cells with iodide-free solutions because the initial drug concentration and distribution across cell membrane is preserved during the experiment. It is particularly important when a direct comparison of compound efficiency is needed. FRTL5 cells were loaded with $Na^{125}I$ in the absence or presence of compounds before an excess of cold NaI (250 μM) was added. Cell-trapped radioiodide was then measured for

90 min. We only tested the compounds that were found to be active in the preliminary radioiodide uptake assay: **1**, **5**, **6**, **10**, **12**, **18**–**20**, **25**–**27**, **29**, and **30** (50 μM) as well as DIDS (1 mM). As expected, radioiodide discharge was almost complete (>95%) in the absence of compound after 90 min; this illustrates the dynamic equilibrium between intra- and extracellular iodide. In this case, the period of time necessary to achieve a 50% discharge ($t_{1/2}$) was 10 min. The results showed that all the tested compounds significantly reduced radioiodide efflux (Figure 3a). In the presence of **1**, the release of radioiodide was strongly inhibited with merely 40% of cell-trapped iodide discharged after 90 min (Figure 3b). This result agrees well with reported values.[14] Compound **19** showed again the best potency with less than 25% iodide discharge after 90 min. As expected, compound **29** was less efficient than **1** and **19** to retain iodide (53% at 90 min). DIDS was found to be the weakest efflux inhibitor with >80% discharge at 90 min ($t_{1/2}$ = 30 min).

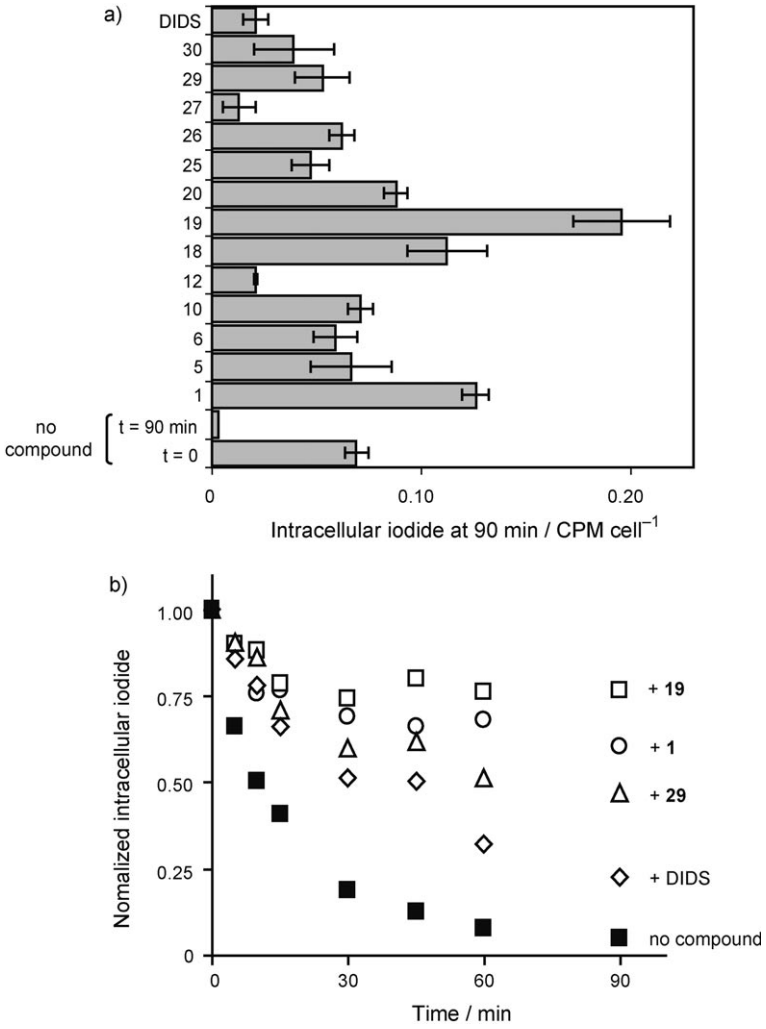


Figure 3. Iodide efflux in the presence of test compounds. FRTL5 cells were incubated for 120 min at 20 °C with $Na^{125}I$ (10 μM, 0.2 μCi per well) in the absence or presence of iodide efflux inhibitors. An excess of cold NaI (250 μM) was then added before cell-associated radioactivity was measured (0, 5, 10, 15, 30, 45, 60, and 90 min). Results are shown for one experiment, which is representative of two independent experiments. Values are the mean of triplicate determinations. Dihydroimidazothiazoles derivatives were tested at 50 μM, DIDS was tested at 1 mM. a) Results are shown for all tested compounds 90 min after the addition of cold NaI (250 μM). CPM, counts per minute. b) Time-dependent iodide efflux for representative compounds: **1** (○), **19** (□), **29** (△), DIDS (◇) and no compound (■). For clarity, data were normalized.

Conclusions

Herein we report the synthesis of a first generation of imidazo[2,1-*b*]thiazole derivatives as iodide efflux inhibitors and the evaluation of their biological properties. The results show that compounds from the dihydroimidazothiazole family are superior to the broad-spectrum anion channel blocker DIDS for enhancing the cellular retention of iodide. SAR studies by using radioiodide uptake in rat thyroid-derived cells (FRTL5) revealed that the 3-aryl-5,6-dihydroimidazo[2,1-*b*]thiazole core is the minimal structure required for activity. We found that the electronic properties of the second aromatic group on the biphenyl moiety significantly affect compound potency, thus opening up new perspectives for the design of more focused libraries. The results show that subtle differences in compound structure have dramatic effects on biological activity; this suggests a very selective mechanism for the recognition of **1** by its target. This study has not only provided important SAR data, but has also identified a new compound (**19**) with enhanced potency compared with reference compound. It could be used in an in vivo disease-oriented model to further validate that cytoreductive gene therapy with radioiodide is a promising concept for the treatment of cancer.

