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Original research paper

Exploration of the chemical space of benzamide-based voltage-gated potassium channel K_V1.3 inhibitors

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ABSTRACT

The voltage-gated potassium channel K_V1.3 is a key regulator of T-cell activation and a validated therapeutic target for autoimmune and inflammatory diseases. In this study, a ligand-based design strategy was employed to expand a library of benzamide-derived K_V1.3 inhibitors. Starting from a previously optimised thiophene-based inhibitor, structural modifications were introduced to the 2-methoxybenzamide moiety and the central tetrahydropyran or cyclohexane scaffold. A series of ketone, hydroxy, and carbamate derivatives was synthesised and evaluated for K_V1.3 inhibition using whole-cell patch-clamp electrophysiology. Structure-activity relationship analysis revealed that *cis*-isomers in the hydroxy series exhibited stronger activity than their *trans* counterparts, with some analogues displaying submicromolar IC_{50} values. In the carbamate series, *trans*-isomers were generally more potent, with *trans*-**18** and *trans*-**16** achieving IC_{50} values of 122 and 166 nmol L^{-1}, respectively. These results provide valuable insights into the design of K_V1.3 inhibitors and support further development of these compounds for immunomodulatory applications.

Keywords: K_V1.3, inhibitor, ion channel, ligand-based design, molecular modeling

INTRODUCTION

Potassium channels are transmembrane proteins that facilitate the selective passage of potassium ions across the plasma membrane following their electrochemical gradient. These channels are classified into different families, with voltage-gated potassium channels (K_V) representing a major group. The K_V1.x (Shaker) subfamily, the largest within this group, consists of eight members (K_V1.1–K_V1.8) (1, 2). K_V1.3 is widely expressed throughout the human body and plays a crucial role in numerous cellular processes. It is located in the plasma membrane, the inner mitochondrial membrane (mitoK_V1.3), the nuclear membrane, and the membrane of the *cis*-Golgi apparatus (3). K_V1.3 expression has been identified in multiple cell types, including neurons, osteoclasts, epithelial cells, and immune cells, such

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as T- and B-lymphocytes, macrophages and microglia, where it contributes to the regulation of membrane potential and calcium signalling (2).

Given the well-established role of T-cells in the pathogenesis of autoimmune diseases, K_V1.3 has emerged as an attractive therapeutic target. It is highly expressed in effector memory T (T_{EM}) cells, which mediate autoimmune disorders, as well as in other leukocytes involved in chronic inflammatory diseases, such as B-lymphocytes, macrophages, microglia, and dendritic cells. Inhibition of K_V1.3 has been shown to induce membrane depolarisation, thereby preventing T-cell proliferation and cytokine production. Consequently, the development of selective K_V1.3 inhibitors that specifically target disease-inducing T_{EM} cells while preserving normal immune function could be beneficial in treating autoimmune and chronic inflammatory conditions, including psoriasis, multiple sclerosis, type 1 diabetes mellitus, atherosclerosis, asthma, and rheumatoid arthritis (4, 5).

K_V1.3 has also been identified as a promising molecular target for anticancer therapy due to its involvement in critical cellular processes, including proliferation, calcium signalling, cell volume regulation, adhesion, migration, apoptosis, and invasion (6). Although K_V1.3 is increasingly recognised as a tumour marker, a definitive pattern distinguishing its expression in cancerous versus healthy cells has not yet been established, as its levels appear to be influenced by the tumour type and disease stage (7). Nevertheless, aberrant K_V1.3 expression has been observed in breast, colon, and prostate tumours, as well as in smooth muscle and skeletal muscle cancers. It is also present in mature neoplastic B-cells in chronic lymphocytic leukaemia, with a notable correlation between its expression and mitochondrial localisation (6). Potential therapeutic strategies for cancer treatment involve selectively inhibiting cancer cell proliferation or inducing apoptosis (8). Induction of apoptosis in cancer cells by K_V1.3 inhibition might be considered as an effective method to selectively kill cancer cells (9). Beyond its roles in immunity and oncology, K_V1.3 has been implicated in pathways regulating energy homeostasis and body weight, making it a potential target for obesity treatment (10).

