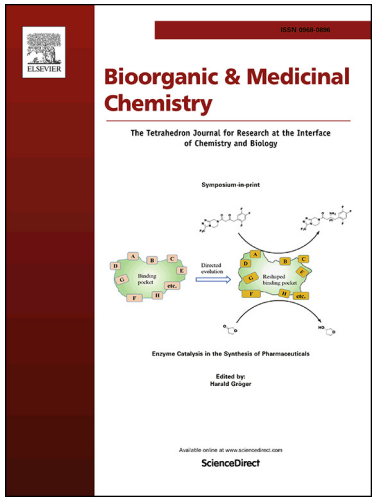
Flinders UNIVERSITY

Accepted Manuscript



Synthesis and evaluation of aminobenzothiazoles as blockers of N- and T-type calcium channels

Anjali Sairaman, Fernanda Caldas Cardoso, Anjie Bispat, Richard J. Lewis, Peter J. Duggan, Kellie L. Tuck

PII: S0968-0896(18)30339-0
DOI: https://doi.org/10.1016/j.bmc.2018.03.031
Reference: BMC 14269

To appear in: *Bioorganic & Medicinal Chemistry*

Received Date: 15 February 2018
Revised Date: 15 March 2018
Accepted Date: 18 March 2018

Please cite this article as: Sairaman, A., Cardoso, F.C., Bispat, A., Lewis, R.J., Duggan, P.J., Tuck, K.L., Synthesis and evaluation of aminobenzothiazoles as blockers of N- and T-type calcium channels, *Bioorganic & Medicinal Chemistry* (2018), doi: https://doi.org/10.1016/j.bmc.2018.03.031

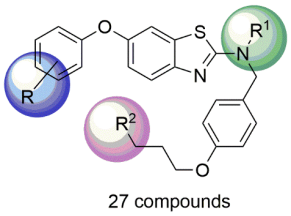
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis and evaluation of aminobenzothiazoles as blockers of N- and T-type calcium channels

Leave this area blank for abstract info.

Anjali Sairaman[a,b,c,d], Fernanda Caldas Cardoso[e], Anjie Bispat[c,d], Richard J. Lewis[e], Peter J. Duggan[c,f], Kellie L. Tuck[d]



27 compounds

ELSEVIER

Bioorganic & Medicinal Chemistry
journal homepage: www.elsevier.com

Synthesis and evaluation of aminobenzothiazoles as blockers of N- and T-type calcium channels

Anjali Sairaman[a,b,c,d], Fernanda Caldas Cardoso[e], Anjie Bispat[c,d], Richard J. Lewis[e], Peter J. Duggan*[c,f], Kellie L. Tuck*[d]

[a] *IITB-Monash Research Academy, Powai, Mumbai 400076, India*
[b] *Department of Chemistry, IIT Bombay, Mumbai 400076, India*
[c] *CSIRO Manufacturing, Bag 10, Victoria 3169, Australia*
[d] *School of Chemistry, Monash University, Victoria 3800, Australia*
[e] *Institute for Molecular Bioscience, The University of Queensland, St Lucia QLD 4072, Australia*
[f] *School of Chemical and Physical Sciences, Flinders University, South Australia 5042, Australia*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pain
Benzothiazole
$Ca_V2.2$
N-type calcium channel
$Ca_V3.2$
T-type calcium channel

ABSTRACT

Both N- and T-type calcium ion channels have been implicated in pain transmission and the N-type channel is a well validated target for the treatment of neuropathic pain. An SAR investigation of a series of substituted aminobenzothiazoles identified a subset of five compounds with comparable activity to the positive control Z160 in a FLIPR-based intracellular calcium response assay measuring potency at both $Ca_V2.2$ and $Ca_V3.2$ channels. These compounds may form the basis for the development of drug leads and tool compounds for assessing *in vivo* effects of variable modulation of $Ca_V2.2$ and $Ca_V3.2$ channels.

1. Introduction

Neuropathic pain is a common form of chronic illness resulting from nerve damage caused by trauma, surgery, infection or disease.[1] It is estimated that at least 3% of the world's population is affected by this condition, with up to 50% of postoperative patients being impacted. Neuronal voltage gated calcium channels (VGCC) mediate the transmembrane flow of calcium (Ca^{2+}) in response to membrane depolarisation and are known to be integral to the transmission of pain. The $Ca_V2.2$ (N-type) channel is a well-validated pain target and this has inspired many groups, including ourselves, to purse inhibitors of the $Ca_V2.2$ channel as potential analgesics.[2-17] Despite the academic and commercial efforts to develop inhibitors of the $Ca_V2.2$ channel, only Prialt (Ziconitide), a synthetic version of peptide ω-conotoxin MVIIA, has reached the clinic. However, its use is limited by its intrathecal mode of delivery and narrow therapeutic window. Of the most advanced small molecule candidates, Z160 (**1**, Figure 1) failed to meet the primary endpoint in phase 2 clinical trials, and the phase 2 clinical trial results of CNV-2197944 (structure not disclosed) were disappointing. Alternate dosing regimens and other therapeutic uses for this compound are being explored.[18] More recently, the $Ca_V3.2$ (T-type) channel has also been recognised as a target for the development of analgesics,[19, 20] and the combined inhibition of $Ca_V2.2$ and $Ca_V3.2$ channels has an analgesic effect in rodent models.[20] In recent years several inhibitors of the $Ca_V3.2$ channel have been reported.[21-32] The positive results obtained in Phase Ib clinical trials with compound Z944 (**2**, Figure 1) were encouraging but further studies with this analogue have apparently not been pursued. NNC 55-0396 (**3**, Figure 1), a stable analogue of Mibefradil, has high selectivity for Ca_V3 channels over high-voltage activated channels, although it was deemed unsuitable for further development.[33] Despite the number of novel small-molecule chemical entities being developed for these targets, not one has reached the market. A review by Beswick describes the

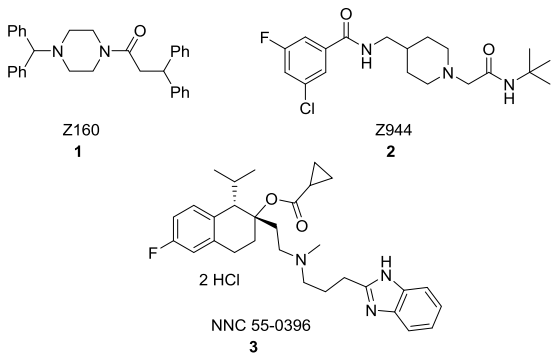


Figure 1. Chemical structures of Z160 **1**, Z944 **2** and NNC 55-0396 **3**.

development of small-molecule inhibitors of $Ca_V2.2$ and Ca_V3 channels in recent years and pointedly notes that recent clinical studies outcomes have been disappointing.[2] Since chronic neuropathic pain is a widespread and debilitating condition, and there is increasing concern about opioid dependence amongst chronic pain sufferers, there is a pressing need to pursue new structural classes of neuronal calcium ion channel blockers.

For a number of years we have conducted an academic research program aimed at developing small-molecule inhibitors of the $Ca_V2.2$ channel, initially concentrating on type-III peptidomimetics of ω-conotoxin GVIA,[34] a 27-residue peptide that binds selectively and essentially irreversibly to $Ca_V2.2$ channels.[13-17] The structure of two of these peptidomimetics (**4** and **5**), that contain a benzothiazole scaffold core, are shown in Figure 2.[16] Their affinity for rat brain $Ca_V2.2$ channels, as measured by a radioligand displacement assay with ^{125}I-GVIA, was encouraging. In an effort to shorten the synthetic route to this class of $Ca_V2.2$ inhibitor, as well as reduce the molecular weight of the peptidomimetics, 'truncated' analogues (**6a** and **7a**) were synthesized.[17] The guanidinium analogue **7a** retained similar activity to compound **5**. It should be noted that the radioligand displacement assay can over-estimate the functional activity of a small molecule $Ca_V2.2$ inhibitor by up to an order of magnitude,[14] and consequently, the inhibition of intracellular calcium responses in living SH-SY5Y neuroblastoma cells, as measured on a FLIPR (Fluorescence Imaging Plate Reader) has become our primary method of screening $Ca_V2.2$ blockers. Similarly, the inhibition of intracellular calcium responses in HEK 293T expressing recombinant *h*$Ca_V3.2$ has become a useful screen for Ca_V3 activity.

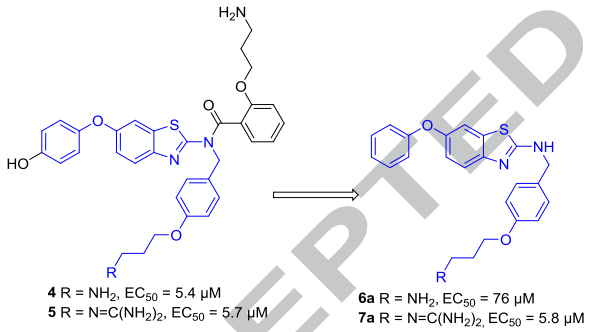


Figure 2. Non-peptide mimics of ω-conotoxin GVIA (**4**, **5**), 'the truncated' analogues (**6a**, **7a**), and the associated radioligand displacement assay data.[16, 17]

In an endeavour to obtain greater potency for the $Ca_V2.2$ channel and to also investigate the potential of these analogues to block the $Ca_V3.2$ channel, we embarked on a proof of principle, systematic investigation of the structure-activity relationship (SAR) for analogues of the 'truncated' series (**6a** and **7a**). With an overarching aim of improving the physicochemical properties of this class of compound, as well as $Ca_V2.2$ and Ca_V3 potency, three regions of the benzothiazole-derived compounds were investigated; the electronegativity of the *para*-aromatic ring substituent (R^1); *N*-methylation of the aminobenzothiazole nitrogen (R^2), removing the H-donor at this site; and dimethyl analogues (R^3), which are much more likely to be appropriate for CNS-active drugs (Figure 3). To enable accurate comparisons with the previous assay data, the 'truncated' analogues (**6a** and **7a**) were included as control compounds in the functional FLIPR assay, and Z160 **1**, and NNC 55-0396 **3** were used as positive controls for the $Ca_V2.2$ and $Ca_V3.2$ channels respectively. The *in vitro* stability in rat plasma for representative classes of compounds is also disclosed.

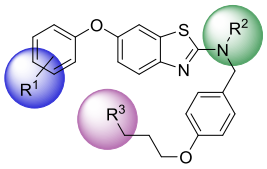
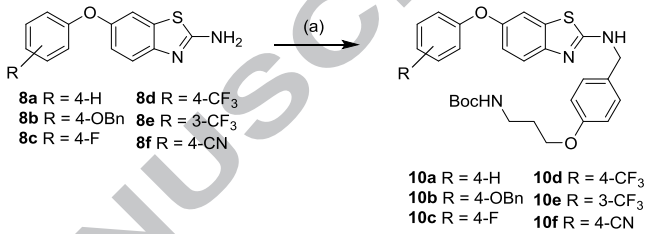


Figure 3. Schematic depiction of the SAR studies conducted of the low molecular weight, 'truncated' analogues, **6a** and **7a**.

2. Chemistry

The synthesis of benzothiazoles (**10a-f**), outlined in Scheme 1, was achieved by treatment of the aminobenzothiazole (**8a-f**) with the aldehyde **9**[17] using a modification of our previously described reductive amination conditions.[17]

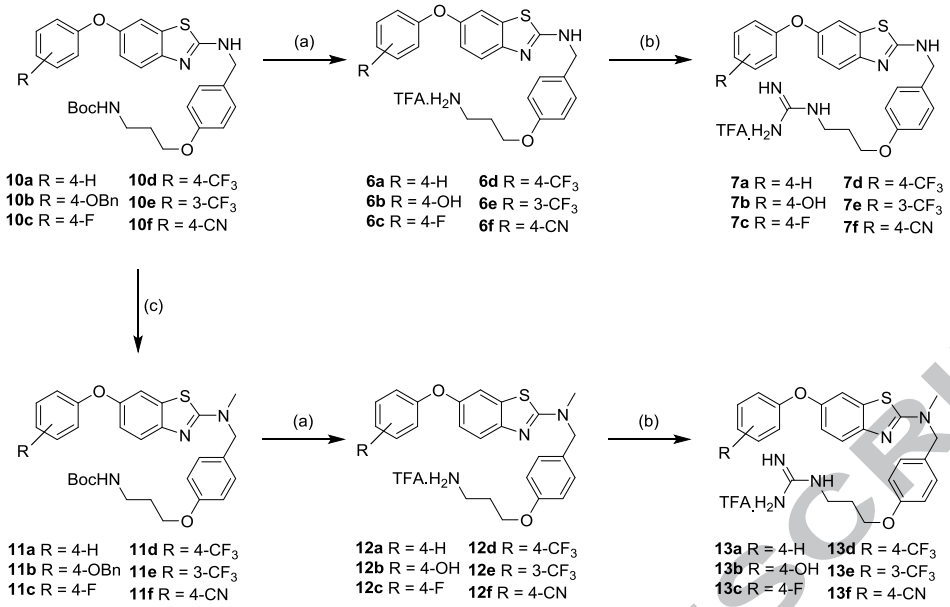


Scheme 1. Reagents and conditions: (a) (i) **9**[17], toluene, cat. p-TSA, reflux, 2 days; (ii) EtOH, $NaBH_4$, reflux, 5 h.

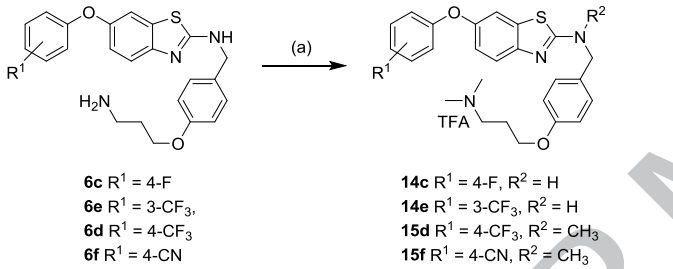
The synthesis of the amino analogues (**6a-f**), the amino *N*-methyl analogues (**12a-f**) and their corresponding monoguanidino analogues (**7a-f** and **13a-f** respectively) is described in Scheme 2. With the desired aminobenzothiazoles (**10a-f**) in hand, removal of the Boc protecting group under acidic conditions gave the corresponding amino analogues (**6a, c-f**), with the exception of the 4-OBn analogue (**6b**) in which deprotection was achieved utilizing TFA and thioanisole. Formation of the monoguanidino analogues (**7a-f**) was accomplished either in one step by treatment of the amine (**6b,c** and **f**) with 1*H*-pyrazole-carboxamidine, or initial reaction of the amine (**6a, d,** and **e**) with *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine followed by removal of the Boc groups under acidic conditions. In order to obtain the *N*-methylated analogues, the aminobenzothiazoles (**10a-f**) were reacted with NaH followed by the addition of 1.2 eq. of MeI. With the advanced intermediates (**11a-f**) in hand, the corresponding amino derivatives (**12a-f**) and corresponding guanidino analogues (**13a-f**) were obtained using similar transformations to those described above.