Experimental Section

General methods: All reagents and solvents were from Sigma–Aldrich. $Pd(PPh_3)_4$ and **1** were prepared according to reported procedures.[14,21] LC–MS analysis was performed on a system equipped with a binary gradient solvent delivery system (LC-20AB, Shimadzu), a photodiode array detector (2996, Waters), and an electrospray ionization mass spectrometer (Micromass-ZQ, Waters). Each compound (5–10 μg) was applied to a 250× 4.6 mm (5 μm) Zorbax SB-C18 (Agilent) equilibrated with MeCN/H_2O, 20:80 and 0.1% formic acid. Samples were eluted by increasing MeCN to 50% (18 min). ^1H NMR spectra were recorded at 300 K in [D_6]DMSO or $CDCl_3$ on a Bruker Avance DPX 400 spectrometer operating at 400 MHz. Infrared spectra were recorded on a Perkin–Elmer 2000 FT-IR system. FRTL5 cells were cultured and seeded in 96-well microtiter plates (isoplate-96, Perkin–Elmer) as described elsewhere.[22]

Radioiodide uptake and efflux measurements:[14] Confluent cell cultures in 96-well microtiter plates were washed (Power washer PW384, Tecan) with uptake buffer (HBSS/HEPES 10 mM) such that 80 μL per well of fresh buffer remained at the end of the cycle, and allowed to stand at RT for 30 min. Solutions of compounds (10 μL per well, 1×10^{-7}–1×10^{-4} M final) and $Na^{125}I$ (10 μL per well, 0.2 μCi, 10 μM final) were rapidly

distributed into the microplates. The cells were allowed to stand at RT for 2 h, washed with cold (+4 °C) uptake buffer (PW384), and the remaining supernatants were immediately discarded. Scintillation cocktail (160 μL per well, Analytic Unisafe 1, Zinsser, Frankfurt, Germany) was added, and the microplates were shaken overnight at RT before the radioactivity was measured (Microbeta Trilux, Turku, Finland). In each plate, the $NaClO_4$-mediated inhibition of NIS was measured as a control. $NaClO_4$ was used in the range 10^{-12}–10^{-3} M. Iodide efflux was measured in FRTL5 cells in the presence or absence of compounds by using the isotopic dilution method. Briefly, FRTL5 cells were allowed to stand at RT with compounds (50 μM) and $Na^{125}I$ (0.2 μCi, 10 μM final) for 120 min before a solution of cold NaI (250 μM final) was added. Cold NaI was added in small volumes (5 μL) from a concentrated solution (2.5 mM) to minimize dilution. Cell-associated radioactivity was then measured at 0, 5, 10, 15, 30, 45, 60, and 90 min after removal of the supernatants, as described above.

Iodide detection in synthesized compounds: Iodide concentration in compound samples was determined by using the Sandell–Kolthoff reaction.[20] Samples were tested in 96-well clear polystyrene microplates by diluting DMSO solutions of compounds (10 mM) in NaCl (4 g L)$^{-1}$, sodium arsenite (8 mM, prepared from As_2O_3 and NaOH) in 230 μL well^{-1} total volume. The reaction was started after the addition (20 μL well^{-1}) of a solution consisting of ammonium cerium(IV) sulfate (40 mM) in 3.6 N H_2SO_4. The absorbance at 420 nm was recorded on a SpectraMax Plus 384 (Molecular Devices, Sunnyvale, USA) after 20 min and compared with KI standards (0, 5, 10, 15, 20, 25, 30 μg L^{-1}).

2-Bromo-biphenyl-4′-yl-acetic acid (43): A mixture of 4-biphenylacetic acid (200 mg, 0.91 mmol), *N*-bromosuccinimide (185 mg, 1.05 mmol) and azobisisobutyronitrile (7.8 mg, 0.047 mmol) in CH_2Cl_2 (10 mL) was refluxed for 18 h and then allowed to cool to RT. The solvent was removed under vacuum, and the resulting solid was dissolved in Et_2O (25 mL) and washed with H_2O (20 mL). The organic layer was dried (Na_2SO_4) and evaporated to afford **43** (149 mg, 57% yield) as a yellow solid. The compound was sufficiently pure (90–95%) to be used in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.66 (m, 6H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.6 H, 1H), 5.43 ppm (s, 1H); IR (KBr): $\tilde{\nu}$ = 3600–2550 (br), 1712, 1486, 1187, 1145, 1005, 641 cm^{-1}; MS (ESI−): *m/z* (%) 289 (50) and 291 (50) $[M-H]^-$.

2-Bromo-biphenyl-4′-yl-acetic acid methyl ester (44): Trimethylsilyldiazomethane (1.35 mmol, 3 equiv) was slowly added to a mixture of 2-bromo-biphenyl-4′-yl-acetic acid **43** (130 mg, 0.45 mmol) in toluene/MeOH, 2:1 (4.5 mL) at RT. The mixture was stirred for 5 h at RT before the solvents were removed. The resulting solid was purified by chromatography (silica, cyclohexane/EtOAc/MeOH, 95:5:1) to afford **44** (96 mg, 72% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.67 (m, 6H), 7.47 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 5.45 (s, 1H), 3.83 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 2950, 1751, 1432, 1409, 1146, 1001, 733, 693 cm^{-1}; MS (ESI+): *m/z* (%) 305 (50), 307 (50) $[M+H]^+$.

2-Bromo-biphenyl-4′-yl-acetaldehyde (45): A 1 M solution of DIBAL-H in CH_2Cl_2 (200 μL mg, 0.2 mmol) was slowly added to a solution of 2-bromo-biphenyl-4′-yl-acetic acid methyl ester **44** (40 mg, 0.13 mmol) in Et_2O (1 mL) at −78 °C under argon. The mixture was stirred for 4 h at −78 °C, then 1 N HCl (200 μL) was added to the cold solution. The hydrolyzed mixture was allowed to warm to RT before Et_2O (10 mL) was added. This solution was washed with 0.1 N HCl (2×2 mL), and the solvent was removed by evaporation. The resulting solid was purified by chromatography (silica, cyclohexane/EtOAc/MeOH, 90:10:1) to afford **45** (12.3 mg, 38% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.61 (d, J = 3.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 5.32 ppm (d, J = 3.6 Hz, 1H); IR (KBr): $\tilde{\nu}$ = 3030, 1683, 1603, 1485, 1288, 1178, 1004, 751, 696 cm^{-1}; MS (ESI−): *m/z* (%) 273 (50), 275 (50) $[M-H]^-$.

General procedure for Suzuki–Miyaura coupling reactions, Method A: A mixture of 3-(4-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydroiodide **21** (1 equiv), boronic acid (1.1 equiv), 2 M aq K_3PO_4 (2 equiv), and freshly prepared tetrakis(triphenylphosphine)-palladium(0) (0.1 equiv) in DMF (1 mL per 100 μmol of **21**) was stirred at 80 °C under argon for 14–16 h. The reaction mixture was cooled to RT, and the solvent was evaporated.