One of the primary challenges in developing K_V1.3 inhibitors lies in the high sequence homology among K_V1.x family members, making it difficult to achieve potent and selective inhibition of K_V1.3. Several K_V1.3 inhibitors have been designed to specifically target K_V1.3 in the plasma membrane. Among them, the psoralen derivative PAP-1 (**1**, Fig. 1) is currently the most potent (IC_{50} = 2 nmol L^{-1}) and selective (*i.e.* 23-fold over K_V1.5) small-molecule K_V1.3 inhibitor (11). The antimycobacterial drug clofazimine (**2**, Fig. 1) is another well-characterised K_V1.3 inhibitor (IC_{50} = 300 nmol L^{-1}), displaying tenfold selectivity over K_V1.1, K_V1.2, K_V1.5, and K_V3.1 (12). Another important K_V1.3 inhibitor, a benzamide derivative known as PAC (**3**, Fig. 1), was identified through a high-throughput screening campaign.

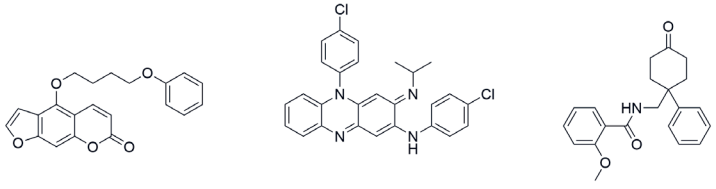


Fig. 1. Structures of known representative K_V1.3 inhibitors PAP-1 (**1**), clofazimine (**2**) and PAC (**3**).

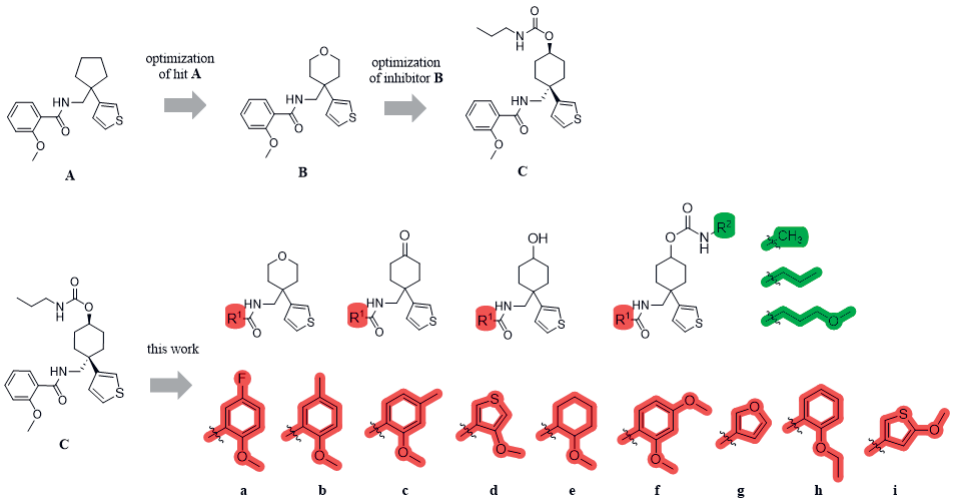


Fig. 2. Optimization of K_v1.3 inhibitor **A**, identified by virtual screening, to more potent analogs **B** and **C**, and further structure-activity relationship investigation in this work.