Conversion of the benzothiazole-derived amines **6c** and **6e** to the *N*,*N*-dimethyl analogues, **14c** and **14e** respectively, was achieved by a reductive amination reaction; addition of paraformaldehyde, followed by *in situ* reduction of the imine using $NaBH_4$ (Scheme 3).[35] The use of similar conditions with the 4-CF_3 and 4-CN benzothiazole-derived amines (**6d** and **6e**) proceeded to give an inseparable mixture of the mono-, bis- and tris- *N*-methylated compounds. Therefore, modification of the reaction conditions, specifically increasing the number of equivalents of paraformaldehyde and $NaBH_4$, allowed the tris-*N*-methylated benzothiazole-derived compounds **15d** and **15f** to be obtained. The benzothiazole-derived *N*,*N*-dimethyl amine **14f** was obtained *via* a two-step procedure, as shown in Scheme 4.

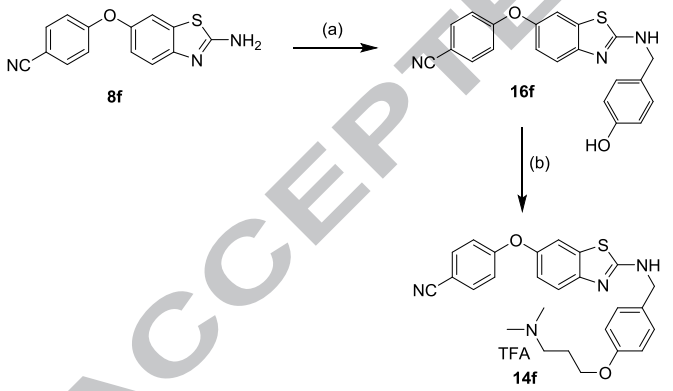
All final compounds were purified by preparative HPLC prior to being tested in the FLIPR assays.



Scheme 2. Reagents and conditions: (a) sat. HCl in dioxane or MeOH, DCM, RT, 1 h, purified by HPLC; OR TFA, thioanisole, RT, 1h, purified by HPLC (b) 1*H*-pyrazole-1-carboxamidine, DIPEA, DMF, RT, 24 h, purified by HPLC; OR (i) *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine, Et_3N, DMF, RT, 12 h; (ii) AcCl, EtOH, RT, 6 h, purified by HPLC; (c) (i) NaH, THF, 0 °C, 30 min; (ii) 1.2 eq. MeI, RT, 4 h.



Scheme 3. Reagents and conditions: (a) paraformaldehyde, $NaBH_4$, cat. TFA, MeOH, RT, 24 h.



Scheme 4. Reagents and conditions: (a) (i) 4-hydroxybenzaldehyde, toluene, cat. p-TSA, reflux, 7 days; (ii) EtOH, $NaBH_4$, reflux, 5 h; (b) 3-chloro-*N*,*N*-dimethylpropan-1-amine, K_2CO_3, THF, RT, 3 days.

3. Biology

Evaluation of the amino and monoguanidino analogues for inhibition of the $Ca_V2.2$ and $Ca_V3.2$ channels was evaluated utilizing a FLIPR calcium imaging assay. Experiments for $Ca_V2.2$ inhibition were performed with neuroblastoma SH-SY5Y cell line in the presence of the L-type calcium channel blocker Nifedipine. Experiments for $Ca_V3.2$ inhibition were performed with HEK 293T cells expressing recombinant human $Ca_V3.2$ α_1 subunit. These assays were performed at the natural resting membrane potential of the immortalised cell lines used, which are more depolarised than nerve cell *in vivo*.

Assessment of the 'truncated' analogues **6a** and **7a**, utilizing the functional FLIPR-based assay for $Ca_V2.2$ activity, revealed them to be up to 5.6 times less potent than the positive control Z160 (Table 1 and Table 2). However, it was found that a number of substitutions on the parent structure **6a** led to compounds with comparable activity to Z160. The data obtained with the amines **6a-f** appear to show a strong correlation with the electron density in the phenoxy ring; electron withdrawing groups, especially at the *para* position, improve inhibition, with the cyano-amine **6f** having equivalent activity to Z160. A similar trend is not obvious in the guanadinium series **7a-f**, and the most potent compound of this series was the parent analogue **7a**. The motivation to methylate at the aminobenzothiazole nitrogen came from a desire to remove the H-donor at this site and so it is interesting to note that a number of compounds in the amine series **12a-f** showed promising activity (Table 3). Again, the results obtained with the guanidinium compounds **13a-f** were less encouraging. Since tertiary amines are a common structural motif in marketed CNS-active drugs whereas primary amines are rare,[36] a selection of compounds were chosen for elaboration to the *N*,*N*-dimethylamines (**14c**, **14e**, **14f**, **15d** and **15f**). It was extremely encouraging to find that four of these compounds (**14c**, **14e**, **15d** and **15f**) gave comparable potencies to the positive control Z160 (Table 4 and Figure 4).

Table 1. Functional inhibition of calcium channels (*h* $Ca_V2.2$ and *h* $Ca_V3.2$) by the $Ca_V2.2$ blocker Z160 **1** and the $Ca_V3.2$ blocker NNC 55-0396 **3**.

$Ca_V2.2$				$Ca_V3.2$		
Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)
1	2	**39**	31-40	3	**45**	32-60
3	2	**7**	2-15	0.3	**2**	0.8–6.3

Turning to the inhibition data obtained against the $Ca_V3.2$ channel, it is interesting to note that in these FLIPR-based intracellular calcium response assays, Z160 (**1**), a compound developed to target N-type calcium channels, shows similar potency towards both $Ca_V2.2$ and $Ca_V3.2$ channels. This is also true for NNC 55-0396 (**3**), which is described as having high

Table 2. Functional inhibition of calcium channels (*h*Ca_V2.2 and *h*Ca_V3.2) by the amino and guanidino compounds **6a-f** and **7a-f**.

Ca_V2.2				Ca_V3.2			Ca_V2.2				Ca_V3.2		
Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)	Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)
6a[a]	10	**218**	173 - 274	ND	**>1000**	ND	**7a**[b]	5	**103**	79 - 135	15	**166**	104 - 265
6b	15	**205**	143 - 293	48	**300**	132 - 683	**7b**	9	**253**	212 - 300	34	**319**	259 - 803
6c	3	**106**	90 - 124	78	**688**	393 - 1208	**7c**	7	**244**	211 - 282	8	**288**	248 - 335
6d	2	**59**	48 - 72	18	**112**	48 - 229	**7d**	9	**167**	129 - 216	10	**195**	152 - 251
6e	9	**144**	103 - 201	21	**171**	93 - 315	**7e**	4	**130**	111 - 151	16	**270**	196 - 372
6f	2	**41**	31 - 56	6	**109**	86 - 140	**7f**	88	**368**	100 - 1354	4	**326**	305 - 345

ND – Not determined

Table 3. Functional inhibition of calcium channels (*h*Ca_V2.2 and *h*Ca_V3.2) by the *N*-methylaminobenzothiazoles **12a-f** and **13a-f**.

Ca_V2.2				Ca_V3.2			Ca_V2.2				Ca_V3.2		
Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)	Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)
12a	7	**49**	33 - 78	16	**95**	39 - 234	**13a**	4	**113**	92 - 137	18	**498**	312 - 602
12b	9	**117**	80 - 172	23	**165**	82 - 334	**13b**	42	**432**	267 - 698	24	**332**	246 - 597
12c	7	**98**	66 - 144	114	**492**	154 - 1564	**13c**	8	**100**	66 - 152	21	**521**	425 - 639
12d	11	**283**	231 - 346	14	**248**	151 - 383	**13d**	8	**185**	150 - 228	10	**212**	165 - 273
12e	2	**77**	67 - 88	22	**239**	137 - 314	**13e**	13	**202**	145 - 281	42	**771**	581-1024
12f	5	**65**	42 - 102	9	**328**	286 - 381	**13f**	7	**143**	112 - 184	6	**153**	125 - 186

Table 4. Functional inhibition of calcium channels (*h*Ca_V2.2 and *h*Ca_V3.2) by the *N*, *N*-dimethyl amino compounds **14c**, **14e** and **14f**, and the tris-*N*-methylated benzothiazole-derived compounds **15d** and **15f**.

Ca_V2.2				Ca_V3.2		
Compd.	SEM	IC_{50} (μM)	95% CI (μM)	SEM	IC_{50} (μM)	95% CI (μM)
14c	2	**40**	31-50	ND	**>1000**	ND
14e	3	**51**	39-67	19	**110**	30-285
14f	51	**105**	24-302	13	**41**	29-94
15d	2	**46**	15-97	7	**54**	22-122
15f	30	**69**	27-229	26	**64**	30-224

ND – Not determined

selectivity for Ca_V3 channels.[33] Its activity is in the single digit micromolar range for both channels (Table 1). For the aminobenzothiazoles, it can be seen that none of the primary amines or guanidinium compounds showed any significant effect, except possibly **12a**, but at an IC_{50}=95 μM, even its activity is marginal (Tables 2 and 3). This data is consistent with the original design of these compounds, which was based around selective N-type channel blockers.[37] Amongst the *N*,*N*-dimethylamines, however, three compounds (**14f**, **15d** and **15f**) showed promising activity against the Ca_V3.2 channel (Table 4 and Figure 4). Further experiments using electrophysiological approaches to evaluate state-dependent inhibition will be performed in due course.

Representative compounds from each structural class (**6c**, **7d**, **12e** and **13e**) were tested for their *in vitro* stability in rat plasma. All compounds showed good stability in rat plasma; after 24 h 75% of the amino **6c** remained, 91% of the monoguanidino **7d**, 100% of the *N*-methyl amino **12e** and 95% of the *N*-methyl guanidine **13e**; (n=3).

The central nervous system multiparameter optimization (CNS MPO) desirability tool, developed by researchers at Pfizer Pharma Therapeutics, utilizes six important physicochemical properties to identify lead compounds with an increased chance of penetrating the CNS; lipophilicity (ClogP); distribution coefficient at pH 7.4 (ClogD); molecular weight; topological polar surface area

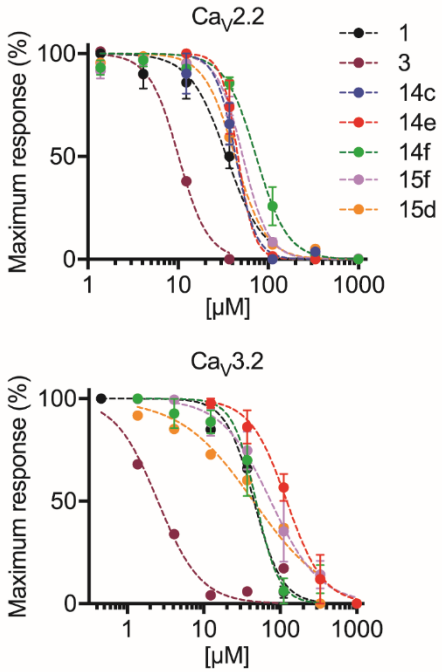


Figure 4. Activity of the *N*, *N*-dimethyl amino and tris-*N*-methylated benzothiazole-derived compounds over N-type and T-type calcium channels determined by fluorescent assays. Concentration-response curves for inhibition of Ca_V2.2. (A) and Ca_V3.2 (B) under application of various concentrations of the *N*, *N*-dimethyl amino compounds **14c**, **14e** and **14f**, the tris-*N*-methylated benzothiazole-derived compounds **15d** and **15f**, and the controls Z160 (compound **1**) and NNC 55-0396 (compound **3**). IC_{50} values calculated are described in Tables 1 and 4. Data are presented as mean ± SEM, *n* = 3 - 4 independent experiments.

(TPSA); number of hydrogen-bond donors (HBDs); and the most basic center (p*K*a).[38, 39] A MPO desirability score of ≥ 4, on a scale of 0–6, indicates that the compound has a strong likelihood of being CNS-penetrating. The MPO score for Z160 was calculated to be 2.3, whereas the dimethylamine **14c**, the most potent aminobenzothiazole against the $Ca_V2.2$ channel, has a value of 2.6. The failure of Z160 to progress beyond phase 2 clinical trials may reflect its less than ideal physicochemical properties for a CNS-active drug, and so it is heartening that aminobenzothiazole analogues have been identified that have similar $Ca_V2.2$ and $Ca_V3.2$ potency as Z160 and slightly improved MPO scores. While there is clearly room for further improvement with respect to physicochemical properties, the compounds listed in Table 4 provide a guide for future endeavours, including their application as tool compounds in probing the *in vivo* effects of variable modulation of $Ca_V2.2$ and $Ca_V3.2$ channels in pain models. In addition, if the aminobenzothiazole-derived compounds do not enter the CNS, peripheral $Ca_V2.2$ and/or $Ca_V3.2$ blockers are still of interest as the analgesic potential associated with peripheral block is underexplored.

4. Conclusions

In summary, an SAR investigation of the previously published 'truncated' analogues **6a** and **7a** has identified a subset of compounds with comparable potency to Z160 **1** at the $Ca_V2.2$ channel. Key improvements came from the incorporation of electron withdrawing groups on the phenoxy substituent and *N*-methylation at both the aminobenzothiazole nitrogen and the pendant amine. Results from tests with representative examples revealed this class of compound to also have a prolonged *in vitro* half-life in rat plasma (>24 h).

The recent surge in interest in the relevance of Ca_V3 channels in pain transmission prompted an investigation of the activity of the aminobenzothiazoles at the $Ca_V3.2$ channel. It was pleasing to note that a small number of compounds (**14f**, **15d** and **15f**) possess promising activity at this target. The analogues listed in Table 4 may also serve as useful tool compounds to investigate the *in vivo* effects of variable modulation of $Ca_V2.2$ and $Ca_V3.2$ channels in pain models. For example, **14c** appears to be highly selective for the N-type channel (as opposed to the two positive controls **1** and **3**, which appear to be non-selective) while **14f** shows some preference for the T-type channel, and **15d** and **15f** are equipotent at these channels.

We are continuing to investigate the aminobenzothiazole scaffold, along with other scaffolds, for the future development of drug leads for the treatment of neuropathic pain. Testing of this class of molecule across a broad range off-targets, as well as further types of calcium channels, awaits selection of a preferred clinical candidate.

5. Experimental

5.1. Chemistry

5.1.1. General Experimental

All starting materials and reagents were obtained from commercial suppliers and used without further purification. The synthesis of compounds **8c**, **8d**, **8e** and **8f** is reported in supplemental material. The aldehyde **9**, and the aminobenzothiazoles **10a** and **10b** were synthesized according to references 16 or 17. Z160 **1** was synthesized according to reference 4; *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide-assisted acylation of *N*-benzhydryl piperazine with 3,3-diphenylpropanoic acid. NNC 55-0396 dihydrochloride **3** was provided by Alomone Labs (Jerusalem, Israel). Air- and moisture-sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100−200 mesh size) with indicated solvents. Thin-layer chromatography (TLC) was conducted with silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate as appropriate. All ^{1}H NMR spectra were recorded on Bruker 400, 500, 600 MHz spectrometers and have been reported in ppm using solvents as internal standards ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm and methanol-d_4 at 3.31 ppm). Multiplicities are denoted as singlet (s), doublet (d), triplet (t), quartet (q),quintet (quin), multiplet (m) or prefixed broad (br), or a combination where necessary. All proton-decoupled ^{13}C NMR spectra and J-Modulated Spin Echo (JMOD) have been reported in ppm using solvents as internal standards ($CDCl_3$ at 77.2 ppm, DMSO-d_6 at 39.5 ppm and Methanol-d_4 at 49.2). ^{19}F NMR spectra were recorded at 376 or 470 MHz operating frequencies. Compounds were analyzed for HRMS on a Bruker mass spectrometer using electrospray ionization or APCI in the positive ion mode. IR spectra were recorded on a Bruker-Tensor FT-IR spectrometer and have been reported in wavenumber (cm^{-1}). Melting points were measured on a Bruker micromelting point apparatus. Preparative HPLC was performed on an Agilent 1260 Infinity Prep LC controller with an Agilent 1260 Infinity Absorbance detector using a Phenomenex Luna C8 column (21.2 x 150 mm, 5 micron) with a 10 mL per minute flow rate. The elution method used for HPLC purification was gradient from 90% buffer A/10% buffer B to 10% buffer A/90% buffer B over 30 min, and then held at to 10% buffer A/90% buffer B for 10 min (buffer A = 0.1% TFA in MilliQ water, buffer B = 0.1% TFA in 80% MeCN/20% MilliQ water).