General procedure for the Hantzsch cyclization reactions, Method B: When 2-bromoketones were used as the starting material (compounds **2**, **26**–**39**), a mixture of 2-bromoketone (1 equiv) and thiourea (2 equiv) was refluxed for 16 h in EtOH (1 mL per 100–200 μmol of thiourea). When acetophenones were used (compounds **21**–**25**), I_2 (2 equiv) was also added to the reaction mixture. In some cases (compounds **2**, **30**, **38**, and **39**) *p*-toluenesulfonic acid (1 equiv) was added to the mixture for the reaction to proceed. The reaction mixture was allowed to cool to RT. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2, washed with 5% $Na_2S_2O_3$, 10% Na_2CO_3, and brine. The organic layer was dried (Na_2SO_4) and evaporated.

2-Biphenyl-4′-yl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (2): The title compound was prepared from 2-bromo-biphenyl-4′-yl-acetaldehyde **45** (10 mg, 0.035 mmol) and 2-imidazolidinethione (3.5 mg, 0.035 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, cyclohexane/EtOAc/MeOH, 90:10:1 then 70:30:1) to afford **2** (7.6 mg, 81% yield) as a colorless oil. The free base was dissolved with 1 N HCl (2 mL), and this solution was lyophilized to afford the hydrochloride salt of **2** as a white solid (6.3 mg). HPLC: t_R = 13.7 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.61 (m, 4H), 7.45 (t, J = 7.2 Hz, 2H), 7.32–7.39 (d, 3H), 6.93 (s, 1H), 4.28 (t, J = 9.2 Hz, 2H), 3.99 ppm (t, J = 9.2 Hz, 2H); MS (ESI+): *m/z* 279 $[M+H]^+$.

3-[1,1′;4′,1″]Terphenyl-4″-yl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (3): The title compound was prepared from **21** (40 mg) and 4-biphenylboronic acid (26.5 mg) according to method A. After evaporation of the solvent, the residue was triturated with 1 N HCl (5 mL), H_2O (5 mL), and CH_2Cl_2 (5 mL), and dried under vacuum to afford the hydrochloride salt of **3** (27.3 mg, 57% yield) as a brown solid. HPLC: t_R = 18.2 min; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.67 (br s, 1H), 7.90 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 8.0 Hz, 2H), 7.49 (t, J = 7.4 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.09 (s, 1H), 4.58 (t, J = 9.6 Hz, 2H), 4.31 ppm (t, J = 9.6 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3570–2360 (br), 1589, 1573, 1573, 1484, 1373, 1151, 1002, 829, 746 cm^{-1}; MS (ESI+): *m/z* 355 $[M+H]^+$.

3-(4-Naphthalen-2-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (4): The title compound was prepared from **21** (40 mg) and 2-naphthylboronic acid (23.0 mg) according to method A. After evaporation of the solvent, the residue was triturated with 1 N HCl (5 mL), H_2O (5 mL), and CH_2Cl_2 (5 mL), and dried under vacuum to afford the hydrochloride salt of **4** (14.2 mg, 32% yield) as a brown solid. HPLC: t_R = 18.0 min; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.66 (br s, 1H), 8.32 (s, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.95 (d, J = 2.0 Hz, 1H), 7.91 (dd, J = 8.8 Hz, J' = 2.0 Hz, 1H), 7.77 (d, J = 8.4 Hz, 2H), 7.56 (m, 2H), 7.10 (s, 1H), 4.59 (t, J = 9.6 Hz, 2H), 4.33 ppm (t, J = 9.6 Hz, 2H); IR (KBr): $\tilde{\nu}$ =

3620–2510 (br), 1588, 1570, 1501, 1371, 1301, 1149, 1010, 814, 758 cm^{-1}; MS (ESI+): *m/z* 329 $[M+H]^+$.

3-(4′-Phenoxyphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (5): The title compound was prepared from **21** (30 mg) and 4-phenoxyphenylboronic acid (21.4 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (silica, cyclohexane/EtOAc/MeOH 80:20:1 then 70:30:1) to afford **5** (3.0 mg, 11% yield) as a tan solid. HPLC: t_R = 18.6 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 7.6 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 5.88 (s, 1H), 4.32 (t, *J* = 9.0 Hz, 2H), 4.01 ppm (t, *J* = 9.0 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 2924, 2854, 1691, 1587, 1486, 1240, 1168, 1006, 755 cm^{-1}; MS (ESI+): *m/z* 371 $[M+H]^+$.

3-(4-Thiophen-3-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (6): The title compound was prepared from **21** (30 mg) and 3-thienylboronic acid (12.9 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, cyclohexane/EtOAc/MeOH, 75:20:5) to afford **6** (13.2 mg, 51% yield) as a yellow solid. HPLC: t_R = 13.5 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.50 (ddd, *J* = 2.8 Hz, *J′* = 1.6 Hz, *J″* = 0.4 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 0.4 Hz, 1H), 7.56 (dd, *J* = 5.6 Hz, *J′* = 0.4 Hz, 1H), 5.76 (s, 1H), 4.29 (t, *J* = 9.2 Hz, 2H), 3.91 ppm (t, *J* = 9.2 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 2954, 2925, 2855, 1734, 1690, 1598, 1460, 1376, 1254, 865, 844, 783 cm^{-1}; MS (ESI+): *m/z* 285 $[M+H]^+$; HRMS-ESI-TOF: *m/z*: calcd for $C_{15}H_{13}N_2S_2$: 285.0520 $[M+H]^+$; found 285.0513.

3-(4-Benzo[*b*]thiophen-3-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (7): The title compound was prepared from **21** (40 mg) and 1-benzothiophene-3-boronic acid (23.9 mg) according to method A. After evaporation of the solvent, the residue was triturated with 1 N HCl (5 mL), H_2O (5 mL), and CH_2Cl_2 (5 mL), and dried under vacuum to afford the hydrochloride salt of **7** (18.4 mg, 41% yield) as a brown solid. HPLC: t_R = 15.8 min; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.89 (br s, 1H), 8.10 (dd, *J* = 6.4 Hz, *J′* = 2.4 Hz, 1H), 7.96 (s, 1H), 7.92 (dd, *J* = 6.4 Hz, *J′* = 2.4 Hz, 1H), 7.78 (s, 4H), 7.46 (ddd, *J* = 7.0 Hz, *J′* = 6.4 Hz, *J′* = 2.4 Hz, 2H), 7.10 (s, 1H), 4.60 (t, *J* = 9.6 Hz, 2H), 4.32 ppm (t, *J* = 9.6 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3660–2400 (br), 1588, 1566, 1520, 1370, 1282, 1147, 1007, 832, 764, 736 cm^{-1}; MS (ESI+): *m/z* 335 $[M+H]^+$.