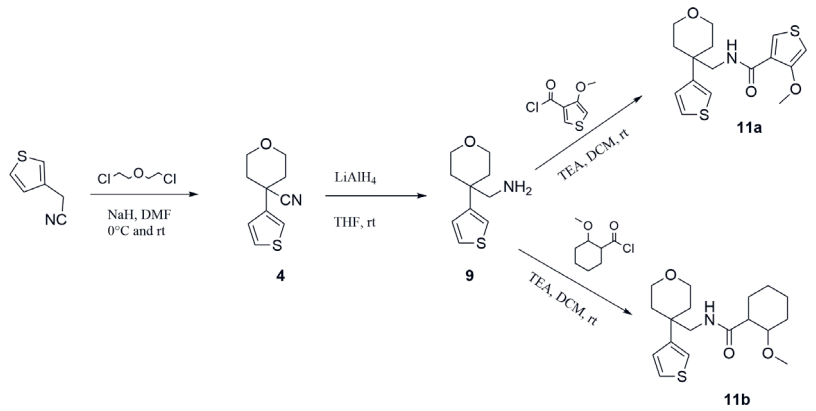
It exhibited an IC_{50} of 200 nmol L^{-1} but lacked selectivity among K_V1.x family members. *In vitro* functional assays demonstrated that this compound reversibly inhibits calcium-dependent T-cell activation and suppresses IL-2 production in a concentration-dependent manner without inducing cytotoxicity or affecting calcium-independent T-cell stimulation pathways (13).

Since the binding site of benzamide-based K_v1.3 inhibitors remains unidentified, we employed a ligand-based drug design strategy, utilising a 3D similarity search of previously reported benzamide inhibitors. This approach led to the discovery of a novel thiophene-based compound **A**, which demonstrated selectivity for K_v1.3 channels (14). Further structural modifications of compound **A** resulted in the development of the 3-thiophene-based inhibitor **B** (Fig. 2), which demonstrated an IC_{50} of 470 nmol L^{-1} and an 18-fold selectivity over related K_v1.x family channels in *Xenopus laevis* oocytes (15). Additional optimisation led to compound **C**, which inhibited K_v1.3-mediated currents in activated human T-lymphocytes with an IC_{50} value of 26.1 nmol L^{-1} (16). In this work, we further investigate the structure-activity relationship (SAR) of this series by extensively modifying the 2-methoxybenzamide moiety of the inhibitor while retaining the 3-thienyl group at position 4 of the core tetrahydropyran or cyclohexane ring (Fig. 2).

EXPERIMENTAL

Chemistry – General

The reagents and solvents used were obtained from commercial sources (*i.e.*, Acros Organics, Sigma-Aldrich, TCI Europe, Merck, Carlo Erba, Apollo Scientific) and were used as provided. Analytical thin-layer chromatography (TLC) was performed on silica gel aluminium sheets (60 F_{254}, 0.20 mm, Merck, Germany). Flash column chromatography was performed on silica gel 60 (particle size 0.040–0.063 mm, Merck). ^{1}H NMR and ^{13}C spectra