5.1.2. General procedure for reductive amination (Procedure A)

A mixture of the aldehyde **9**[17] (1.1 eq., 5.53 mmol) and the thiazolyl amine (1 eq., 4.61 mmol) were dissolved in dry toluene (150 mL). To this a catalytic amount of *p*TSA (0.05 eq., 0.23 mmol) was added and the reaction mixture was refluxed using Dean-Stark apparatus for 2.5 days. The reaction mixture was cooled to ~70 °C. This solution containing the intermediate imine was added to a solution of $NaBH_4$ (2 eq., 11.53 mmol) in dry EtOH (100 mL). After the reaction mixture was refluxed for 5 h, solvent was removed *in vacuo* and water was added. After extraction with DCM the combined organic layers were sequentially washed with water and brine, dried (Na_2SO_4) and the volatiles removed *in vacuo*. The crude product was purified by column chromatography.

5.1.3. General procedure for methylation (Procedure B)

Under nitrogen atmosphere, the oil residue from sodium hydride (2.2 eq., 0.693 mmol) as removed by washing with dry petroleum ether. To this was added dry THF (6 mL) and the suspension cooled to 0 °C. After the dropwise addition of the compound to be methylated (1 eq., 0.287 mmol) in dry THF (6 mL), the reaction was stirred at ambient temperature for 30 min. After recooling the solution to 0 °C, methyl iodide (1.2 eq., 0.315 mmol) that had been passed through neutral alumina was added dropwise. After the reaction mixture was stirred at ambient temperature for 4 h the reaction was quenched with ice and extracted with DCM. The combined organic layers were washed with water and concentrated. The crude product was purified using column chromatography.

5.1.4. General procedure for the synthesis of amine target compounds (Procedure C)

To the Boc-protected compound (0.250 mmol, 1 eq.) in dry DCM was added a saturated solution of HCl in dioxane or MeOH (1 mL). After the reaction mixture was stirred at ambient temperature under an inert atmosphere for 2 h, volatiles were removed *in vacuo* and the crude product was purified by preparative HPLC.

5.1.5. General procedure for the synthesis of guanidinium target compounds (Procedure D)

The free amine precursor (1 eq., 0.2 mmol) was dissolved in dry DMF (2 mL), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (1 eq., 0.2 mmol) and Et_3N (1 eq., 0.2 mmol) were added and the reaction mixture stirred at ambient temperature under an inert atmosphere for 12 h. Ice and DCM (15 mL) were added to the reaction mixture, the organic layer was separated and the aqueous layer extracted with DCM (2 x 15 mL). The combined organic layers were successively washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product and purified by column chromatography.

To the intermediate product (1 eq., 0.15 mmol), dissolved in dry EtOH (2 mL) at 0 °C, was added freshly distilled acetyl chloride (1.5 mL). After the reaction mixture was stirred at ambient temperature for 6 h, volatiles were removed *in vacuo* followed by the subsequent addition and removal of EtOH to remove excess HCl. The crude product was purified by preparative HPLC.

5.1.6. General procedure for the synthesis of guanidinium target compounds (Procedure E)

To the amine precursor (1 eq., 0.115 mmol), dissolved in dry DMF (1 mL) and under an inert atmosphere, was added 1*H*-pyrazole-1-carboxamidine (1.5 eq., 0.173 mmol) and DIPEA, TEA or K_2CO_3 (2 eq., 0.3 mmol). After the reaction mixture was stirred at ambient temperature for 24 h the volatiles were removed *in vacuo* and the crude product was purified by preparative HPLC.

5.1.7. Synthesis of tertiary amines (Procedure F)

Following the procedure of Gribble,[35] to the precursor (30 mg, 0.063 mmol), suspended in MeOH (3 mL), was added sodium borohydride (24 mg, 0.64 mmol) and paraformaldehyde (36 mg, 1.2 mmol). After TFA (0.6 mL) was added dropwise, the reaction mixture was stirred under an inert atmosphere at ambient temperature for 24 h. The reaction mixture was then poured to a mixture of 25% $NaOH_{(aq.)}$ (10 mL) and crushed ice. The pH was adjusted to ~11 and the mixture extracted with DCM (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and the volatiles removed *in vacuo*. The crude product was purified by preparative HPLC.

*5.1.8. tert-Butyl(3-(4-(((6-phenoxybenzothiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**10a**)*[17]

The title compound was synthesized according to general procedure A with the thiazole amine **8a** (700 mg, 2.89 mmol) and the aldehyde **9**[17] (969 mg, 3.47 mmol). Compound **10a** was obtained as a solid (1.0 g, 68%) after purification by column chromatography [30% EtOAc: 70% hexanes].

R_f: 0.20 (20% EtOAc: 80% hexanes); M.P: 142-144 °C; IR (cm^{-1}) : 3392, 2977, 1689, 1260, 1174, 1051, 870; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.4 Hz, 1H), 7.33–7.27 (complex, 4H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.02–6.97 (complex, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 1H), 4.55 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.33 (q, *J* = 5.6 Hz, 2H), 1.99 (quin, *J* = 5.6 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 158.5, 158.3, 156.0, 151.7, 145.7, 131.4, 129.7, 129.6, 129.1, 122.7, 119.5, 118.6, 118.0, 114.7, 111.9, 79.3, 65.8, 48.8, 38.0, 29.5, 28.4; HRMS (ESI): *m/z* calcd for $C_{28}H_{31}N_3NaO_4S$ $(M+Na)^+$ 528.1927, found 528.1925.

*5.1.9. N-(4-(3-Aminopropoxy) benzyl)-6-phenoxybenzothiazol-2-amine trifluoroacetate (**6a**)*[17]

The title compound was synthesized according to general procedure C with **10a** (250 mg, 0.495 mmol), DCM (4 mL) and sat. HCl in dioxane (2.5 mL) to give the title compound **6a** as a solid (185 mg, 92%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.25 (10% MeOH: 90% DCM); M.P: 238–240 °C, IR (cm^{-1}) : 3443, 2920, 1630, 1247, 1022, 872; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.46 (d, *J* = 8.8 Hz, 1H), 7.37-7.32 (complex, 5H), 7.12 (t, *J* = 7.2 Hz, 1H), 7.07 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 4H), 4.60 (s, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.16 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.3, 160.1, 158.5, 155.9, 137.9, 131.3, 130.7, 129.0, 127.2, 125.2, 120.4, 119.9, 117.0, 116.2, 113.8, 66.5, 38.7, 28.4; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{24}N_3O_2S$ $(M+H)^+$ 406.1584, found 406.1582.

*5.1.10. 2-(3-(4-(((6-Phenoxybenzothiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**7a**)*[17]

The title compound was synthesized according to general procedure D, compound **7a** was obtained as oil (79%, two steps).

The intermediate di-Boc protected compound was synthesized with **6a** (150 mg, 0.370 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (115 mg, 0.370 mmol), TEA (0.05 mL, 0.4 mmol) and DMF (2 mL). The crude product was purified by column chromatography (25% EtOAc: 75% hexanes) to give the intermediate as an oil (190 mg, 79%).

R_f: 0.25 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3324, 2978, 1724, 1614, 1220, 1137, 1050, 807; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.50 (s, 1H), 8.65 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.34–7.29 (complex, 4H), 7.22 (d, *J* = 2.0 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.05 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H), 6.99–6.93 (complex, 4H), 4.55 (s, 2H), 4.06 (t, *J* = 5.6 Hz, 2H), 3.66 (q, *J* = 6.0 Hz, 2H), 2.09 (quin, *J* = 6.0 Hz, 2H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.7, 158.8, 158.2, 156.3, 153.3, 152.3, 129.9, 129.3, 123.1, 123.2, 118.8, 118.7, 118.4, 118.3, 115.0, 112.1, 83.2, 79.5, 66.7, 49.2, 39.3, 28.8, 28.5, 28.3; HRMS (ESI): *m/z* calcd for $C_{34}H_{42}N_5O_6S$ $(M+H)^+$ 648.2850, found 648.2848.

The title compound was synthesized with the bis-Boc protected guanylated compound (105 mg, 0.162 mmol), EtOH (3 mL) and acetyl chloride (0.93 mL, 12.98 mmol). The title compound was obtained as a sticky solid (80 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.18 (10% MeOH: 90% DCM); M.P: 171–174 °C; IR (cm^{-1}): 3339, 1627, 1328, 1126, 935, 737; ^{1}H NMR (CD_3OD, 500 MHz): δ 7.57 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.41–7.37 (complex, 4H), 7.19–7.14 (complex, 2H), 7.02 (d, *J* = 8.0 Hz, 4H), 4.68 (s, 2H), 4.09 (t, *J* = 5.5 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.08 (quin, *J* = 6.5 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 160.6, 159.9, 159.2, 158.9, 158.8, 154.4, 131.2, 131.1, 130.5, 130.4, 124.5, 120.2, 119.8, 119.7, 119.4, 118.4, 116.1, 115.9, 113.4, 66.2, 39.8, 39.7, 29.7; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.1; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_5O_2S$ $(M+H)^+$ 448.1802, found 448.1802.

*5.1.11. tert-Butyl (3-(4-((methyl(6-phenoxybenzothiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**11a**)*

The title compound was synthesized according to general procedure B with **10a** (200 mg, 0.396 mmol), dry THF (4 mL),

NaH (33 mg, 0.87 mmol) and MeI (67 mg, 0.48 mmol). After column chromatography purification [25% EtOAc: 75% hexanes] compound **11a** was obtained as a semi-solid (195 mg, 95%).

R_f: 0.29 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3362, 2954, 1708, 1490, 1249, 1174, 1048, 757; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54 (d, *J* = 8.7 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.27 (d, *J* = 5.8 Hz, 1H), 7.26 (d, *J* = 8.7 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 7.03 (dd, *J* = 2.5, 8.7 Hz, 1H), 6.99 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 4.80 (br s, 1H), 4.68 (s, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.33 (q, *J* = 6.1 Hz, 2H), 3.10 (s, 3H), 1.98 (t, *J* = 6.1 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 158.6, 158.6, 156.2, 151.2, 149.7, 132.0, 129.8, 129.1, 128.6, 122.8, 119.5, 118.6, 118.0, 114.8, 112.1, 79.4, 66.0, 56.1, 38.2, 37.7, 29.7, 28.6; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}N_3NaO_4S$ $(M+Na)^+$ 542.2084, found 542.2087.

*5.1.12. N-(4-(3-Aminopropoxy)benzyl)-N-methyl-6-phenoxybenzothiazol-2-amine (**12a**)*

The title compound was synthesized according to general procedure C with with **11a** (44 mg, 0.085 mmol), DCM (1mL) and 1.25 M HCl in MeOH (1 mL). The title compound was obtained as cream solid (56 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.20 (10% MeOH: 90% DCM); IR (cm^{-1}): 3422, 2938, 1625, 1248, 1049, 926, 833; ^1H NMR (CD_3OD, 600 MHz): δ 7.49 (d, *J* = 8.7 Hz, 1H), 7.39 – 7.33 (complex, 3H), 7.33 – 7.28 (complex, 2H), 7.10 (tt, *J* = 7.4, 1.1 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.00 – 6.95 (complex, 4H), 4.75 (s, 2H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.18 (t, *J* = 7.3 Hz, 2H), 3.15 (s, 3H), 2.16 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz): δ 171.2, 160.6, 160.5, 153.8, 150.9, 133.5, 131.7, 131.1, 130.9, 124.8, 120.7, 120.4, 119.8, 116.7, 113.8, 67.1, 57.7, 39.5, 39.1, 29.2; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.6; HRMS (APCI): *m/z* calcd for $C_{24}H_{26}N_3O_2S$ $(M+H)^+$ 420.1740, found 420.1738.

*5.1.13. 2-(3-(4-((Methyl(6-phenoxybenzothiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13a**)*

The title compound was synthesized according to general procedure D, compound **13a** was obtained as oil (60%, two steps).

The intermediate di-Boc protected compound was synthesized with **12a** (200 mg, 0.480 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (149 mg, 0.480 mmol), TEA (0.13 mL, 0.95 mmol) and DMF (5 mL). The crude product was purified by column chromatography (20% EtOAc: 80% hexanes) to give the intermediate as an oil (190 mg, 58%).

R_f: 0.32 (30% EtOAc: petroleum ether); IR (cm^{-1}): 3334, 2930, 1722, 1635, 1456, 1136, 1027, 935, 757; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.51 (s, 1H), 8.65 (br s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.07–7.00 (m, 2H), 6.98 (d, *J* = 8.0 Hz, 3H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.67 (s, 2H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.64 (q, *J* = 4.0 Hz, 2H), 3.09 (s, 3H), 2.07 (quin, *J* = 6.0 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.5, 163.7, 158.6, 158.5, 156.3, 153.3, 151.2, 149.7, 131.9, 129.8, 129.1, 128.6, 122.8, 119.6, 118.6, 118.0, 114.9, 112.0, 83.2, 79.4, 66.6, 56.1, 39.2, 37.7, 28.7, 28.4, 28.3, 28.2; HRMS (ESI): *m/z* calcd for $C_{35}H_{44}N_5O_6S$ $(M+H)^+$ 662.3007, found 662.3002.

The title compound was synthesized with the bis-Boc protected guanylated compound (190 mg, 0.287 mmol), EtOH (4 mL) and acetyl chloride (1.8 mL, 23 mmol). The title compound was obtained as a solid (125 mg, 97%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.21 (10% MeOH: 90% DCM); M.P: 161–164 °C; I.R: (cm^{-1}): 3422, 2938, 1625, 1248, 1049, 926, ^1H NMR (CD_3OD, 400 MHz): δ 7.53 (d, *J* = 8.8 Hz, 1H), 7.41 (d, J = 2.4 Hz, 1H), 7.39–7.34 (complex, 2H), 7.33 (d, *J* = 8.8 Hz, 2H), 7.15-7.10 (complex, 2H), 7.02-6.97 (complex, 4H), 4.78 (s, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 3.43 (t, *J* = 6.8 Hz, 2H), 3.32 (s, 3H), 2.10 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.4, 160.3, 159.4, 154.2, 131.1, 130.4, 129.0, 124.5, 120.1, 119.5, 118.9, 116.1, 113.4, 66.2, 57.8, 39.7, 38.8, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.1; HRMS (ESI): *m/z* calcd for $C_{25}H_{27}N_5O_2S$ $(M+H)^+$ 462.1958, found 462.1962.