3-[3′,5′-(Bistrifluoromethyl)phenyl-4-yl-phenyl]-5,6-dihydroimidazo[2,1-*b*]thiazole (8): The title compound was prepared from **21** (30 mg) and 3,5-bis(trifluoromethyl)phenylboronic acid (25.9 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, cyclohexane/EtOAc/MeOH, 70:30:1 then 50:50:1) to afford **8** (8.8 mg, 23% yield) as a tan solid. HPLC: t_R = 16.2 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (s, 2H), 7.90 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 5.94 (s, 1H), 4.34 (t, *J* = 9.4 Hz, 2H), 4.00 ppm (t, *J* = 9.4 Hz, 2H); MS (ESI+): *m/z* 415 $[M+H]^+$.

3-(3′-Trifluoromethylphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (9): The title compound was prepared from **21** (30 mg) and 3-trifluoromethylphenylboronic acid (19.2 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, cyclohexane/EtOAc/MeOH, 70:30:1 then 50:50:1) to afford **9** (11.7 mg, 38% yield) as a tan solid. HPLC: t_R = 15.4 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.65 (s, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 5.93 (s, 1H), 4.30 (t, *J* = 9.4 Hz, 2H), 4.01 ppm (t, *J* = 9.4 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3257, 2926, 1695, 1593, 1335, 1263, 1165, 1123, 1005, 802, 701 cm^{-1}; MS (ESI+): *m/z* 347 $[M+H]^+$.

3-(2′-Trifluoromethylphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (10): The title compound was prepared from **21** (40 mg) and 2-trifluoromethylphenylboronic acid (25.4 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified twice by chromatography (neutral alumina, cyclohexane/EtOAc/MeOH, 70:30:1 then 50:50:1) to afford **10** (13.4 mg, 9% yield) as a tan solid. HPLC: t_R = 15.0 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 5.79 (s, 1H), 4.28 (t, *J* = 9.0 Hz, 2H), 3.92 ppm (t, *J* = 9.0 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3059, 2925, 1696, 1603, 1315, 1262, 1171, 1125, 1005, 769, 736 cm^{-1}; MS (ESI+): *m/z* 347 $[M+H]^+$.

3-(4′-Methyl-3′-nitrophenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrochloride (11): The title compound was prepared from **21** (40 mg) and 4-methyl-3-nitrophenylboronic acid (24.2 mg) according to method A. After evaporation of the solvent, the residue was triturated with 1 N HCl (5 mL), H_2O (5 mL), and CH_2Cl_2 (5 mL), and dried under vacuum to afford the hydrochloride salt of **11** (5.7 mg, 14% yield) as a tan solid. HPLC: t_R = 15.7 min; ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 9.63 (br s, 1H), 8.30 (d, *J* = 2.0 Hz, 1H), 8.03 (dd, *J* = 8.0 Hz, *J′* = 2.0 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.10 (s, 1H), 4.56 (t, *J* = 9.6 Hz, 2H), 4.30 (t, *J* = 9.6 Hz, 2H), 2.55 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 3570–2640 (br), 1579, 1518, 1356, 1290, 1156, 1009, 822, 757 cm^{-1}; MS (ESI+): *m/z* 338 $[M+H]^+$.

3-(4′-Acetylphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (12): The title compound was prepared from **21** (30 mg) and 4-acetylphenylboronic acid (16.3 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **12** (10.3 mg, 36% yield) as a tan solid. HPLC: t_R = 14.9 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 8.4 Hz, 4H), 7.54 (d, *J* = 8.0 Hz, 2H), 5.82 (s, 1H), 4.29 (t, *J* = 9.0 Hz, 2H), 3.93 (t, *J* = 9.0 Hz, 2H), 2.65 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 3051, 2923, 2854, 1677, 1600, 1358, 1266, 1183, 1002, 820, 598 cm^{-1}; MS (ESI+): *m/z* 321 $[M+H]^+$.

3-(3′-Chlorophenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (13): The title compound was prepared from **21** (40 mg) and 3-chlorophenylboronic acid (21.0 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **13** (6.4 mg, 16% yield) as

a brown solid. HPLC: $t_R = 16.2$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.61 (d, $J = 8.0$ Hz, 2H), 7.59 (t, $J = 1.6$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.48 (dt, $J = 8.0$ Hz, $J' = 1.6$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.36 (dt, $J = 8.0$ Hz, $J' = 1.6$ Hz, 1H), 5.81 (s, 1H), 4.29 (t, $J = 9.4$ Hz, 2H), 3.93 ppm (t, $J = 9.4$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3203$, 2957, 2927, 1728, 1691, 1594, 1262, 1026, 786, 691 cm^{-1}; MS (ESI+): *m/z* (%) 313 (100), 315 (35) $[M+H]^+$.

3-(3′-Nitrophenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (14): The title compound was prepared from **21** (40 mg) and 3-nitrophenylboronic acid (22.4 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **14** (18.6 mg, 64% yield) as a brown solid. HPLC: $t_R = 14.8$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.47 (s, 1H), 8.24 (d, $J = 8.0$ Hz, 1H), 7.93 (d, $J = 8.0$ Hz, 1H), 7.69 (d, $J = 8.0$ Hz, 2H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.57 (d, $J = 8.0$ Hz, 2H), 5.85 (s, 1H), 4.31 (t, $J = 9.0$ Hz, 2H), 3.94 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} = 2924$, 2855, 1695, 1594, 1529, 1349, 1262, 731 cm^{-1}; MS (ESI+): *m/z* 324 $[M+H]^+$.

3-(4′-Thiomethylphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (15): The title compound was prepared from **21** (30 mg) and 4-thiomethylphenylboronic acid (16.9 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **15** (5.1 mg, 18% yield) as a brown solid. HPLC: $t_R = 14.3$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$ (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.4$ Hz, 2H), 7.49 (d, $J =$ 8.4 Hz, 2H), 7.34 (d, $J = 8.4$ Hz, 2H), 5.82 (s, 1H), 4.30 (t, $J = 9.0$ Hz, 2H), 3.95 (t, $J = 9.0$ Hz, 2H), 2.54 ppm (s, 3H); IR (KBr): $\tilde{\nu} = 3362$, 2924, 2854, 1710, 1601, 1453, 1179, 1007, 682 cm^{-1}; MS (ESI+): *m/z* 325 $[M+H]^+$.