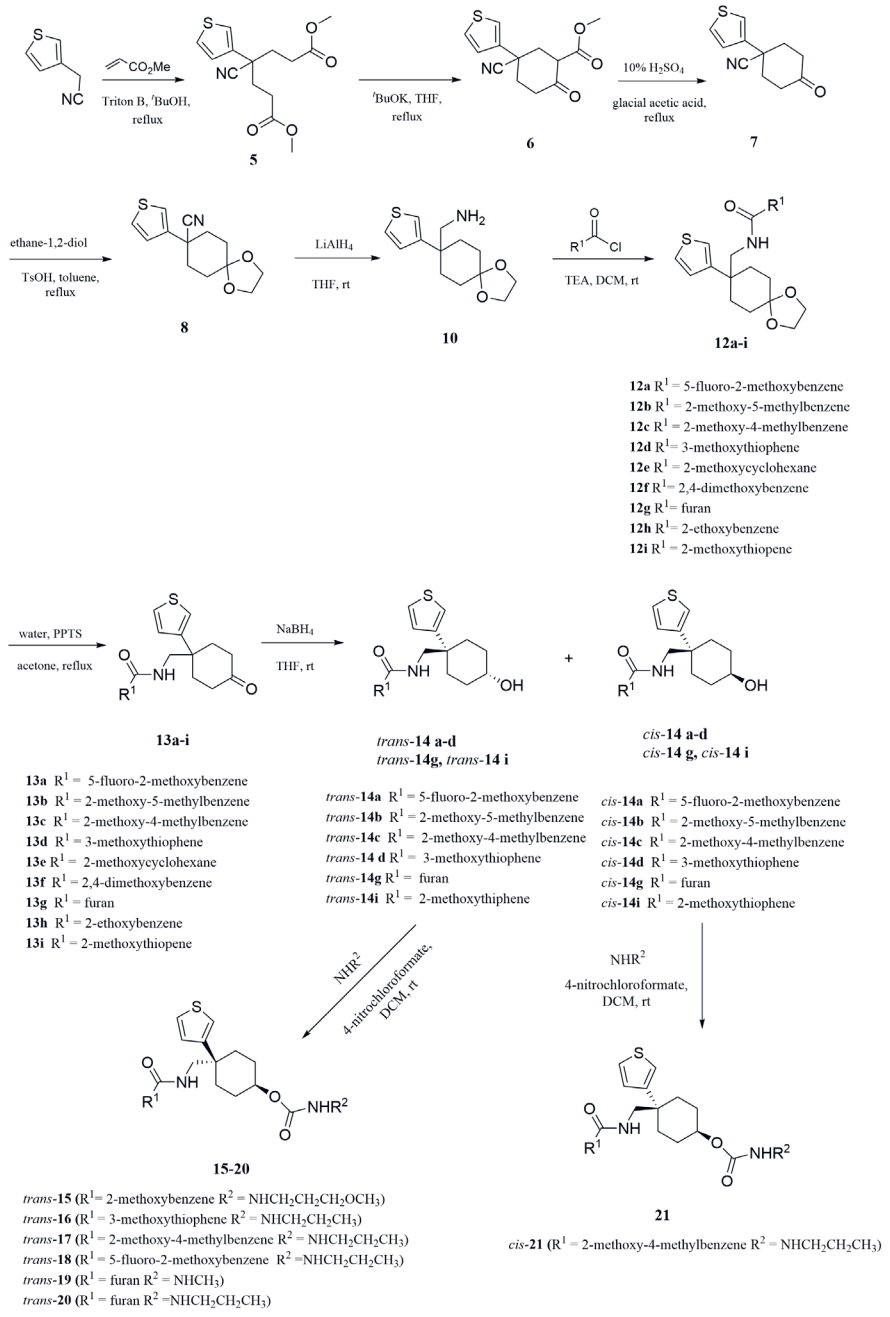


Scheme 1. Synthesis of the target compounds **11a** and **11b**.

were recorded at 400 and 100 MHz, respectively, on a Bruker Avance III NMR spectrometer (Bruker, USA) at 295 K. The chemical shifts (δ) are reported in ppm and are referenced to the deuterated solvent used. HRMS measurements were performed on a LC-MS/MS system (Q Executive Plus; Thermo Scientific, USA). Mass spectrometry measurements were performed on an Expression CMS^L mass spectrometer (Advion, USA). Analytical reversed-phase UPLC analyses were performed using a modular system (Thermo Scientific Dionex UltiMate 3000 modular system; Thermo Fisher Scientific Inc., USA). Method: Waters Acquity UPLC® HSS C18 SB column (2.1 × 50 mm, 1.8 μm), t = 40 °C; injection volume = 5 μL; flow rate = 0.4 mL min^{-1}; detector λ = 254 nm; mobile phase A (0.1 % trifluoroacetic acid (TFA) in water, *V*/*V*), mobile phase B acetonitrile (MeCN). Gradient: 0–2 min, 10 % B; 2–10 min, 10–90 % B; 10–12 min, 90 % B. Purities of the tested compounds were established to be ≥ 95 % at 254 nm, as determined by UPLC. The syntheses of the compounds are illustrated in Schemes 1 and 2, experimental procedures and characterisation data are provided in the Supporting Information.