*5.1.14. 4-((2-((4-(3-Aminopropoxy)benzyl)amino)benzothiazol-6-yl)oxy)phenol trifluoroacetate (**6b**)*

To compound **10b**[16] (50 mg, 0.080 mmol) was added a solution of. TFA (0.9 mL) and thioanisole (0.24 mL, 2.0 mmol). After the reaction was stirred at ambient temperature, under a nitrogen atmosphere, for 1 h the volatiles were removed *in vacuo*. The crude product was triturated with 2:1 (EtOAc: hexanes), 2:1 (ether: hexanes) and hexanes to remove residual thioanisole. The title compound **6b** was obtained as a colourless oil (35 mg, 82%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.4 (10% MeOH: 90% DCM); IR (cm^{-1}): 3445, 2923, 1674, 1136, 841, 770; ^1H NMR (CD_3OD, 400 MHz): δ 7.42 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 2.4 Hz, 1H), 7.01–6.96 (complex, 3H), 6.88– 6.77 (complex, 4H), 4.59 (s, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.15 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.3, 160.1, 157.3, 155.4, 150.6, 142.4, 139.3, 130.6, 129.6, 122.0, 118.9, 117.5, 117.3, 116.1, 112.0, 66.4, 38.7, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.9; HRMS (ESI): *m/z* calcd for $C_{23}H_{24}N_3O_3S$ $(M+H)^+$ 422.1538, found 422.1539.

*5.1.15. 2-(3-(4-(((6-(4-Hydroxyphenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**7b**)*

The title compound was synthesized according to general procedure D, compound **7b** was obtained as oil (62%, two steps).

The intermediate di-Boc protected compound was synthesized with **6b** (80 mg, 0.15 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (48 mg, 0.15 mmol), TEA (0.11 mL, 0.77 mmol) and DMF (3 mL). The crude product was purified by column chromatography (50% EtOAc: 50% hexanes) to give the intermediate as an oil (63 mg, 62%).

R_f: 0.28 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3322, 2928, 1726, 1648, 1214, 919, 809; ^1H NMR ($CDCl_3$, 500 MHz): 11.63 (s, 1H), 8.81 (s, 1H), 7.40 (s, 4H), 7.03–6.98 (complex, 7H), 4.64 (s, 2H), 4.12 (br s, 2H), 3.73 (br s, 2H), 2.17 (br s, 2H), 1.62 (s, 9H), 1.61 (9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 163.5, 158.8, 158.7, 156.3, 153.3, 152.7, 152.6, 150.5, 150.3, 129.3, 120.6, 117.5, 117.4, 116.7, 114.9, 110.5, 83.3, 79.7, 66.6, 39.3, 28.8, 28.4, 28.3; HRMS (ESI): *m/z* calcd for $C_{34}H_{41}N_5O_7S$ $(M+H)^+$ 664.2805, found 664.2806.

The title compound was synthesized with the bis-Boc protected guanylated compound (63 mg, 0.095 mmol), EtOH (3 mL) and acetyl chloride (0.54 mL, 7.6 mmol). The title compound was obtained as a sticky colourless solid (50 mg, quant.). A little amount was further purified by preparative HPLC.

R_f: 0.22 (10% MeOH: 90% DCM); IR (cm^{-1}): 3445, 2923, 1674, 1136, 841, 770; ^1H NMR (CD_3OD, 400 MHz): δ 7.44 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.04 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 2.09 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.1, 160.1, 158.9, 156.5,

155.2, 151.0, 130.5, 130.4, 129.2, 122.1, 121.7, 118.5, 118.1, 117.5, 117.4, 116.0, 115.2, 112.1, 111.8, 66.2, 39.8, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.9; HRMS (ESI): *m/z* calcd for $C_{24}H_{25}N_5O_3S$ $(M)^+$. 463.1678, found 463.1691.

*5.1.16. 4-((2-((4-(3-tert-Butyl(3-(4-(((6-(4-(benzyloxy)phenoxy)benzo[d]thiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl)carbamate (**11b**)*

The title compound was synthesized according to general procedure C, with **10b** (200 mg, 0.327 mmol), dry THF (9 mL), NaH (28 mg, 0.72 mmol) and MeI (0.02 mL, 0.39 mmol). After column chromatography purification [20% EtOAc: 80% hexanes], compound **33** was obtained as oil (170 mg, 83%).

R_f: 0.27 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3322, 2928, 1726, 1648, 1214, 919, 809; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 8.8 Hz, 1H), 7.45–7.37 (complex, 4H), 7.35–7.31 (complex, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.95 (s, 4H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 2H), 4.76 (s, 1H), 4.68 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 3.13 (s, 3H), 1.97 (quin, *J* = 6.0 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.1, 158.8, 156.2, 155.0, 151.6, 137.2, 129.3, 128.8, 128.2, 127.7, 120.1, 119.2, 117.9, 116.1, 114.9, 110.7, 79.4, 70.7, 66.1, 56.7, 38.2, 38.2, 29.7, 28.6; HRMS (ESI): *m/z* calcd for $C_{36}H_{40}N_3O_5S$ $(M+H)^+$ 626.2683, found 626.2686.

*5.1.17. 4-((2-((4-(3-Aminopropoxy)benzyl)(methyl)amino)benzo[d]thiazol-6-yl)oxy)phenol trifluoroacetate (**12b**)*

To compound **11b** (100 mg, 0.160 mmol) was added a solution of TFA (1.8 mL) and thioanisole (0.48 mL, 4.0 mmol). After the reaction was stirred at ambient temperature, under a nitrogen atmosphere, for 1 h the volatiles were removed *in vacuo*. The crude product was triturated with 2:1 (EtOAc: hexanes), 2:1 (ether: hexanes) and hexanes to remove residual thioanisole. The title compound **12b** was obtained as a colourless oil (85 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.42 (10% MeOH: 90% DCM); IR (cm^{-1}): 3435, 2925, 1670, 1076, 840, 770; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.47 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 2.8, 8.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.23 (s, 3H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.14 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.1, 160.0, 155.8, 155.0, 151.3, 131.2, 130.3, 129.6, 121.6, 119.1, 118.8, 118.6, 117.4, 116.1, 111.5, 66.4, 57.5, 38.8, 38.7, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.1; HRMS (ESI): *m/z* calcd for $C_{24}H_{26}N_3O_3S$ $(M+H)^+$ 436.1695, found 436.1684.

*5.1.18. 2-(3-(4-(((6-(4-Hydroxyphenoxy)benzo[d]thiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13b**)*

The title compound was synthesized according to general procedure D, compound **13b** was obtained as oil (35% yield over two steps).

The intermediate di-Boc protected compound was synthesized with **12b** (95 mg, 0.18 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (57 mg, 0.18 mmol), TEA (0.08 mL, 0.5 mmol) and DMF (3 mL). The crude product was purified by column chromatography (50% EtOAc: 50% hexanes) to give the intermediate as an oil (70 mg, 56%).

R*f*: 0.25 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3335, 2920, 1721, 1640, 1136, 817; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.49 (s, 1H), 8.70 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.20–7.15 (complex, 3H), 6.94–6.80 (m, 7H), 4.64 (s, 2H), 4.00 (br s, 2H), 3.62 (br s, 2H), 3.09 (s, 3H), 2.04 (br s, 2H), 1.49 (s, 9H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.4, 163.4, 158.5, 156.3, 153.2, 152.7, 150.7, 148.2, 131.4, 129.0, 128.3, 120.3, 119.2, 117.4, 116.6, 114.8, 110.4, 83.3, 79.7, 66.5, 56.4, 39.9, 37.9, 28.7, 28.4, 28.2; HRMS (ESI): *m/z* calcd for $C_{35}H_{43}N_5O_7S$ $(M+H)^+$ 678.2961, found 678.2962.

The title compound was synthesized with bis-Boc protected guanylated compound (70 mg, 0.10 mmol), EtOH (2 mL) and acetyl chloride (0.59 mL, 8.3 mmol). The title compound was obtained as a colourless oil (35 mg, 62%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.43 (10% MeOH: 90% DCM); IR (cm^{-1}): 3163, 2860, 1606, 1119, 1049, 824; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.46 (d, *J* = 8.8 Hz, 1H), 7.31-7.27 (complex, 3H), 7.05 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 9.2 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.20 (s, 3H), 2.07 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.1, 160.4, 158.9, 156.3, 155.2, 155.1, 130.4, 130.1, 128.8, 121.7, 118.8, 118.5, 117.4, 116.2, 111.6, 66.2, 58.0, 39.7, 38.9, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0; HRMS (ESI): *m/z* calcd for $C_{25}H_{27}N_5O_3S$ $(M)^+$. 477.1835, found 477.1847.

*5.1.19. tert-Butyl (3-(4-(((6-(4-fluorophenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**10c**)*

The title compound was synthesized according to general procedure A with the thiazole amine **7** (1.2 g, 4.6 mmol) and the aldehyde **9**[17] (1.54 g, 5.53 mmol). Compound **10c** was obtained as a colourless solid. (2.0 g, 77%)

R_f: 0.43 (20% EtOAc: 80% hexanes); M.P: 145-147 °C, IR (cm^{-1}): 3433, 2925, 2854, 1630, 1412, 1315, 1263, 1026, 779; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, *J* = 8.7 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.02−6.92 (complex, 5H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.77 (br s, 1H), 4.53 (s, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.31 (q, *J* = 6.2 Hz, 2H), 1.96 (quin, *J* = 6.2 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.0, 159.9 (d, *J* = 239.5 Hz), 158.7, 156.2, 154.0, 152.5, 147.6, 131.0, 129.4, 129.3, 119.9 (d, *J* = 8.1 Hz), 119.4, 118.1, 116.5 (d, *J* = 23.3 Hz), 114.9, 111.5, 79.4, 66.0, 49.1, 38.2, 29.7, 28.6; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -121.3; HRMS (ESI): *m/z* calcd for $C_{28}H_{30}FN_3NaO_4S$ 546.1833, found 546.1836.

*5.1.20. N-(4-(3-Aminopropoxy)benzyl)-6-(4-fluorophenoxy)benzo[d]thiazol-2-amine trifluoroacetate (**6c**)*

The title compound was synthesized according to general procedure C with **10c** (200 mg, 0.382 mmol), DCM (1 mL) and sat. HCl in dioxane (1 mL) to give the title compound **9c** as a solid (150 mg, 93%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.21 (10% MeOH: 90% DCM); M.P: 169–171 °C; IR (cm^{-1}): 3417, 1659, 1549, 1500, 1458, 1352, 1205, 1117; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.54 (d, *J* = 7.2 Hz, 1H), 7.45−7.40 (complex, 3H), 7.19 (d, *J* = 9.2 Hz, 1H), 7.15−7.11 (complex, 2H), 7.08−7.02 (m, 4H), 4.67 (s, 2H), 4.15 (t, *J* = 6.0 Hz, 2H), 3.16 (t, *J* = 6.0 Hz, 2H), 2.16 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 169.4, 161.8 (d, *J* = 239.6 Hz), 160.5, 156.9, 154.3, 154.3, 135.6, 130.9, 128.3, 126.4, 122.1 (d, *J* = 7.5 Hz), 120.3, 117.8 (d, *J* = 23.5 Hz), 116.3, 113.6, 66.6, 50.6, 38.8, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -122.9, -77.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{23}FN_3O_2S$ 424.1490, found 424.1487.

5.1.21. 2-(3-(4-(((6-(4-Fluorophenoxy)benzo[d]thiazol-2

*yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**7c**)*

The title compound was synthesized according to general procedure E with **6c** (100 mg, 0.236 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (35 mg, 0.24 mmol), potassium carbonate (65 mg, 0.47 mmol) and DMF (1 mL). Purification with ammoniacal silica gel, eluting with 10% MeOH: 90% DCM gave the title compounds **7c** as a solid (80 mg, 76%) which was further purified by preparative HPLC.

R_f: 0.2 (10% MeOH: 90% DCM); M.P: 179–181 °C; IR (cm^{-1}): 3341, 1629, 1331, 1130, 935, 725; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.44 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.09 (t, *J* = 8.8 Hz, 2H), 6.99–6.91 (complex, 5H), 4.56 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 2.08 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.9, 159.6 (d, *J* = 241.1 Hz), 158.5, 157.9, 155.0 (d, *J* = 1.8 Hz), 151.7, 150.0, 132.6, 132.0, 129.7, 120.3 (d, *J* = 8.5 Hz), 119.6, 118.3, 117.4 (d, *J* = 23.1 Hz), 115.3, 113.0, 65.7, 47.6, 38.8, 29.1; ^{19}F NMR (CD_3OD, 376 MHz): δ -122.6, -77.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{25}FN_5O_2S$ $(M+H)^+$ 466.1708, found 466.1711.

*5.1.22. tert-Butyl(3-(4-(((6-(4-fluorophenoxy)benzothiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl) carbamate (**11c**)*

The title compound was synthesized according to general procedure B with **10c** (150 mg, 0.287 mmol), dry THF (4 mL), NaH (27 mg, 0.69 mmol) and MeI (45 mg, 0.32 mmol). After column chromatography purification at 25% EtOAc: 75% hexanes compound **11c** was obtained as a colourless solid (105 mg, 68%).

R_f: 0.45 (20% EtOAc: 80% hexanes); M.P: 91–93 °C; IR (cm^{-1}): 3436, 2925, 2854, 1712, 1501, 1203, 1174, 1092, 818; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.54 (d, *J* = 8.7 Hz, 1H), 7.24 –7.21 (complex, 3H), 7.02–6.92 (complex, 5H), 6.86 (d, *J* = 8.6 Hz, 2H), 4.77 (br s, 1H), 4.67 (s, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.32 (q, *J* = 6.2 Hz, 2H), 3.10 (s, 3H), 1.99 (quin, *J* = 5.9 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz,): δ 168.4, 159.6 (d, *J* = 239.6 Hz), 158.7, 156.2, 154.3, 151.9, 132.2, 131.8, 129.2, 128.5, 119.6 (d, *J* = 8.1 Hz), 119.5, 118.2, 116.4 (d, *J* = 23.2 Hz), 114.9, 111.4, 79.4, 66.0, 56.2, 38.2, 37.9, 29.7, 28.6; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -121.3; HRMS (ESI): *m/z* calcd for $C_{29}H_{33}FN_3O_4S$ $(M+H)^+$ 538.2170, found 538.2173.

*5.1.23. N-(4-(3-Aminopropoxy)benzyl)-6-(4-fluorophenoxy)-N-methylbenzothiazol-2-amine trifluoroacetate (**12c**)*

The title compound was synthesized according to general procedure C with **11c** (80 mg, 0.15 mmol), DCM (1 mL) and sat. HCl in dioxane (1 mL) to give the title compound **12c** as oil (60 mg, 92%) with purification by trituration using DCM and hexanes (1: 10). Further purification by preparative HPLC gave an analytically pure sample.

R_f: 0.23 (10% MeOH: 90% DCM); IR (cm^{-1}): 3435, 2925, 2855, 1624, 1308, 1048, 1024, 816; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.49 (d, *J* = 8.8 Hz, 1H), 7.36 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.11–6.96 (complex, 7H), 4.75 (s, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.18 (s, 3H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.17 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.5, 161.4 (d, *J* = 238.6 Hz), 159.9, 154.0, 148.3, 131.9, 131.9, 130.3, 129.9, 121.0 (d, *J* = 8.2 Hz), 119.6, 119.4, 117.5 (d, *J* = 23.6 Hz), 116.0, 112.8, 66.4, 57.3, 38.8, 38.6, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -122.5, -77.0; HRMS (ESI): *m/z* calcd for $C_{24}H_{25}FN_3O_2S$ $(M+H)^+$ 438.1648, found 438.1646.