3-(4′-Methoxyphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (16): The title compound was prepared from **21** (40 mg) and 4-methoxyphenylboronic acid (20.4 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **16** (7.6 mg, 21% yield) as a tan solid. HPLC: $t_R = 14.6$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 8.4$ Hz, 2H), 7.54 (d, $J = 8.4$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.00 (d, $J = 8.4$ Hz, 2H), 5.78 (s, 1H), 4.26 (t, $J = 9.0$ Hz, 2H), 3.93 (t, $J = 9.0$ Hz, 2H), 3.86 ppm (s, 3H); IR (KBr): $\tilde{\nu} = 2925$, 2855, 1688, 1600, 1496, 1249, 1179, 1034, 822 cm^{-1}; MS (ESI+): *m/z* 309 $[M+H]^+$.

3-(4′-Hydroxyphenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (17): The title compound was prepared from **21** (30 mg) and 4-hydroxyphenylboronic acid (13.9 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was triturated with H_2O (5 mL), CH_2Cl_2 (5 mL), and dried under vacuum to afford to afford **17** (23.0 mg, 86% yield) as a brown solid. HPLC: $t_R = 11.8$ min; ^{1}H NMR (400 MHz, $[D_6]$DMSO): $\delta = 9.62$ (s, 1H), 7.67 (d, $J = 8.4$ Hz, 2H,), 7.58 (d, $J = 8.4$ Hz, 2H), 7.53 (d, $J = 8.0$ Hz, 2H), 6.85 (d, $J = 8.0$ Hz, 2H), 6.31 (s, 1H), 4.12 (t, $J = 9.0$ Hz, 2H), 4.02 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} = 2880$, 2580, 2361, 1661, 1593, 1495, 1287, 1174, 975, 824 cm^{-1}; MS (ESI+): *m/z* 295 $[M+H]^+$.

3-[4′-(Hydroxymethyl)phenyl-4-yl-phenyl]-5,6-dihydroimidazo-[2,1-*b*]thiazole (18): The title compound was prepared from **21** (30 mg) and 4-(hydroxymethyl)phenylboronic acid (15.3 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was triturated with H_2O (5 mL), CH_2Cl_2 (5 mL), and dried under vacuum to afford to afford **18** (23.0 mg, 95% yield) as a brown solid. HPLC: $t_R = 13.3$ min; ^{1}H NMR (400 MHz, $[D_6]$DMSO): $\delta = 7.72$ (d, $J = 8.0$ Hz, 2H), 7.66 (d, $J = 7.6$ Hz, 2H), 7.62 (d, $J = 8.0$ Hz, 2H), 7.41 (d, $J = 7.6$ Hz, 2H), 6.20 (s, 1H), 5.23 (br s, 1H), 4.53 (s, 2H), 4.09 (t, $J = 9.0$ Hz, 2H), 3.91 ppm (t, $J =$ 9.0 Hz, 2H); IR (KBr): $\tilde{\nu} = 3116$, 2871, 1664, 1592, 1495, 1372, 1053, 977, 805 cm^{-1}; MS (ESI+): *m/z* 309 $[M+H]^+$; HRMS-ESI-TOF: *m/z*: calcd for $C_{18}H_{17}N_2OS$: 309.1062 $[M+H]^+$; found 309.1056.

3-(4′-Aminophenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (19): The title compound was prepared from **21** (30 mg) and 4-aminophenylboronic acid pinacol ester (22.0 mg) according to method A. After evaporation of the solvent, the residue was dissolved in 1 N HCl (10 mL) and washed with EtOAc (2×3 mL). The aqueous phase was basified with 4 N NaOH to pH >10 and extracted with EtOAc (5×5 mL). The organic phases were pooled, washed with brine (3 mL), dried (Na_2SO_4), and evaporated to afford **19** (23.2 mg, 87% yield) as an off-white solid. HPLC: $t_R = 11.4$ min; ^{1}H NMR (400 MHz, $[D_6]$DMSO): $\delta = 7.59$ (d, $J = 8.0$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.39 (d, $J = 8.4$ Hz, 2H), 6.63 (d, $J = 8.4$ Hz, 2H), 6.12 (s, 1H), 5.30 (s, 2H), 4.08 (t, $J = 9.0$ Hz, 2H), 3.89 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3310$, 3122, 2925, 1649, 1594, 1497, 1367, 973, 821 cm^{-1}; MS (ESI+): *m/z* 294 $[M+H]^+$; HRMS-ESI-TOF: *m/z*: calcd for $C_{17}H_{16}N_3S$: 294.1065 $[M+H]^+$; found 294.1067.

3-(3′-Aminophenyl-4-yl-phenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (20): The title compound was prepared from **21** (30 mg) and 3-aminophenylboronic acid (17.4 mg) according to method A. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (10 mL) and washed with 10% Na_2CO_3 (3 mL) and brine (3 mL). The organic layer was dried (Na_2SO_4) and evaporated. The resulting solid was purified by chromatography (silica, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **20** (8.4 mg, 32% yield) as a brown solid. HPLC: $t_R = 12.0$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.61$ (d, $J =$ 8.4 Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 2H), 7.24 (d, $J = 8.0$ Hz, 1H), 6.99 (d, $J = 8.0$ Hz, 1H), 6.91 (s, 1H), 6.71 (d, $J = 8.0$ Hz, 1H), 5.78 (s, 1H), 4.29 (t, $J = 9.0$ Hz, 2H), 3.93 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} =$ 2956, 2923, 2854, 1729, 1595, 1460, 1377, 1270, 736 cm^{-1}. MS (ESI+): *m/z* 294 $[M+H]^+$; HRMS-ESI-TOF: *m/z*: calcd for $C_{17}H_{16}N_3S$: 294.1065 $[M+H]^+$; found 294.1064.