Patch-clamp electrophysiology

Mouse L929 fibroblasts stably expressing m$K_v1.3$, were a gift from Dr. K. George Chandy (University of California, Irvine, USA). All experiments were conducted with an EPC-10 amplifier (HEKA, Germany) in the whole-cell configuration with a holding potential of –80 mV. Pipette resistances averaged around 2.5 MΩ. Compound solutions were prepared fresh in Na^+ Ringer from 10 mmol L^{-1} stock solutions in DMSO directly before the experiments. For current measurements, we used an internal pipette solution containing 160 mmol L^{-1} KF, 2 mmol L^{-1} $MgCl_2$, 10 mmol L^{-1} HEPES, and 10 mmol L^{-1} EGTA, with a pH of 7.2 and an osmolarity of ~300 mOsm. Sodium Ringer was used as an external solution containing the following: 160 mmol L^{-1} NaCl, 4.5 mmol L^{-1} KCl, 2 mmol L^{-1} $CaCl_2$, 1 mmol L^{-1} $MgCl_2$, and 10 mmol L^{-1} HEPES, with a pH of 7.4 and an osmolarity of ~300 mOsm. Currents were elicited with a 200-ms voltage step to + 40 mV, followed by 45 seconds of holding at a resting membrane potential of –80 mV. A use-dependence protocol, whereby cells were pulsed to 40 mV every 1 second, was used prior to the step protocol for the compound to ensure that channel kinetics were as expected. If currents exceeded 2 nA,



12a R^1 = 5-fluoro-2-methoxybenzene
12b R^1 = 2-methoxy-5-methylbenzene
12c R^1 = 2-methoxy-4-methylbenzene
12d R^1= 3-methoxythiophene
12e R^1 = 2-methoxycyclohexane
12f R^1= 2,4-dimethoxybenzene
12g R^1= furan
12h R^1= 2-ethoxybenzene
12i R^1 = 2-methoxythiopene

13a R^1 = 5-fluoro-2-methoxybenzene
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13d R^1 = 3-methoxythiophene
13e R^1 = 2-methoxycyclohexane
13f R^1 = 2,4-dimethoxybenzene
13g R^1 = furan
13h R^1 = 2-ethoxybenzene
13i R^1 = 2-methoxythiopene

trans-**14a** R^1 = 5-fluoro-2-methoxybenzene
trans-**14b** R^1 = 2-methoxy-5-methylbenzene
trans-**14c** R^1 = 2-methoxy-4-methylbenzene
trans-**14 d** R^1 = 3-methoxythiophene
trans-**14g** R^1 = furan
trans-**14i** R^1 = 2-methoxythiphene

cis-**14a** R^1 = 5-fluoro-2-methoxybenzene
cis-**14b** R^1 = 2-methoxy-5-methylbenzene
cis-**14c** R^1 = 2-methoxy-4-methylbenzene
cis-**14d** R^1 = 3-methoxythiophene
cis-**14g** R^1 = furan
cis-**14i** R^1 = 2-methoxythiophene

trans-**15** (R^1= 2-methoxybenzene R^2 = $NHCH_2CH_2CH_2OCH_3$)
trans-**16** (R^1 = 3-methoxythiophene R^2 = $NHCH_2CH_2CH_3$)
trans-**17** (R^1 = 2-methoxy-4-methylbenzene R^2 = $NHCH_2CH_2CH_3$)
trans-**18** (R^1 = 5-fluoro-2-methoxybenzene R^2 =$NHCH_2CH_2CH_3$)
trans-**19** (R^1 = furan R^2 = $NHCH_3$)
trans-**20** (R^1 = furan R^2 =$NHCH_2CH_2CH_3$)

cis-**21** (R^1 = 2-methoxy-4-methylbenzene R^2 = $NHCH_2CH_2CH_3$)

Scheme 2. Synthesis of the target compounds **13a–i**, *trans*-**14a–d**, *trans*-**14g**, *trans*-**14i**, *cis*-**14a–d**, *cis*-**14g**, *cis*-**14i**, *trans*-**15–20** and *cis*-**21**.

60–80 % series resistance compensation was used. Concentration-dependent current inhibition, measured as reduction of area under the current curve, was fitted with the Hill equation using GraphPad Prism 8 (GraphPad Software, USA). All data points represent at least 3 independent experiments and are presented as mean ± standard deviation (SD). IC_{50} values are reported with 95 % confidence intervals (CI).