*5.1.24. 2-(3-(4-(((6-(4-Fluorophenoxy)benzo[d]thiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13c**)*

The title compound was synthesized according to general procedure D, compound **13c** was obtained as oil (59% yield over two steps).

The intermediate di-Boc protected compound was synthesized with **12c** (110 mg, 0.251 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (78 mg, 0.25 mmol), TEA (0.04 mL, 0.3 mmol) and DMF (3 mL). The crude product was purified by column chromatography (30% EtOAc: 70% hexanes) to give the intermediate as a semi-solid (110 mg, 59%).

R_f: 0.21 (20% EtOAc: 80% hexanes); IR (cm^{-1}): 3430, 2925, 1722, 1618, 1322, 1136, 809; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.50 (s, 1H), 8.64 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 8.5 Hz, 3H), 7.01–6.90 (complex, 7H), 4.67 (s, 2H), 4.05 (t, *J* = 5.6 Hz, 2H), 3.65 (q, *J* = 6.0 Hz, 2H), 3.09 (s, 3H), 2.09 (quin, *J* = 6.0 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 163.7, 159.5 (d, *J* = 239.3 Hz), 158.6, 156.3, 154.3 (d, *J* = 2.5 Hz), 153.3, 151.7, 149.7, 132.0, 129.1, 128.6, 119.6 (d, *J* = 8.3 Hz), 118.1, 116.4 (d, *J* = 22.9 Hz), 114.8, 111.5, 83.2, 79.4, 66.6, 56.2, 39.2, 37.7, 28.7, 28.5, 28.3; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -121.3, HRMS (ESI): m/z calcd for $C_{35}H_{42}FNaN_5O_6S$ $(M+Na)^+$ 702.2732, found 702.2729.

The title compound was synthesized with bis-Boc protected guanylated compound (110 mg, 0.162 mmol), EtOH (2 mL) and acetyl chloride (0.93 mL, 13 mmol). The title compound was obtained as an oil (80 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.25 (10% MeOH: 90% DCM); IR (cm^{-1}): 3350, 2919, 1626, 1204, 1048, 758; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.50 (d, *J* = 8.8 Hz, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.31 (d, *J* = 6.4 Hz, 2H), 7.12–7.06 (complex, 3H), 7.03–6.96 (complex, 4H), 4.76 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 3.20 (s, 3H), 2.09 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 150 MHz): δ 170.5, 160.9 (d, *J* = 238.8 Hz), 160.0, 158.9, 158.9, 155.7 (d, *J* = 2.1 Hz), 153.7, 149.3, 132.4, 130.2, 130.0, 120.9 (d, *J* = 8.1 Hz), 119.8, 119.3, 117.4 (d, *J* = 23.2 Hz), 116.0, 112.8, 66.2, 57.1, 40.3, 39.8, 38.5, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -122.7, -76.9; HRMS (ESI): *m/z* calcd for $C_{25}H_{27}FN_5O_2S$ $(M+H)^+$ 480.1864, found 480.1870.

*5.1.25. N-(4-(3-(Dimethylamino)propoxy)benzyl)-6-(4-fluorophenoxy)benzo[d]thiazol-2-amine trifluoroacetate (**14c**)*

The title compound was synthesized according to general procedure F with **20** (20 mg, 0.050 mmol), paraformaldehyde (57 mg, 1.9 mmol), $NaBH_4$ (38 mg, 1.0 mmol), TFA (0.5 mL) and MeOH (2 mL). After purification by HPLC the title compound was obtained as a semi-solid (10 mg, 48%).

R_f: 0.21 (10% MeOH: 90% DCM); ^{1}H NMR (CD_3OD, 400 MHz): δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.38-7.35 (complex, 3H), 7.12-7.06 (m, 3H), 7.03-6.96 (complex, 4H), 4.61 (s, 2H), 3.35 (m, 2H), 2.94 (s, 6H), 2.21 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 169.1, 161.1 (d, *J* = 238.6 Hz), 159.5, 159.2, 155.6, 154.1, 147.8, 131.9, 130.3, 120.9 (d, *J* = 8.1 Hz), 119.3, 119.0, 117.5 (d, *J* = 23.4 Hz), 115.8, 112.9, 66.1, 57.0, 43.8, 25.9; ^{19}F NMR (376 MHz, CD_3OD): δ -122.4, -76.9; HRMS (APCI): *m/z* calcd for $C_{25}H_{26}O_2N_3FS$ $(M)^{+\cdot}$ 451.1724 found 451.1726.

*5.1.26. tert-Butyl(3-(4-(((6-(4-(trifluoromethyl)phenoxy)benzothiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**10d**)*

The title compound was synthesized according to general procedure A with the thiazole amine **8d** (400 mg, 1.29 mmol) and the aldehyde **9**[17] (432 mg, 1.55 mmol). Compound **10d** was

obtained as a solid. (404 mg, 55%) after purification by column chromatography [25% EtOAc: hexanes].

R_f: 0.23 (35% EtOAc: 65% hexanes); M.P: 170–171 °C; IR (cm^{-1}): 3334, 2872, 1712, 1680, 1121, 911, 741; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.55 (d, *J* = 8.4 Hz, 2H), 7.48 (dd, *J* = 1.2 Hz, 8.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 2.0, 8.4 Hz, 3H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.55 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.34 (q, *J* = 6.0 Hz, 2H), 1.99 (quin, *J* = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.3, 161.6, 158.7, 156.2, 150.2, 149.7, 131.8, 129.6, 129.3, 127.3 (q, *J* = 3.8 Hz), 125.7 (q, *J* = 269.8 Hz), 124.8 (q, *J* = 32.5 Hz), 119.8, 119.2, 117.3, 114.9, 113.1, 79.5, 66.0, 49.0, 38.2, 29.7, 28.6; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -61.7; HRMS (ESI): *m/z* calcd for $C_{29}H_{31}F_3N_3O_4S$ $(M+H)^+$ 574.1987, found 574.1971.

*5.1.27. N-(4-(3-Aminopropoxy)benzyl)-6-(4-(trifluoromethyl)phenoxy)benzothiazol-2-amine trifluoroacetate (**6d**)*

The title compound was synthesized according to general procedure C with **10d** (150 mg, 0.262 mmol), DCM (3 mL) and sat. HCl in dioxane (1.5 mL) to give the title compound **6d** as a solid (140 mg, 96%) after trituration DCM: hexanes (1: 10). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.19 (10% MeOH: 90% DCM); M.P: 235–237 °C; IR (cm^{-1}): 3431, 2921, 1648, 1333, 1106, 805; ^1H NMR (CD_3OD, 400 MHz): δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.11–7.07 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.17 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 169.7, 162.1, 160.4, 154.6, 137.2, 130.9, 128.7 (q, *J* = 3.8 Hz), 128.4, 126.8, 126.6 (q, *J* = 32.5 Hz), 125.8 (q, *J* = 268.4 Hz), 121.7, 119.4, 116.9, 116.3, 115.7, 66.6, 50.6, 38.8, 28.6; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0, -63.2; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}F_3N_3O_2S$ $(M+H)^+$ 474.1463, found 474.1457.

*5.1.28. 2-(3-(4-(((6-(4-(Trifluoromethyl)phenoxy)benzothiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**7d**)*

The title compound was synthesized according to general procedure D compound **7d** was obtained as a solid (60%, two steps).

The intermediate, *2-(3-(4-(((6-(4-(trifluoromethyl)phenoxy)-benzothiazol-2-yl)amino)methyl)phenoxy)propyl)di-tertbuty lesterguanidine* was synthesized with **6d** (100 mg, 0.196 mmol), *N, N′*-di-Boc-1*H*-pyrazole-1-carboxamidine (61 mg, 0.20 mmol), TEA (0.03 mL, 0.2 mmol) and DMF (2 mL). The crude product was purified by column chromatography (25% EtOAc: 75% hexanes) to give the intermediate as an oil (90 mg, 64%).

R_f: 0.22 (25% EtOAc: 75% hexanes); IR (cm^{-1}): 3322, 2931, 1724, 1635, 1137, 810, 759; ^1H NMR ($CDCl_3$, 500 MHz): δ 11.50 (s, 1H), 8.64 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.00–6.92 (complex, 6H), 4.54 (s, 2H), 4.02 (br s, 2H), 3.61 (q, *J* = 5.5 Hz, 2H), 2.05 (t, *J* = 5.5 Hz, 2H), 1.48 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 163.7, 161.4, 158.8, 156.3, 153.3, 150.5, 129.3, 128.7, 128.5, 127.3 (q, *J* = 3.6 Hz), 125.4 (q, *J* = 269.4 Hz), 124.9 (q, *J* = 31.6 Hz), 124.7, 119.5, 119.3, 117.4, 115.0, 113.1, 83.2, 79.5, 66.6, 49.2, 39.2, 29.9, 28.8, 28.5, 28.3; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -61.7; HRMS (ESI): *m/z* calcd for $C_{35}H_{41}F_3N_5O_6S$ $(M+H)^+$ 716.2730, found 716.2704.

The title compound was synthesized with the bis-Boc protected guanylated compound (90 mg, 0.12 mmol), EtOH (2 mL) and acetyl chloride (0.68 mL, 9.5 mmol). The title compound was obtained as a solid (60 mg, 94%) after trituration with DCM and hexanes (1: 10). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.22 (10% MeOH: 90% DCM); M.P: 195–197 °C; IR (cm^{-1}) : 3412, 2919, 1642, 1177, 804; ^1H NMR (CD_3OD, 400 MHz): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.45 (d, *J* = 2.4 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.12-7.08 (complex, 3H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.09 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.5, 162.0, 160.6, 158.9, 154.6, 136.8, 131.0, 128.7 (q, *J* = 3.7 Hz), 128.1, 127.1 (q, *J* = 266.0 Hz) 126.7, 126.6 (q, *J* = 35.5 Hz), 126.4, 121.8, 119.4, 116.8, 115.7, 66.3, 50.6, 39.8, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -79.6, -63.3; HRMS (ESI): calcd for $C_{25}H_{25}F_3N_5O_2S$ $(M+H)^+$ 516.1681, found 516.1674.

*5.1.29. tert-Butyl(3-(4-((methyl(6-(4-(trifluoromethyl)phenoxy)benzothiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**11d**)*

The title compound was synthesized according to general procedure B with **10d** (190 mg, 0.330 mmol), dry THF (10 mL), NaH (28 mg, 0.73 mmol) and MeI (56 mg, 0.40 mmol). After column chromatography purification [20% EtOAc: 80% hexanes] compound **11d** was obtained as a solid (130 mg, 77%).

R_f: 0.25 (35% EtOAc: 65% hexanes); M.P: 98–100 °C; IR (cm^{-1}): 3420, 2929, 1706, 1122, 760; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (t, *J* = 8.4 Hz, 3H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 2H), 7.04–7.00 (complex, 3H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.79 (s, 1H), 4.69 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.33 (q, *J* = 6.0 Hz, 2H), 3.11 (s, 3H), 1.98 (quin, *J* = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.8, 161.7, 158.7, 156.2, 150.2, 149.7, 132.0, 129.2, 128.4, 127.2 (q, *J* = 3.6 Hz), 125.6 (q, *J* = 269.8 Hz), 124.7 (q, *J* = 32.5 Hz), 119.7, 119.2, 117.2, 114.9, 112.9, 79.4, 66.0, 56.2, 38.2, 37.9, 29.7, 28.6; ^{19}F NMR ($CDCl_3$, 470 MHz,): δ -61.6; HRMS (ESI): calcd for $C_{30}H_{33}F_3N_3O_4S$ $(M+H)^+$ 588.2144, found 588.2155.

*5.1.30. N-(4-(3-Aminopropoxy)benzyl)-N-methyl-6-(4-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-amine trifluoroacetate (**12d**)*

The title compound was synthesized according to general procedure C with **11d** (120 mg, 0.204 mmol), DCM (3 mL) and sat. HCl in dioxane (1.5 mL). The title compound **12d** was obtained as an oil (95 mg, 92%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.22 (10% MeOH: 90% DCM); IR (cm^{-1}) : 3408, 2925, 1627, 1066, 766; ^1H NMR (CD_3OD, 400 MHz): δ 7.63 (d, *J* = 8.8 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.10-7.06 (complex, 3H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.17-3.13 (complex, 5H), 2.17 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.8, 163.3, 159.9, 151.4, 150.7, 132.8, 130.3, 130.2, 128.4 (q, *J* = 3.5 Hz), 127.3 (q, *J* = 266.2 Hz), 125.8 (q, *J* = 32.2 Hz), 120.5, 120.2, 118.4, 116.0, 114.4, 66.4, 57.1, 38.8, 38.5, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.8, -63.2; HRMS (ESI): calcd for $C_{25}H_{24}F_3N_3O_2S$ $(M+H)^+$ 488.1620, found 488.1638.

*5.1.31. 2-(3-(4-((Methyl(6-(4-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13d**)*

The title compound was synthesized according to general procedure D, compound **13d** was obtained as oil (39%, two steps).

The intermediate di-Boc protected compound was synthesized with **12d** (80 mg, 0.16 mmol), *N,N′*-di-Boc-1*H*-pyrazole-1-carboxamidine (51 mg, 0.16 mmol), TEA (0.02 mL, 0.2 mmol)

and DMF (2 mL). The crude product was purified by column chromatography (20% EtOAc: 80% hexanes) to give the intermediate as a semi-solid (55 mg, 49%).

R_f: 0.25 (25% EtOAc: 75% hexanes) IR (cm^{-1}): 3337, 2926, 1725, 1633, 1137, 759; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.50 (s, 1H), 8.64 (s, 1H), 7.57–7.54 (m, 3H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.04–7.00 (complex, 3H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.69 (s, 2H), 4.06 (t, *J* = 5.6 Hz, 2H), 3.66 (q, *J* = 5.6 Hz, 2H), 3.11 (s, 3H), 2.09 (quin, *J* = 5.6 Hz, 2H), 1.50 (s, 18H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.9, 163.7, 161.7, 158.6, 156.3, 153.3, 150.6, 149.6, 132.2, 129.1, 128.5, 127.2 (q, *J* = 3.4 Hz), 125.5 (q, *J* = 268.7 Hz), 124.6 (q, *J* = 32.2 Hz), 119.7, 119.2, 117.2, 114.9, 113.0, 83.2, 79.5, 66.6, 56.2, 39.2, 37.8, 28.8, 28.5, 28.3; ^{19}F NMR ($CDCl_3$, 470 MHz,): δ -61.7; HRMS (ESI): *m/z* calcd for $C_{36}H_{43}F_3N_5O_6S$ $(M+H)^+$ 730.2886, found 730.2859.

The title compound was synthesized with the bis-Boc protected guanylated compound (60 mg, 0.08 mmol), EtOH (3 mL) and acetyl chloride (0.47 mL, 6.6 mmol). The title compound was obtained as a solid (41 mg, 80%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.24 (10% MeOH: 90% DCM); IR (cm^{-1}): 3337, 2926, 1725, 1633, 1137, 759; ^1H NMR (CD_3OD, 400 MHz): δ 7.64 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.13 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 4.75 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 2.07 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.8, 163.2, 160.1, 158.9, 151.5, 150.2, 132.5, 130.2, 129.8, 128.4 (q, *J* = 3.8 Hz), 127.2 (q, *J* = 268.6 Hz), 125.8 (q, *J* = 32.4 Hz), 120.5, 120.0, 118.4, 116.0, 114.4, 66.2, 57.2, 39.7, 38.5, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.1, -63.2; HRMS (ESI): *m/z* calcd for $C_{26}H_{27}F_3N_5O_2S$ $(M+H)^+$ 530.1832, found 530.1829.