3-(4-Iodophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydroiodide (21): The title compound was prepared from 4-iodoacetophenone (1.1 g, 4.5 mmol) and 2-imidazolidinethione (830 mg, 9 mmol) according to method B. For this compound, a precipitate was formed at the end of the reaction. The solid was collected by filtration, washed with EtOH (2×10 mL), and dried under vacuum to afford the hydroiodide salt of **21** (1.81 g, 88% yield) as a white solid. HPLC: $t_R = 10.8$ min;^{1}H NMR (400 MHz, $[D_6]$DMSO): $\delta = 9.56$ (br s, 1H), 7.90 (d, $J = 8.4$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.03 (s, 1H), 4.47 (t, $J = 9.6$ Hz, 2H), 4.26 ppm (t, $J = 9.6$ Hz, 2H); IR (KBr): $\tilde{\nu} =$ 3077, 2933, 1732, 1582, 1485, 1397, 1276, 974, 726, 531 cm^{-1}; MS (ESI+): *m/z* 329 $[M+H]^+$. For biological evaluations, a fraction of the hydroiodide salt was resuspended in CH_2Cl_2, washed with 5% $Na_2S_2O_5$, 10% Na_2CO_3, and brine. The organic layer was dried

(Na_2SO_4) and evaporated to afford the free base of **21** as a white solid. HPLC: $t_R = 10.8$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$ (d, $J =$ 8.4 Hz, 2H), 7.16 (d, $J = 8.4$ Hz, 2H), 5.75 (s, 1H), 4.27 (t, $J = 9.2$ Hz, 2H), 3.84 ppm (t, $J = 9.2$ Hz, 2H); MS (ESI+): m/z 329 $[M+H]^+$.

3-Naphthalen-1-yl-5,6-dihydroimidazo[2,1-*b*]thiazole (22): The title compound was prepared from 1′-acetonaphthone (44.6 μL, 0.29 mmol) and 2-imidazolidinethione (60 mg, 0.59 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **22** (7.5 mg, 10% yield) as a white solid. HPLC: $t_R = 11.1$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$ (dd, $J = 6.0$ Hz, $J' =$ 3.6 Hz, 1H), 7.96 (dd, $J = 7.6$ Hz, $J' = 2.0$ Hz, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.62 (t, $J = 6.8$ Hz, 1H), 7.61 (t, $J = 6.8$ Hz, 1H), 7.56 (d, $J =$ 6.0 Hz, 1H), 7.54 (s, 1H), 6.46 (s, 1H), 4.45 (t, $J = 9.2$ Hz, 2H), 3.99 ppm (t, $J = 9.2$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3052$, 2954, 2869, 2360, 1704, 1594, 1366, 1242, 1021, 804, 777 cm^{-1}; MS (ESI+): m/z 253 $[M+H]^+$.

3-(3-Hydroxyphenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (23): The title compound was prepared from 3-hydroxyphenylacetophenone (1.5 g, 7.4 mmol) and 2-imidazolidinethione (1 g, 14.7 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **23** (1.36 g, 53% yield) as a white solid. HPLC: $t_R = 5.4$ min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.70$ (br s, 1H), 7.26 (t, $J = 7.6$ Hz, 1H), 6.97 (dt, $J = 7.6$ Hz, $J' = 1.2$ Hz, 1H), 6.92 (t, $J = 2.0$ Hz, 1H), 5.85 (ddd, $J = 7.6$ Hz, $J' = 2.0$ Hz, $J'' = 1.2$ Hz, 1H), 6.49 (s, 1H), 4.15 ppm (q, $J = 4.0$ Hz, 4H); IR (KBr): $\tilde{\nu} = 3277$, 3174, 2884, 1591, 1570, 1477, 1370, 1237, 1147, 847, 774 cm^{-1}; MS (ESI+): m/z 219 $[M+H]^+$.

4-(5,6-Dihydroimidazo[2,1-*b*]thiazol-3-yl)benzoic acid (24): The title compound was prepared from 4-acetylbenzoic acid (150 mg, 0.91 mmol) and 2-imidazolidinethione (112 mg, 1.09 mmol) according to method B. After alkaline liquid–liquid extraction, 1 N HCl was added to the organic layer. The precipitate that formed in the organic layer was collected by filtration. The resulting solid was triturated with H_2O (5 mL), CH_2Cl_2 (5 mL), and dried under vacuum to afford **24** (101 mg, 45% yield) as a bright-yellow solid. HPLC: $t_R =$ 4.0 min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 8.04$ (d, $J = 8.4$ Hz, 2H), 7.76 (d, $J = 8.4$ Hz, 2H), 7.14 (s, 1H), 4.53 (t, $J = 9.0$ Hz, 2H), 4.28 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3320$–2190 (br), 1687, 1587, 1434, 1294, 1008, 723, 535 cm^{-1}. MS (ESI+): m/z 247 $[M+H]^+$.

5,6,9,10-Tetrahydro-7-thia-8,10a-diazapentaleno[1,2-*a*]naphthalene (25): The title compound was prepared from α-tetralone (1 g, 6.8 mmol) and 2-imidazolidinethione (1.4 g, 13.6 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (neutral alumina, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **25** (165 mg, 12% yield) as a tan solid. HPLC: $t_R = 9.2$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (d, $J = 7.6$ Hz, 1H), 7.22–7.32 (m, 3H), 4.33 (t, $J = 9.0$ Hz, 2H), 4.18 (t, $J = 9.0$ Hz, 2H), 3.02 (t, $J = 7.8$ Hz, 2H), 2.64 ppm (t, $J = 7.8$ Hz, 2H); IR (KBr): $\tilde{\nu} =$ 3093, 2936, 2837, 1708, 1612, 1390, 1292, 1196, 1020, 764, 642 cm^{-1}; MS (ESI+): m/z 229 $[M+H]^+$; HRMS-ESI-TOF: m/z: calcd for $C_{13}H_{13}N_2S$: 229.0799 $[M+H]^+$; found 229.0793.

3-Phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (26): The title compound was prepared from 2′-bromoacetophenone (497 mg, 2.5 mmol) and 2-imidazolidinethione (250 mg, 2.5 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **26** (430 mg, 85% yield) as yellow crystals. HPLC: $t_R =$ 6.3 min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.38$ (s, 5H), 5.69 (s, 1H), 4.24 (t, $J = 9.0$ Hz, 2H), 3.84 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} =$ 3114, 2944, 2871, 1595, 1374, 1237, 967, 769, 703 cm^{-1}; MS (ESI+): m/z 203 $[M+H]^+$.

3-(4-Bromophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole (27): The title compound was prepared from 2,4′-dibromoacetophenone (200 mg, 0.72 mmol) and 2-imidazolidinethione (73.5 mg, 0.72 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **27** (88 mg, 44% yield) as a white solid. HPLC: $t_R = 7.9$ min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.62$ (d, $J = 8.8$ Hz, 2H), 7.49 (d, $J = 8.8$ Hz, 2H), 6.20 (s, 1H), 4.06 (t, $J =$ 9.2 Hz, 2H), 3.84 ppm (t, $J = 9.2$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3111$, 2951, 2850, 1610, 1488, 1237, 1169, 1008, 834, 799, 677 cm^{-1}; MS (ESI+): m/z (%) 281 (50) and 283 (50) $[M+H]^+$.

3-(4-Bromophenyl)-2-methyl-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (28): The title compound was prepared from 2,4′-dibromopropiophenone (250 mg, 0.86 mmol) and 2-imidazolidinethione (88 mg, 0.86 mmol) according to method B. For this compound, a precipitate was formed at the end of the reaction. The solid was collected by filtration, washed with EtOH, cold H_2O, then EtOH to afford **28** (157 mg, 49% yield) as a white solid. HPLC: $t_R =$ 8.2 min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.49$ (s, 1H), 7.77 (d, $J =$ 8.4 Hz, 2H), 7.48 (d, $J = 8.4$ Hz, 2H), 4.22 (m, 4H), 2.22 ppm (s, 3H); IR (KBr): $\tilde{\nu} = 3780$–2320 (br), 1597, 1479, 1250, 966, 849, 632 cm^{-1}; MS (ESI+): m/z (%) 295 (50) and 297 (50) $[M+H]^+$.

3-Naphthalen-2-yl-5,6-dihydro-imidazo[2,1-*b*]thiazole hydrobromide (29): The title compound was prepared from 2-bromo-2′-acetonaphthone (50 mg, 0.18 mmol) and 2-imidazolidinethione (20.5 mg, 0.2 mmol) according to method B. For this compound, a precipitate was formed at the end of the reaction. The solid was collected by filtration, washed with EtOH, cold H_2O, then EtOH to afford **29** (29.6 mg, 49% yield) as a yellow solid. HPLC: $t_R =$ 12.3 min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.66$ (s, 1H), 8.23 (s, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.97–8.06 (m, 2H), 7.74 (dd, $J = 8.4$ Hz, $J' = 1.6$ Hz, 1H), 7.62 (m, 2H), 7.15 (s, 1H), 4.64 (t, $J = 9.0$ Hz, 2H), 4.32 ppm (t, $J = 9.0$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3180$–2100 (br), 1585, 1556, 1278, 1125, 962, 871, 755 cm^{-1}; MS (ESI+): m/z 253 $[M+H]^+$; HRMS-ESI-TOF: m/z: calcd for $C_{15}H_{13}N_2S$: 253.0799 $[M+H]^+$; found 253.0790.

3-(4-Nitrophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole hydrobromide (30): The title compound was prepared from 2′-bromo-4-nitroacetophenone (1 g, 4.1 mmol) and 2-imidazolidinethione (418 mg, 4.1 mmol) according to method B except that *p*-toluenesulfonic acid (390 mg, 2.1 mmol) was also added to the reaction mixture. For this compound, a precipitate was formed at the end of the reaction. The solid was collected by filtration, washed with EtOH, cold H_2O, then EtOH to afford **30** (1.1 g, 82% yield) as a bright-red solid. HPLC: $t_R = 7.0$ min; ^{1}H NMR (400 MHz, [D$_6$]DMSO): $\delta = 9.68$ (s, 1H), 8.35 (d, $J = 8.8$ Hz, 2H), 7.92 (d, $J = 8.8$ Hz, 2H), 7.29 (s, 1H), 4.55 (t, $J = 9.2$ Hz, 2H), 4.30 ppm (t, $J = 9.2$ Hz, 2H); IR (KBr): $\tilde{\nu} = 3121$, 2947, 2849, 1595, 1510, 1344, 1103, 856, 704 cm^{-1}; MS (ESI+): m/z 248 $[M+H]^+$.

4-Biphenyl-4-yl-thiazol-2-ylamine (31): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and thiourea (14 mg, 0.18 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, hexane/EtOAc/MeOH, 70:30:1) to afford **31** (36 mg, 78% yield) as a white solid. HPLC: $t_R = 14.2$ min; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.85$ (d, $J = 8.4$ Hz, 2H), 7.62 (d, $J = 8.4$ Hz, 2H), 7.61–7.65 (m, 2H), 7.44 (t, $J = 7.6$ Hz, 2H), 7.35 (t, $J = 7.6$ Hz, 1H), 6.78 (s, 1H), 4.97 ppm (br s, 2H); IR (KBr): $\tilde{\nu} = 3438$, 3287, 3109,

1630, 1523, 1331, 852, 769, 737, 699 cm^{-1}; MS (ESI+): *m/z* 253 $[M+H]^+$.

(4-Biphenyl-4-yl-thiazol-2-yl)methylamine (32): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and 1-methyl-2-thiourea (16.4 mg, 0.18 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **32** (40.2 mg, 83% yield) as a tan solid. HPLC: t_R = 14.6 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 8.4 Hz, 2H), 7.63 (m, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 5.35 (br s, 1H), 3.03 ppm (d, *J* = 4.8 Hz, 3H); IR (KBr): $\tilde{\nu}$ = 3243, 31088, 1581, 1403, 1056, 735, 691 cm^{-1}; MS (ESI+): *m/z* 267 $[M+H]^+$.

(4-Biphenyl-4-yl-thiazol-2-yl)phenylamine (33): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and 1-phenyl-2-thiourea (27.7 mg, 0.18 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **33** (33.4 mg, 56% yield) as a white solid. HPLC: t_R = 15.8 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, 2H, *J* = 8.4 Hz), 7.66 (d, *J* = 8.4 Hz, 2H), 7.65 (m, 2H), 7.33–7.48 (m, 7H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.89 ppm (s, 1H); IR (KBr): $\tilde{\nu}$ = 3376, 3036, 1601, 1551, 1404, 1300, 844, 731, 687 cm^{-1}; MS (ESI+): *m/z* 329 $[M+H]^+$.

Benzyl(4-biphenyl-4-yl-thiazol-2-yl)amine (34): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and *N*-benzyl-thiourea (30.3 g, 0.18 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **34** (24.8 mg, 40% yield) as a white solid. HPLC: t_R = 16.3 min; ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 8.60 (br s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.46 (m, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 4.56 ppm (s, 2H); IR (KBr): $\tilde{\nu}$ = 3059, 2723, 1629, 1490, 764, 695 cm^{-1}; MS (ESI+): *m/z* 343 $[M+H]^+$.