*5.1.32. N-(4-(3-(Dimethylamino)propoxy)benzyl)-N-methyl-6-(4-(trifluoromethyl)phenoxy)benzo[d] thiazol-2-amine trifluoroacetate (**15d**)*

The title compound was synthesised according to the general procedure F with **6d** (33.4 mg, 0.07 mmol), dry THF (10 mL), paraformaldehyde (78 mg, 2.6 mmol), $NaBH_4$ (60 mg, 1.6 mmol) and TFA (1.0 mL) and the reaction mixture stirred for 48 h. After purification by HPLC the title compound was obtained as an oil (34 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.26 (10% MeOH: 90% DCM); IR (cm^{-1}): 2976, 2903, 2360, 2175, 2155, 1678, 1610, 1454, 1326, 1203, 1140, 1066, 842, 801, 726, 683, 656; ^1H NMR (CD_3OD, 600 MHz): δ 7.65 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.48 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.30 (complex, 2H), 7.13 – 7.08 (complex, 3H), 7.00 – 6.96 (complex, 2H), 4.77 (s, 2H), 4.13 (t, *J* = 5.8 Hz, 2H), 3.37 (m, 2H), 3.18 (s, 3H), 2.96 (s, 6H), 2.23 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 170.7, 163.1, 159.7, 151.4, 150.0, 132.4, 130.1, 130.1, 129.7, 128.3 (q, *J* = 3.9 Hz), 125.4, 120.4, 119.9, 118.32, 118.29, 115.88, 115.86, 115.4, 114.3, 66.0, 57.0, 56.9, 43.6, 38.4, 25.8. ^{19}F NMR (CD_3OD, 376 MHz): δ -77.3, -63.2; HRMS (APCI): *m/z* calcd for $C_{27}H_{29}N_3F_3O_2S$ $(M+H)^{+\cdot}$ 516.1933, found 516.1929.

*5.1.33. (3-{4-[(6-(3-Trifluoromethylphenoxy)benzothiazol-2-ylamino)methyl]phenoxy}propyl)-carbamic acid tert-butyl ester (**10e**)*

The title compound was synthesized according to general procedure A with the thiazole amine **8e** (350 mg, 1.13 mmol) and the aldehyde **9**[17] (378 mg, 1.35 mmol). Compound **10e** was obtained after purification by column chromatography [20% EtOAc: 80% hexanes] as a solid (450 mg, 61%).

R_f: 0.40 (25% EtOAc: 75% hexanes); M.P: 166–168 °C; IR (cm^{-1}): 3384, 3010, 2879, 1676, 1171, 1022, 757; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, *J* = 8.7 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.6 Hz, 3H), 7.27 (s, 1H), 7.20 (s, 1H), 7.13 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.03 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.89 (dt, *J* = 2.8, 9.6 Hz, 2H), 4.76 (br s, 1H), 4.56 (s, 2H), 4.02 (t, *J* = 3.5 Hz, 2H), 3.34 (q, *J* = 6.1 Hz, 2H), 1.99 (quin, *J* = 6.2 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.2, 158.7, 158.6, 156.0, 150.7, 148.1, 132.8, 132.4 (q, *J* = 33.9 Hz), 131.0, 130.3, 129.2, 129.1, 125.1 (q, *J* = 270.8 Hz), 120.8, 119.4, 119.3 (q, *J* = 3.7 Hz), 118.8, 114.8, 114.5 (q, *J* = 3.7 Hz), 112.6, 79.3, 65.9, 49.0, 38.0, 29.5, 28.4; ^{19}F NMR ($CDCl_3$, 470 MHz): δ -62.7; HRMS: *m/z* calcd for $C_{29}H_{31}F_3N_3O_4S$ $(M+H)^+$ 574.1982, found 574.1986.

*5.1.34. N-(4-(3-Aminopropoxy)benzyl)-6-(3-(trifluoromethyl)phenoxy)benzothiazol-2-amine (**6e**)*

The title compound was synthesized according to general procedure C with **10e** (100 mg, 0.174 mmol), DCM (2 mL) and sat. HCl in dioxane (1 mL) to give the title compound **6e** as a solid (75 mg, 90%). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.20 (10% MeOH: 90% DCM); M.P: 142–144 °C; IR (cm^{-1}): 3163, 2860, 1606, 1119, 1049, 824; ^1H NMR (CD_3OD, 400 MHz): δ 7.60 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 2.4 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.28-7.25 (complex, 3H), 7.04 (d, *J* = 8.8 Hz, 2H), 4.69 (s, 2H), 4.51 (t, *J* = 6.0 Hz, 2H), 3.18 (t, *J* = 7.2 Hz, 2H), 2.19 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.6, 160.4, 159.7, 152.5, 147.7, 133.5 (q, *J* = 32.3 Hz), 132.8, 132.1, 131.4, 130.3, 126.7 (q, *J* = 269.9 Hz), 122.2, 120.5 (q, *J* = 3.8 Hz), 120.1, 119.3, 115.9, 115.4 (q, *J* = 3.8 Hz), 114.3, 66.4, 38.8, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.9, -64.3; HRMS (ESI): calcd for $C_{24}H_{23}F_3N_3O_2S$ $(M+H)^+$ 474.1458, found 474.1455.

*5.1.35. 2-(3-(4-(((6-(3-(Trifluoromethyl)phenoxy)benzothiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine (**7e**)*

The title compound was synthesized according to general procedure D, compound **7e** was obtained as oil (39%, two steps).

The intermediate di-Boc protected compound was synthesized with **6e** (100 mg, 0.196 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (61 mg, 0.20 mmol), TEA (0.08 mL, 0.6 mmol) and DMF (2 mL). The crude product was purified by column chromatography (20% EtOAc: 80% hexanes) to give the intermediate as a semi-solid (90 mg, 78%).

R_f: 0.28 (25% EtOAc: 75% hexanes); M.P: 63–65 °C; IR (cm^{-1}): 3335, 2931, 1730, 1635, 810; ^1H NMR ($CDCl_3$, 400 MHz): δ 11.51 (s, 1H), 8.66 (t, *J* = 4.8 Hz, 1H), 7.45–7.38 (complex, 2H), 7.31–7.29 (complex, 3H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.19 (s, 1H), 7.13 (dd, *J* = 2.1 Hz, 8.2 Hz, 1H), 7.00 (dd, *J* = 2.5 Hz, 8.7 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 4.55 (s, 2H), 4.04 (t, *J* = 5.7 Hz, 2H), 3.64 (q, *J* = 6.3 Hz, 2H), 2.08 (quin, *J* = 5.8 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.5, 163.7, 159.0, 158.7, 156.3, 153.3, 150.6, 131.7, 130.4, 129.5, 128.6, 124.3 (q, *J* = 265.8 Hz), 123.4 (d, *J* = 23.2 Hz), 120.8, 120.6, 119.7, 119.3, 118.9, 114.9, 114.6 (q, *J* = 3.7 Hz), 112.7, 83.2, 79.4, 66.6, 49.1, 39.2, 28.7, 28.5, 28.2; ^{19}F NMR ($CDCl_3$, 376 MHz,): δ -62.8; HRMS (ESI): calcd for $C_{35}H_{40}F_3N_5NaO_6S$ $(M+Na)^+$ 738.2544, found 738.2547.

The title compound was synthesized with the bis-Boc protected guanylated compound (90 mg, 0.12 mmol), EtOH (2 mL) and acetyl chloride (0.68 mL, 9.5 mmol). The title compound was obtained as a solid (55 mg, 88%) after trituration

with hexanes and diethyl ether. A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.32 (10% MeOH: 90% DCM); M.P: 180–182 °C; IR (cm^{-1}): 3354, 2855, 1634, 1329, 1125, 940, 824; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.54–7.50 (complex, 2H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.40-7.35 (complex, 3H), 7.22–7.21 (complex, 2H), 7.14 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.61 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.09 (quin, *J* = 6.4 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 169.6, 160.6, 159.4, 159.0, 158.9, 158.8, 155.1, 136.6, 133.9 (q, *J* = 32.4 Hz), 132.4, 130.9, 128.1, 126.7, 126.3 (q, *J* = 270.1 Hz), 123.1, 121.4 (q, *J* = 3.8 Hz), 121.3, 116.8, 116.3, 116.2 (q, *J* = 3.8 Hz),115.2, 66.4, 50.7, 39.8, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.9, -64.3; HRMS (ESI): calcd for $C_{25}H_{25}F_3N_5O_2S$ $(M+H)^+$ 516.1676, found 516.1673.

*5.1.36. tert-Butyl(3-(4-((methyl(6-(3-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**11e**)*

The title compound was synthesized according to general procedure B with **10e** (100 mg, 0.174 mmol), dry THF (4 mL), NaH (15 mg, 0.38 mmol) and MeI (27 mg, 0.19 mmol). After column chromatography purification [40% EtOAc: 60% hexanes] compound **11e** was obtained as a solid (75 mg, 74%).

R_f: 0.51 (30% EtOAc: 70% hexanes); M.P: 84–86 °C; IR (cm^{-1}): 3361, 2930, 1705, 1601, 1168, 1049, 932; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (dd, *J* = 3.5 Hz, 8.7 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 2.5 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 7.13 (d, *J* = 11.2 Hz, 1H), 7.03 (dd, *J* = 2.2 Hz, 8.7 Hz, 1H), 6.87 (d, *J*= 8.4 Hz, 2H), 4.78 (s, 1H), 4.69 (s, 2H), 4.01 (t, *J* = 5.9 Hz, 2H), 3.32 (q, *J* = 5.9 Hz, 2H), 3.12 (s, 3H), 1.98 (quin, *J* = 5.9 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 159.2, 158.7, 158.3, 156.2, 153.7, 150.1, 132.4 (q, *J* = 32.1 Hz), 132.1, 130.4, 129.2, 128.5, 125.2 (q, *J* = 266.7 Hz), 120.8, 119.7, 119.2 (d, *J* = 4.5 Hz), 119.0, 114.9, 114.4, 112.6, 79.4, 66.0, 56.2, 38.2, 37.9, 29.7, 28.6; ^{19}F NMR ($CDCl_3$, 470 MHz,): δ -62.7; HRMS (ESI): *m/z* calcd for $C_{30}H_{33}F_3N_3O_4S$ $(M+H)^+$ 588.2135, found 588.2138.

*5.1.37. N-(4-(3-Aminopropoxy)benzyl)-N-methyl-6-(3-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-amine trifluoroacetate (**12e**)*

The title compound was synthesized according to general procedure C with **11e** (210 mg, 0.426 mmol), DCM (4 mL) and sat. HCl in dioxane (2.5 mL). The title compound **12e** was obtained as a solid (200 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.19 (10% MeOH: 90% DCM); M. P: 71–74 °C; IR (cm^{-1}): 3433, 2925, 1450, 1328, 1127, 1064, 817; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.57–7.52 (complex, 2H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.23-7.21 (complex, 2H), 7.14 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.77 (s, 2H), 4.13 (t, *J* = 6.0 Hz, 2H), 3.21 (s, 3H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.18 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.8, 160.7, 159.9, 151.9, 150.2, 133.5 (q, *J* = 32.3 Hz), 132.6, 132.0, 130.3, 130.1, 126.8 (q, *J* = 270.4 Hz), 122.1, 120.4 (q, *J* = 3.9 Hz), 120.2, 120.0, 116.0, 115.2 (q, *J* = 4.1 Hz), 114.1, 66.4, 57.1, 38.8, 38.5, 28.5, ^{19}F NMR (CD_3OD, 376 MHz): δ -76.8, -64.3; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}F_3N_3O_2S$ $(M+H)^+$ 488.1620, found 488.1614.

*5.1.38. 2-(3-(4-((Methyl(6-(3-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13e**)*

The title compound was synthesized according to general procedure D, compound **13e** was obtained as oil (50%, two steps).

The intermediate di-Boc protected compound was synthesized with **12e** (100 mg, 0.205 mmol), *N*,*N*′-di-Boc-1*H*-pyrazole-1-carboxamidine (64 mg, 0.21 mmol), TEA (0.03 mL, 0.2 mmol) and DMF (2 mL). The crude product was purified by column chromatography (30% EtOAc: 70% hexanes) to give the intermediate as an oil (75 mg, 50%).

R_f: 0.48 (30% EtOAc: 70% hexanes); IR (cm^{-1}): 3331, 2930, 1722, 1614, 1328, 1134, 1026, 810; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.51 (s, 1H), 8.67 (t, *J* = 4.7 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.30–7.28 (complex, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.20 (s, 1H), 7.13 (dd, *J* = 2.0 Hz, 8.4 Hz, 1H), 7.03 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.69 (s, 2H), 4.06 (t, *J* = 5.6 Hz, 2H), 3.66 (q, *J* = 6.4 Hz, 2H), 3.1 (s, 3H), 2.09 (quin, *J* = 6.0 Hz, 2H), 1.49 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 163.7, 159.2, 158.6, 156.3, 153.3, 150.4, 150.0, 132.4 (q, *J* = 32.4 Hz), 132.2, 130.3, 129.1, 128.4, 125.3 (q, *J* = 272.3 Hz), 120.7, 119.7, 119.2 (q, *J* = 4.0 Hz), 118.9, 114.8, 114.4 (q, *J* = 3.7 Hz), 83.2, 79.4, 66.6, 56.2, 39.2, 37.8, 28.7, 28.5, 28.3; ^{19}F NMR ($CDCl_3$, 376 MHz,): δ -63.0; HRMS (ESI): *m/z* calcd for $C_{36}H_{43}F_3N_5O_6S$ $(M+H)^+$ 730.2881, found 730.2883.

The title compound was synthesized with the bis-Boc protected guanylated compound (80 mg, 0.11 mmol), EtOH (2 mL) and acetyl chloride (0.70 mL, 8.8 mmol). The title compound was obtained as a sticky solid (60 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.25 (10% MeOH: 90% DCM); IR (cm^{-1}): 3339, 1627, 1328, 1126, 935, 737; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.53–7.50 (complex, 2H), 7.44 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.30-(d, *J* = 8.7 Hz, 2H), 7.20-7.18 (complex, 2H), 7.08 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 4.74 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 6.8 Hz, 2H), 3.15 (s, 3H), 2.07 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 125 MHz): δ 170.2, 160.8, 159.4, 159.0, 158.8, 154.8, 137.9, 133.9 (q, *J* = 32.4 Hz), 132.4, 130.8, 126.9, 126.6, 126.3 (q, *J* = 270.0 Hz), 123.2, 121.6, 121.4 (q, *J* = 3.7 Hz), 117.2, 116.4, 116.1 (q, *J* = 3.2 Hz), 115.1, 66.3, 59.7, 40.2, 39.7, 29.7; ^{19}F NMR (CD_3OD, 376 MHz,): δ 76.9, -64.3; HRMS (ESI): *m/z* calcd for $C_{26}H_{27}F_3N_5O_2S$ $(M+H)^+$ 530.1832, found 530.1827.

*5.1.39. N-(4-(3-(Dimethylamino)propoxy)benzyl)-6-(3-(trifluoromethyl)phenoxy)benzo[d]thiazol-2-amine trifluoroacetate (**14e**)*

The title compound was synthesized according to general procedure F with **6e** (30 mg, 0.063 mmol), paraformaldehyde (36 mg, 0.64 mmol), $NaBH_4$ (24 mg, 0.64 mmol), TFA (0.6 mL) and MeOH (3 mL). After purification by HPLC the title compound was obtained as a semi-solid (18 mg, 53%).