Allyl(4-biphenyl-4-yl-thiazol-2-yl)amine (35): The title compound was prepared from 2′-bromo-4-phenylacetophenone (78.2 mg, 0.28 mmol) and 1-allyl-2-thiourea (33 mg, 0.28 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **35** (60.1 mg, 72% yield) as a white solid. HPLC: t_R = 15.1 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.0 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.77 (s, 1H), 5.98 (ddt, *J* = 17.2 Hz, *J′* = 10.4 Hz, *J″* = 1.6 Hz, 1H), 5.36 (dd, *J* = 17.2 Hz, *J″* = 1.6 Hz, 1H), 5.31 (br s, 1H), 5.24 (dd, *J* = 10.4 Hz, *J″* = 1.6 Hz, 1H), 3.98 ppm (tt, *J* = 6.0 Hz, *J″* = 1.6 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3220, 2972, 1591, 1327, 918, 851, 767, 734, 695 cm^{-1}; MS (ESI+): *m/z* 293 $[M+H]^+$.

(4-Biphenyl-4-yl-3-methyl-3*H*-thiazol-2-ylidene)methylamine (36): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and *N*,*N*′-dimethyl-2-thiourea (18.9 mg, 0.18 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **36** (46.1 mg, 91% yield) as a white solid. HPLC: t_R = 14.9 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.48 (t, *J* = 7.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 5.87 (s, 1H), 3.27 (s, 3H), 3.08 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 3253, 2954, 1621, 1399, 975, 850, 831, 764, 693 cm^{-1}; MS (ESI+): *m/z* 281 $[M+H]^+$.

(4-Biphenyl-4-yl-3-propyl-3*H*-thiazol-2-ylidene)propylamine (37): The title compound was prepared from 2′-bromo-4-phenylacetophenone (172 mg, 0.625 mmol) and *N*,*N*′-dimethyl-2-thiourea (100 mg, 0.625 mmol) according to method B. After evaporation of the solvent, the residue was purified by chromatography (silica, EtOAc/MeOH/Et_3N, 90:10:0.5) to afford **37** (170.6 mg, 81% yield) as a tan solid. HPLC: t_R = 15.7 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, *J* = 8.0 Hz, 4H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.40 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 5.79 (br s, 1H), 3.76 (br s, 2H), 3.13 (t, *J* = 7.2 Hz, 2H), 1.73 (q, *J* = 7.2 Hz, 2H), 1.59 (q, *J* = 7.2 Hz, 2H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.74 ppm (t, *J* = 7.2 Hz, 3H); IR (KBr): $\tilde{\nu}$ = 2962, 2931, 2873, 1623, 1485, 1239, 849, 765, 697 cm^{-1}; MS (ESI+): *m/z* 337 $[M+H]^+$.

3-Biphenyl-4-yl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidine hydrobromide (38): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and 3,4,5,6-tetrahydro-2-pyrimidinethione (21.1 mg, 0.18 mmol) according to method B except that *p*-toluenesulfonic acid (34.6 mg, 0.18 mmol) was also added to the reaction. For this compound, a precipitate was formed at the end of the reaction. The solid was collected by filtration, washed with EtOH, cold H_2O, then EtOH to afford **38** (40.2 mg, 59% yield) as a white solid. HPLC: t_R = 15.3 min; ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 10.40 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 7.2 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.04 (s, 1H), 3.96 (t, *J* = 5.6 Hz, 2H), 3.51 (br s, 2H), 2.03 ppm (t, *J* = 5.6 Hz, 2H); IR (KBr): $\tilde{\nu}$ = 3050, 2936, 1609, 1484, 1373, 1316, 1185, 771, 755, 694 cm^{-1}; MS (ESI+): *m/z* 293 $[M+H]^+$.

3-Biphenyl-4-yl-imidazo[2,1-*b*]thiazole (39): The title compound was prepared from 2′-bromo-4-phenylacetophenone (50 mg, 0.18 mmol) and 2-mercaptoimidazole (18.0 mg, 0.18 mmol) according to method B except that *p*-toluenesulfonic acid (34.6 mg, 0.18 mmol) was also added to the reaction. After evaporation of the solvent, the residue was purified by chromatography (silica, CH_2Cl_2 then CH_2Cl_2/EtOH, 97:3) to afford **39** (40.9 mg, 82% yield) as a tan solid. HPLC: t_R = 11.5 min; ^1H NMR (400 MHz, $[D_6]$DMSO): δ = 8.03 (s, 1H), 7.86 (s, 4H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.54 (s, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.37 ppm (s, 1H). IR (KBr): $\tilde{\nu}$ = 2923, 2854, 1729, 1663, 1462, 1112, 847, 765, 696 cm^{-1}. MS (ESI+): *m/z* 277 $[M+H]^+$.

4-Biphenyl-4-yl-3-methyl-3*H*-thiazol-2-ylideneamine (40): A mixture of methyl methanesulfonate (116 mg, 1.1 mmol) and 4-biphenyl-4-yl-thiazol-2-ylamine **31** (265.2 mg, 1.1 mmol) was refluxed in toluene for 18 h and then allowed to cool to RT. The mixture was evaporated, and the residue was purified by preparative HPLC by using a 150×19 mm XBridge 5 μm C_{18} (Waters) equilibrated with MeCN/H_2O (1:1). The gradient of MeCN was increased to 90% at 40 min. The fractions of interest were pooled and the solvent was evaporated to afford **40** (1.8 mg, 1% yield) as a white solid. HPLC: t_R = 14.0 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.33 (br s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 2H), 7.42 (m, 3H), 6.46 (s, 1H), 3.71 ppm (s, 3H); IR (KBr): $\tilde{\nu}$ = 2925, 1632, 1564, 1485, 1403, 750, 697 cm^{-1}; MS (ESI+): *m/z* 267 $[M+H]^+$.

3-Biphenyl-4-yl-7-methyl-5,6-dihydroimidazo[2,1-*b*]thiazol-7-ium mesylate (41): A mixture of methyl methanesulfonate (18.3 mg, 0.21 mmol) and 3-biphenyl-4′-yl-5,6-dihydroimidazo[2,1-*b*]thiazole **1** (20 mg, 0.072 mmol) was refluxed in toluene for 4 h and then allowed to cool to RT. The precipitate that formed upon cooling was collected by filtration. The solid was recrystallized from EtOH/EtOAc (1:1) to afford **41** (17.3 mg, 60% yield) as white crystals. HPLC: t_R = 14.7 min; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (s, 4H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H),

6.71 (s, 1H), 4.71 (t, $J=8.8$ Hz, 2H), 4.68 (t, $J=8.8$ Hz, 2H), 3.25 (s, 3H), 3.76 ppm (s, 3H); IR (KBr): $\tilde{\nu}=3900$–2870 (br), 1611, 1412, 1196, 736 cm^{-1}; MS (ESI+): m/z 293 $[M+H]^+$.

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