R_f: 0.18 (10% MeOH: DCM); ^{1}H NMR (CD_3OD, 400 MHz): δ 7.57–7.53 (m, 2H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.24–7.22 (complex, 2H), 7.19 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.64 (s, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.357 (m, 2H), 2.94 (s, 6H), 2.23 (m, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 169.6, 160.0, 159.9, 153.8, 142.3, 133.9 (q, *J* = 32.6 Hz), 132.2, 130.6, 130.0, 129.1, 126.7 (q, *J* = 270.1 Hz), 122.7, 121.0 (q, *J* = 3.7 Hz), 120.7, 118.0, 116.0, 115.8 (q, *J* = 3.5 Hz), 114.7, 66.1, 56.9, 43.8, 25.9; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0, -64.3; HRMS (APCI): *m/z* calcd for $C_{26}H_{26}O_2N_3F_3S$ $(M)^{+\cdot}$ 501.1692 found 501.1697.

*5.1.40. tert-Butyl (3-(4-(((6-(4-cyanophenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)carbamate (**10f**)*

The title compound was synthesized according to general procedure A with the thiazole amine **1f** (350 mg, 1.32 mmol) and the aldehyde **9**[17] (402 mg, 1.44 mmol). Compound **10f** was obtained as a solid (304 mg, 54%) after purification by column chromatography [25% EtOAc: 75% hexanes].

R_f: 0.25 (25% EtOAc: 75% hexanes); M.P:143-144 °C; IR (cm^{-1}): 3395, 3182, 2974, 2226, 1685, 1248, 1055, 980, 820, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 6.4 Hz, 1H), 7.31-7.28 (complex, 3H), 7.01-6.96 (m, 3H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.77 (s, 1H), 4.55 (s, 2H), 4.01 (t, *J* = 6.0 Hz, 2H), 3.33 (q, *J* = 6.0 Hz, 2H), 1.98 (quin, *J* = 6.4 Hz, 2H), 1.43 (s, 9H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 162.4, 162.3, 158.8, 156.2, 155.5, 149.5, 134.3, 129.3, 119.5, 119.0, 117.6, 115.0, 114.7, 113.4, 105.8, 66.0, 49.2, 38.1, 29.7, 28.6, HRMS (APCI): m/z calcd $C_{29}H_{30}O_4N_4S$ $(M)^{+\cdot}$ 530.1988, found 530.1984.

*5.1.41. 4-((2-((4-(3-Aminopropoxy)benzyl)amino)benzo[d]thiazol-6-yl)oxy)benzonitrile trifluoroacetate (**6f**)*

To the Boc-protected compound **10f** (70 mg, 0.13 mmol) in dry DCM (3 mL) was added sat. HCl in MeOH (1.5 mL). The reaction mixture was stirred under nitrogen atmosphere at ambient temperature for 24 h. The reaction mixture was diluted with MeOH (5 mL) and solvent was removed *in vacuo* to give a sticky solid **6f** (50 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample

R_f: 0.18 (10% MeOH: 90% DCM); IR (cm^{-1}): 2937, 2227, 1670, 1124, 720; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.12 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.60 (s, 2H), 4.13 (t, *J* = 5.6 Hz, 2H), 3.17 (t, *J* = 7.6 Hz, 2H), 2.16 (quin, *J* = 6.0 Hz, 2H), ^{13}C NMR (CD_3OD, 100 MHz): δ 169.6, 164.2, 159.5, 150.9, 150.6, 135.6, 132.1, 130.2, 120.3, 119.9, 119.9, 118.7, 115.8, 114.7, 106.5, 66.4, 38.8, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -76.9; HRMS (APCI): *m/z* calcd for $C_{24}H_{22}O_2N_4S$ $(M)^{+\cdot}$ 430.1458, found 430.1462.

*5.1.42. 2-(3-(4-(((6-(4-Cyanophenoxy)benzo[d]thiazol-2-yl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**7f**)*

The title compound was synthesized according to general procedure E with **6f** (45 mg, 0.11 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (23 mg, 0.16 mmol), DIPEA (0.04 mL, 0.2 mmol) and DMF (1 mL). Removal of the solvent *in vacuo* gave a sticky solid (45 mg, 90%) which was further purified by preparative HPLC.

R_f: 0.20 (10% MeOH: 90% DCM); IR (cm^{-1}): 3320, 2231, 1661, 1458, 1085, 815; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.71 (d, *J* = 9.2 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 7.18 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 2H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.42 (t, *J* = 3.6 Hz, 2H), 2.09 (quin, *J* = 6.0 Hz, 2H), ^{13}C NMR (CD_3OD, 150 MHz): δ 169.6, 164.0, 159.8, 159.0, 158.8, 151.1, 148.8, 135.6, 131.3, 130.3, 120.5, 119.9, 119.5, 119.1, 118.8, 115.8, 114.8, 106.5, 66.2, 39.7, 29.7; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0; HRMS (ESI): *m/z* calcd for $C_{25}H_{25}N_6O_2S$ $(M+H)^+$ 473.1760, found 473.1739.

*5.1.43. tert-Butyl (3-(4-(((6-(4-cyanophenoxy)benzo[d]thiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl)carbamate (**11f**)*

The title compound was synthesized according to general procedure B with **10f** (260 mg, 0.490 mmol), dry THF (15 mL), NaH (47 mg, 1.2 mmol) and MeI (83 mg, 0.59 mmol). After column chromatography purification [25% EtOAc: 75% hexanes] compound **11f** was obtained as a semi-solid (180 mg, 69%).

R_f: 0.27 (25% EtOAc: 75% hexanes); IR (cm^{-1}): 3355, 3061, 2225, 1699, 1163, 835, 734; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.61-7.56 (complex, 3H), 7.31 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.04 (dd, *J* = 2.4, 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 1H), 4.70 (s, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.34 (q, *J* = 6.4 Hz, 2H), 3.14 (s, 3H), 1.98 (quin, *J* = 6.0 Hz, 2H), 1.43 (s, 9H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.8, 162.6, 159.1, 158.8, 156.1, 149.0, 134.3, 129.2, 128.1, 128.1, 119.7, 119.5, 119.0, 117.5, 114.9, 113.2, 105.7, 79.4, 66.0, 56.4, 38.2, 38.1, 29.7, 28.6, HRMS (APCI): m/z calcd for $C_{30}H_{32}O_4N_4S$ $(M)^{+\cdot}$ 544.2139, found 544.2142.

*5.1.44. 4-((2-((4-(3-Aminopropoxy)benzyl)(methyl)amino)benzo[d]thiazol-6-yl)oxy)benzonitrile trifluoroacetate (**12f**)*

The title compound was synthesized according to general procedure C with **11f** (75 mg, 0.14 mmol), DCM (2 mL) and sat. HCl in dioxane (2 mL). The title compound was obtained as an oil (65 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.20 (10% MeOH: 90% DCM); IR (cm^{-1}): 3381, 2978, 2226, 1706, 1250, 838; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.70 (d, *J* = 9.2 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 1H), 7.52 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.16 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 4.78 (s, 2H), 4,13 (t, *J* = 5.6 Hz, 2H), 3.21 (s, 3H), 3.17 (t, *J* = 7.2 Hz, 2H), 2.17 (quin, *J* = 5.6 Hz, 2H), ^{13}C NMR (CD_3OD, 100 MHz): δ 170.9, 164.0, 160.0, 151.0, 149.7, 135.6, 132.2, 130.3, 129.8, 120.8, 119.9, 119.8, 118.8, 116.1, 114.8, 106.8, 66.4, 57.3, 38.7, 38.7, 28.5; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0; HRMS (APCI): *m/z* calcd for $C_{25}H_{24}O_2N_4S$ $(M)^{+\cdot}$ 444.1616, found 444.1614.

*5.1.45. 2-(3-(4-(((6-(4-Cyanophenoxy)benzo[d]thiazol-2-yl)(methyl)amino)methyl)phenoxy)propyl)guanidine trifluoroacetate (**13f**)*

The title compound was synthesized according to general procedure E with **12f** (55 mg, 0.11 mmol), 1*H*-pyrazole-1-carboxamidine hydrochloride (25 mg, 0.17 mmol), DIPEA (0.04 mL, 0.2 mmol) and DMF (1 mL). Removal of the solvent *in vacuo* gave a sticky solid (55 mg, 92%) which was further purified by preparative HPLC.

R_f: 0.22 (10% MeOH: 90% DCM); IR (cm^{-1}): 3345, 2984, 2224, 1654, 1243, 1111, 926, 832; ^{1}H NMR (CD_3OD, 400 MHz): δ 7.70 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.49 (d, *J* = 2.4 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.11 (dd, *J* = 2.4, 8.8 Hz, 1H), 7.07 (d, *J* = 9.2 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.41 (t, *J* = 3.2 Hz, 2H), 3.16 (s, 3H), 2.09 (quin, *J* = 6.0 Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz): δ 170.9, 164.1, 160.1, 150.9, 135.6, 132.5, 130.3, 129.8, 120.8, 120.0, 119.8, 118.8, 118.8, 116.0, 114.8, 106.8, 66.2, 57.2, 39.8, 38.6, 29.8; ^{19}F NMR (CD_3OD, 376 MHz): δ -77.0; HRMS (APCI): *m/z* calcd for $C_{26}H_{26}N_6O_2S$ $(M)^{+\cdot}$ 486.1838, found 486.1842.

*5.1.46. 4-((2-((4-Hydroxybenzyl)amino)benzo[d]thiazol-6-yl)oxy)benzonitrile (**16f**)*

The title compound was prepared according to the general procedure A except with 4-hydroxybenzaldehyde. The thiazole amine **8f** (252 mg, 0.94 mmol), 4-hydroxybenzaldehyde (172 mg, mmol) and *p*-TSA (8 mg, 0.05 mmol) were dissolved in toluene

(125 mL) and refluxed for 7 days. After removal toluene *in vacuo*, dry MeOH (50 mL) and $NaBH_4$ (100 mg, 2.6 mmol) were added and the mixture refluxed overnight. The title compound was obtained as a solid (220 mg, 63%) after purification by column chromatography [50 % EtOAc: 50 % hexanes], purity 90% by LC analysis. A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.36 (50 % EtOAc: 50 % hexanes); M.P: 217–222 °C; IR (cm^{-1}): 3327, 3019, 2849, 2479, 2291, 2234, 2113, 1739, 1725, 1595, 1572, 1543, 1503, 1450, 1426, 1373, 1354, 1230, 1218, 1185, 1165, 1104, 1090, 974, 923, 861, 812, 718, 678, 668; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.51 (d, *J* = 5.8 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 2H), 7.10 – 6.97 (m, 3H), 6.73 (d, *J* = 8.1 Hz, 2H), 4.46 (d, *J* = 5.2 Hz, 2H). ^{13}C NMR (151 MHz, DMSO) δ 166.5, 162.13, 162.12, 156.6, 148.1, 134.6, 131.5, 128.9, 128.6, 118.8, 118.7, 118.6, 117.3, 115.1, 113.7, 104.5, 47.0; HRMS (APCI): *m/z* calcd. for $C_{21}H_{15}N_3O_2S$ $(M+H)^+$ 374.0963, found, 374.0958.

*5.1.47. 4-((2-((4-(3-(Dimethylamino)propoxy)benzyl)amino)benzo[d]thiazol-6-yl)oxy)benzonitrile (**14f**)*

To a solution of **16f** (40 mg, 0.11 mmol) in THF (15 mL) was added dimethylaminopropylchloride hydrochloride (384 mg, 2.4 mmol) and K_2CO_3 (878 mg, 6.4 mmol). The reaction mixture was stirred at 50 ℃ for 4 days with the progress of the reaction monitored by LC, 70% conversion to the title compound. A portion was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.15 (10% MeOH: 90% DCM); IR (cm^{-1}):3392, 3328, 2975, 2928, 1678, 1599, 1552, 1503, 1456, 1420, 1382, 1238, 1203, 1184, 1140, 1088, 880, 837, 802, 723, 674; ^{1}H NMR (CD_3OD, 600 MHz) δ 7.75 – 7.70 (complex, 2H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 1H), 7.42 – 7.37 (complex, 2H), 7.12 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.11 – 7.07 (complex, 2H), 7.02 – 6.97 (complex, 2H), 4.63 (s, 2H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.40 (m, 2H), 2.97 (s, 6H), 2.25 (m, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 170.3, 164.65, 164.64, 160.38, 160.37, 152.18, 136.32, 132.26, 131.0, 121.4, 120.5, 120.0, 119.6, 116.6, 115.7, 107.6, 66.8, 57.7, 50.4, 44.5, 26.6. HRMS (APCI): *m/z* calcd for $C_{26}H_{27}N_4O_2S$ $(M+H)^{+\cdot}$ 459.1849, found 459.1846.

*5.1.48. 4-((2-((4-(3-(dimethylamino)propoxy)benzyl)(methyl)amino)benzo[d]thiazol-6-yl)oxy)benzonitrile (**15f**)*

The title compound was synthesised according to the general procedure F with **6f** (65 mg, 0.15 mmol), dry THF (10 mL), paraformaldehyde (146 mg, 4.8 mmol), $NaBH_4$ (78 mg, 2.1 mmol) and TFA (2.5 mL) the reaction mixture stirred for 48 hours. The title compound was obtained as an oil (100 mg, quant.). A small amount was purified by HPLC in order to obtain an analytically pure sample.

R_f: 0.31 (10% MeOH: 90% DCM); IR (cm^{-1}): 2929, 2855, 2227, 1681, 1598, 1548, 1502, 1457, 1366, 1251, 1233, 1177, 1131, 1050, 926, 836, 800, 722; ^{1}H NMR (CD_3OD, 600 MHz) δ 7.74 – 7.69 (complex, 2H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 2.5 Hz, 1H), 7.34 – 7.30 (complex, 2H), 7.11 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.10 – 7.06 (complex, 2H), 7.01 – 6.96 (complex, 2H), 4.78 (s, 2H), 4.14 (t, *J* = 5.7 Hz, 2H), 3.38 (dd, *J* = 9.1, 6.6 Hz, 3H), 3.18 (s, 3H), 2.97 (s, 6H), 2.24 (dq, *J* = 7.7, 5.7 Hz, 2H); ^{13}C NMR (CD_3OD, 150 MHz) δ 170.8, 164.0, 159.6, 150.8, 150.6, 135.4, 132.7, 130.1, 120.5, 120.0, 119.7, 118.6, 115.9, 114.6, 106.6, 66.0, 56.90, 56.87, 43.7, 38.4, 25.8. ^{19}F NMR (376 MHz, MeOD) δ -76.8; HRMS (APCI): *m/z* calcd for $C_{26}H_{29}N_4O_2S$ $(M+H)^{+\cdot}$ 473.2011, found 473.2005.

5.2. Biological evaluations

5.2.1. Calcium influx assay

Ca^{2+} responses were measured using FLIPR^{TETRA} and Calcium 4 dye (Molecular Devices, CA, USA) using the neuroblastoma cell line SH-SY5Y for the N-type hCa_V2.2 assay[40, 41] and HEK 293T expressing recombinant hCa_V3.2 for the T-type assay. SH-SY5Y and hCa_V3.2 HEK 293T cells were plated at 40,000 and 10,000 cells per well, respectively, in 384-well flat clear-bottom black plates (Corning, NY, USA) and cultured at 37°C in a humidified 5% CO_2 incubator 48 h. The medium was removed and cells loaded with 20 µl/well Calcium 4 dye reconstituted in assay buffer containing (in mM) 140 NaCl, 11.5 glucose, 5.9 KCl, 1.4 $MgCl_2$, 1.2 NaH_2PO_4, 5 $NaHCO_3$, 1.8 $CaCl_2$ and 10 HEPES pH 7.4 and incubated for 30 min at 37°C in a humidified 5% CO_2 incubator. For Ca_V2.2 assays, 10 µM nifedipine (Ca_V1 blocker) was added to the dye. Ca^{2+} fluorescence responses were recorded using excitation 470–495 nm and emission 515–575 nm for 10 s to set the baseline, then again 600 s after addition of compounds at various concentrations and for a further 300 s after addition of 90 mM or 40 mM KCl for Ca_V2.2 and Ca_V3.2 responses, respectively.

5.2.2. Data analysis

Curve fitting was achieved using GraphPad Prism Version 6 (GraphPad Software Inc, San Diego, CA, USA) with nonlinear regression with log[inhibitor] versus normalized response and variable Hill slope for dose-responses. Data were represented as mean ± 95% CI and SEM from triplicates in Tables 1-4, and mean ± SEM from n = 3 – 4 independent experiments in Figure 4.

5.2.3. In vitro rat plasma stability studies

The *in vitro* stability assay was according to a reported procedure.[42] To rat plasma (1 mL), at 37 °C was added the a MeOH stock of desired compound (final concentration 120 µM). At regular time points (0, 15, 30, 45, 60, 120, 240, 480, 1440 min) an aliquot (50 µL) was removed and added to ice-cold acetonitrile containing, 120 µM quinoline as the internal standard, in order to deproteinize the plasma. The solution was centrifuged at 3000 rpm for 10 min at rt and the supernatant was diluted with equal volume of Milli-Q water and analysed by HPLC. The same procedure was repeated with 0.01 M PBS buffer instead of rat plasma for blank study.

Acknowledgments

Monash University, IITB and CSIRO are acknowledged for funding, as well as IITB-Monash Research Academy and Professor Krishna Kaliappan for supporting A.S. during her PhD studies. This work was also supported by a NHMRC Program Grant (569927) and NHMRC Fellowship (APP1019761, RJL). We thank Prof. Emmanuel Bourinet (Institute of Functional Genomics, Montpellier University, FR) and Prof. Edward Perez-Reyes (School of Medicine, University of Virginia, USA) for the Ca_V3.2 cell line.

References and notes

1. Yawn, B. P.; Wollan, P. C.; Weingarten, T. N.; Watson, J. C.; Hooten, W. M.; Melton, L. J. *Pain Med.* **2009,** *10*, 586-593.
2. Beswick, P., 7.03 - Progress in the Discovery of Ca Channel Blockers for the Treatment of Pain A2 - Chackalamannil, Samuel. In *Comprehensive Medicinal Chemistry III*, Rotella, D.; Ward, S. E., Eds. Elsevier: Oxford, 2017; pp 65-130.

3. Yamamoto, T.; Takahara, A. *Curr. Top. Med. Chem.* **2009,** *9*, 377-395.
4. Zamponi, G. W.; Feng, Z.-P.; Zhang, L.; Pajouhesh, H.; Ding, Y.; Belardetti, F.; Pajouhesh, H.; Dolphin, D.; Mitscher, L. A.; Snutch, T. P. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 6467-6472.
5. Beebe, X.; Darczak, D.; Henry, R. F.; Vortherms, T.; Janis, R.; Namovic, M.; Donnelly-Roberts, D.; Kage, K. L.; Surowy, C.; Milicic, I.; Niforatos, W.; Swensen, A.; Marsh, K. C.; Wetter, J. M.; Franklin, P.; Baker, S.; Zhong, C.; Simler, G.; Gomez, E.; Boyce-Rustay, J. M.; Zhu, C. Z.; Stewart, A. O.; Jarvis, M. F.; Scott, V. E. *Bioorg. Med. Chem.* **2012,** *20*, 4128-4139.
6. Scott, V. E.; Vortherms, T. A.; Niforatos, W.; Swensen, A. M.; Neelands, T.; Milicic, I.; Banfor, P. N.; King, A.; Zhong, C.; Simler, G.; Zhan, C.; Bratcher, N.; Boyce-Rustay, J. M.; Zhu, C. Z.; Bhatia, P.; Doherty, G.; Mack, H.; Stewart, A. O.; Jarvis, M. F. *Biochem. Pharmacol.* **2012,** *83*, 406-418.
7. Subasinghe, N. L.; Wall, M. J.; Winters, M. P.; Qin, N.; Lubin, M. L.; Finley, M. F. A.; Brandt, M. R.; Neeper, M. P.; Schneider, C. R.; Colburn, R. W.; Flores, C. M.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 4080-4083.
8. Shao, P. P.; Ye, F.; Chakravarty, P. K.; Varughese, D. J.; Herrington, J. B.; Dai, G.; Bugianesi, R. M.; Haedo, R. J.; Swensen, A. M.; Warren, V. A.; Smith, M. M.; Garcia, M. L.; McManus, O. B.; Lyons, K. A.; Li, X.; Green, M.; Jochnowitz, N.; McGowan, E.; Mistry, S.; Sun, S.-Y.; Abbadie, C.; Kaczorowski, G. J.; Duffy, J. L. *J. Med. Chem.* **2012,** *55*, 9847-9855.
9. Pajouhesh, H.; Feng, Z.-P.; Zhang, L.; Pajouhesh, H.; Jiang, X.; Hendricson, A.; Dong, H.; Tringham, E.; Ding, Y.; Vanderah, T. W.; Porreca, F.; Belardetti, F.; Zamponi, G. W.; Mitscher, L. A.; Snutch, T. P. *Bioorg. Med. Chem. Lett.* **2012,** *22*, 4153-4158.
10. Borzenko, A.; Pajouhesh, H.; Morrison, J.-L.; Tringham, E.; Snutch, T. P.; Schafer, L. L. *Bioorg. Med. Chem. Lett.* **2013,** *23*, 3257-3261.
11. Shao, P. P.; Ye, F.; Chakravarty, P. K.; Herrington, J. B.; Dai, G.; Bugianesi, R. M.; Haedo, R. J.; Swensen, A. M.; Warren, V. A.; Smith, M. M.; Garcia, M. L.; McManus, O. B.; Lyons, K. A.; Li, X.; Green, M.; Jochnowitz, N.; McGowan, E.; Mistry, S.; Sun, S.-Y.; Abbadie, C.; Kaczorowski, G. J.; Duffy, J. L. *ACS Med. Chem. Lett.* **2013,** *4*, 1064-1068.
12. Mollica, A.; Costante, R.; Novellino, E.; Stefanucci, A.; Pieretti, S.; Zador, F.; Samavati, R.; Borsodi, A.; Benyhe, S.; Vetter, I.; Lewis, R. J. *Chem. Biol. Drug Des.* **2015,** *86*, 156-162.
13. Baell, J. B.; Duggan, P. J.; Forsyth, S. A.; Lewis, R. J.; Lok, Y. P.; Schroeder, C. I.; Shepherd, N. E. *Tetrahedron* **2006,** *62*, 7284-7292.
14. Tranberg, C. E.; Yang, A.; Vetter, I.; McArthur, J. R.; Baell, J. B.; Lewis, R. J.; Tuck, K. L.; Duggan, P. J. *Mar. Drugs* **2012,** *10*, 2349-2368.
15. Gleeson, E. C.; Graham, J. E.; Spiller, S.; Vetter, I.; Lewis, R. J.; Duggan, P. J.; Tuck, K. L. *Mar. Drugs* **2015,** *13*, 2030-2045.
16. Baell, J. B.; Duggan, P. J.; Forsyth, S. A.; Lewis, R. J.; Phei Lok, Y.; Schroeder, C. I. *Bioorg. Med. Chem.* **2004,** *12*, 4025-4037.
17. Duggan, P. J.; Lewis, R. J.; Phei, L. Y.; Lumsden, N. G.; Tuck, K. L.; Yang, A. *Bioorg. Med. Chem. Lett.* **2009,** *19*, 2763-2765.
18. http://www.calchan.co.uk/?page_id=15, V2197944 | Convergence Pharmaceuticals. Viewed 15/02/2018.
19. Choi, K.-H. *Expert Opinion on Drug Discovery* **2013,** *8*, 919-931.
20. Zamponi, G. W. *Nat. Rev. Drug Discovery* **2015,** *15*, 19-34.
21. Siegrist, R.; Pozzi, D.; Jacob, G.; Torrisi, C.; Colas, K.; Braibant, B.; Mawet, J.; Pfeifer, T.; de Kanter, R.; Roch, C.; Kessler, M.; Corminboeuf, O.; Bezençon, O., *J. Med. Chem.* **2016,** *59*, 10661-10675.
22. Remen, L.; Bezençon, O.; Simons, L.; Gaston, R.; Downing, D.; Gatfield, J.; Roch, C.; Kessler, M.; Mosbacher, J.; Pfeifer, T.; Grisostomi, C.; Rey, M.; Ertel, E. A.; Moon, R., *J. Med. Chem.* **2016,** *59*, 8398-8411.
23. Shipe, W. D.; Barrow, J. C.; Yang, Z.-Q.; Lindsley, C. W.; Yang, F. V.; Schlegel, K.-A. S.; Shu, Y.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Uebele, V. N.; Nuss, C. E.; Connolly, T. M.; Doran, S. M.; Fox, S. V.; Kraus, R. L.; Marino, M. J.; Graufelds, V. K.; Vargas, H. M.; Bunting, P. B.; Hasbun-Manning, M.; Evans, R. M.; Koblan, K. S.; Renger, J. J., *J. Med. Chem.* **2008,** *51*, 3692-3695.
24. Yang, Z.-Q.; Barrow, J. C.; Shipe, W. D.; Schlegel, K.-A. S.; Shu, Y.; Yang, F. V.; Lindsley, C. W.; Rittle, K. E.; Bock, M. G.; Hartman, G. D.; Uebele, V. N.; Nuss, C. E.; Fox, S. V.; Kraus, R. L.; Doran, S. M.; Connolly, T. M.; Tang, C.; Ballard, J. E.; Kuo, Y.; Adarayan, E. D.; Prueksaritanont, T.; Zrada, M. M.; Marino, M. J.; Graufelds, V. K.; DiLella, A. G.; Reynolds, I. J.; Vargas, H. M.; Bunting, P. B.; Woltmann, R. F.; Magee, M. M.; Koblan, K. S.; Renger, J. J., *J. Med. Chem.* **2008,** *51*, 6471-6477.
25. Yang, Z.-Q.; Schlegel, K.-A. S.; Shu, Y.; Reger, T. S.; Cube, R.; Mattern, C.; Coleman, P. J.; Small, J.; Hartman, G. D.; Ballard, J.; Tang, C.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S.; Fox, S. V.; Garson, S. L.; Li, Y.; Kraus, R. L.; Uebele, V. N.; Taylor, A. B.; Zeng, W.; Fang, W.; Chavez-Eng, C.; Troyer, M. D.; Luk, J. A.; Laethem, T.; Cook, W. O.; Renger, J. J.; Barrow, J. C., *ACS Med. Chem. Lett.* **2010,** *1*, 504-509.
26. Bezençon, O.; Remeň, L.; Richard, S.; Roch, C.; Kessler, M.; Ertel, E. A.; Moon, R.; Mawet, J.; Pfeifer, T.; Capeleto, B., *Bioorg. Med. Chem. Lett.* **2017,** *27*, 5326-5331.
27. Bezençon, O.; Heidmann, B.; Siegrist, R.; Stamm, S.; Richard, S.; Pozzi, D.; Corminboeuf, O.; Roch, C.; Kessler, M.; Ertel, E. A.; Reymond, I.; Pfeifer, T.; de Kanter, R.; Toeroek-Schafroth, M.; Moccia, L. G.; Mawet, J.; Moon, R.; Rey, M.; Capeleto, B.; Fournier, E., *J. Med. Chem.* **2017,** *60*, 9769-9789.
28. Son, Y. K.; Hong, D. H.; Li, H.; Kim, D.-J.; Na, S. H.; Park, H.; Jung, W.-K.; Choi, I.-W.; Park, W. S., *J. Pharmacol. Sci.* **2014,** *125*, 312-319.
29. Todorovic, S. M.; Jevtovic-Todorovic, V. *Pflügers Arch.* **2014,** *466*, 701-706.
30. Renneberg, D.; Hubler, F.; Rey, M.; Hess, P.; Delahaye, S.; Gatfield, J.; Iglarz, M.; Hilpert, K. *Bioorg. Med. Chem. Lett.* **2015,** *25*, 3941-3946.
31. Reger, T. S.; Yang, Z.-Q.; Schlegel, K.-A. S.; Shu, Y.; Mattern, C.; Cube, R.; Rittle, K. E.; McGaughey, G. B.; Hartman, G. D.; Tang, C.; Ballard, J.; Kuo, Y.; Prueksaritanont, T.; Nuss, C. E.; Doran, S. M.; Fox, S. V.; Garson, S. L.; Li, Y.; Kraus, R. L.; Uebele, V. N.; Renger, J. J.; Barrow, J. C. *Bioorg. Med. Chem. Lett.* **2011,** *21*, 1692-1696.
32. Zhang, Q.; Xia, Z.; Joshi, S.; Scott, V. E.; Jarvis, M. F. *ACS Med. Chem. Lett.* **2015,** *6*, 641-644.
33. Li, M.; Hansen, J. B.; Huang, L.; Keyser, B. M.; Taylor, J. T. *Cardiovasc. Drug Rev.* **2005,** *23*, 173-196.
34. Duggan, P. J.; Tuck, K. L. *Toxins* **2015,** *7*, 4175-98.
35. Gribble, G. W.; Nutaitis, C. F. *Synthesis* **1987,** *1987*, 709-711.
36. Alelyunas, Y. W.; Empfield, J. R.; McCarthy, D.; Spreen, R. C.; Bui, K.; Pelosi-Kilby, L.; Shen, C. *Bioorg. Med. Chem. Lett.* **2010,** *20*, 7312-7316.
37. Baell, J.; Forsyth, S.; Gable, R.; Norton, R.; Mulder, R. *J. Comput.-Aided Mol. Des*. **2001**, *15*, 1119–1136.
38. Wager, T. T.; Hou, X.; Verhoest, P. R.; Villalobos, A. *ACS Chem. Neurosci.* **2010,** *1*, 435-449.
39. Wager, T. T.; Hou, X.; Verhoest, P. R.; Villalobos, A. *ACS Chem. Neurosci.* **2016,** *7*, 767-775.
40. Vetter, I.; Lewis, R. J. *Biochem. Pharmacol.* **2010,** *79*, 908-20.
41. Sousa, S. R.; Vetter, I.; Ragnarsson, L.; Lewis, R. J. *PLoS One* **2013,** *8*, e59293.
42. Konsoula, R.; Jung, M. *Int. J. Pharm.* **2008,** *361*, 19-25.

Supplementary Material

The synthesis of compounds **8c**, **8d**, **8e** and **8f**, ^{1}H and ^{13}C /JMOD NMR spectra of novel final compounds.