RESULT AND DISCUSSION

Chemistry

Based on our previously published compounds (15, 16), we further investigated the SAR for $K_V1.3$ inhibition (Fig. 2). We synthesised compounds **11a** and **11b**, in which the 3-thiophene and tetrahydropyran moieties were retained, whereas the 2-methoxyphenyl group of compound **B** was replaced with either a 2-methoxycyclohexyl or 3-methoxythiophenyl moiety, respectively. Next, the tetrahydropyran ring was substituted with a cyclohexane ring bearing keto, hydroxy, or carbamate groups. Compounds **13a–i** contain a ketone at the 4-position of the cyclohexane ring and feature various modifications of the 2-methoxybenzamide moiety. Reduction of the ketone in compounds **13a–h** produced the corresponding hydroxy analogues: *trans*-**14a–d**, *cis*-**14a–d**, *trans*-**14g**, *cis*-**14g**, *trans*-**14i**, and *cis*-**14i**. These hydroxy compounds were then further modified to generate methylcarbamate-, propylcarbamate-, and 3-methoxypropylcarbamate-containing derivatives **15–21**. All hydroxy- and carbamate-substituted compounds were obtained as diastereomeric mixtures, which were subsequently separated into their *cis*- and *trans*-isomers using column chromatography. The synthetic routes for these new compounds are outlined in Schemes 1 and 2.

In Scheme 1, thiophene-3-acetonitrile was reacted with 1-chloro-2-(2-chloroethoxy) ethane in the presence of sodium hydride (NaH, 60 % dispersion in mineral oil) under an argon atmosphere at room temperature, yielding the intermediate 4-(thiophen-3-yl)tetrahydro-2*H*-pyran-4-carbonitrile (**4**). The nitrile group was subsequently reduced using lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran (THF) to produce the primary amine **9**. This amine was then reacted with either 4-methoxythiophene-3-carbonyl chloride or 2-methoxycyclohexane-1-carbonyl chloride to afford the final compounds **11a** and **11b**.

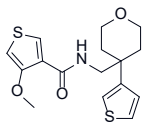
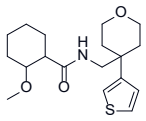
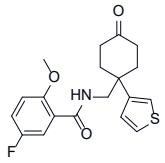
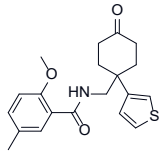
For the synthesis of cyclohexane-based analogues (Scheme 2), thiophene-3-acetonitrile was refluxed in *tert*-butanol and subjected to a double Michael addition in the presence of methyl acrylate and benzyl trimethylammonium hydroxide (Triton B), yielding the diester intermediate **5**. In the following step, compound **5** was deprotonated using potassium *tert*--butoxide and underwent Dieckmann condensation to form the 4-heteroaryl-4-cyano-2-carbomethoxycyclohexanone derivative **6**. The 2-carboxymethyl group was then removed by heating at 100 °C in a mixture of 10 % sulfuric acid and glacial acetic acid, producing 4-oxo--1-(thiophen-3-yl)cyclohexane-1-carbonitrile (**7**). The ketone group of **7** was protected with ethylene glycol, forming compound **8**. Subsequent reduction of the nitrile group using $LiAlH_4$ in THF provided the primary amine **10**, which was then acylated with various acyl chlorides to produce intermediates **12a–i**. Deprotection of the ketone yielded compounds **13a–i**. Selective reduction of the ketone group in **13a–i** using sodium borohydride ($NaBH_4$) produced diastereomeric mixtures of alcohols **14a–i**, which were separated into their *cis*- and *trans*-isomers by column chromatography. The resulting hydroxy analogues were reacted with 4-nitrochloroformates to form 4-nitrophenyl carbonate intermediates, which were sub-

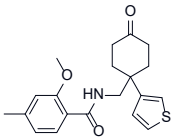
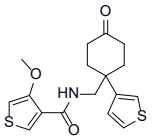
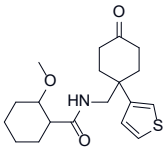
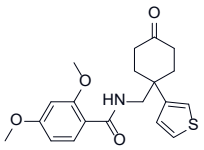
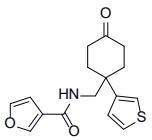
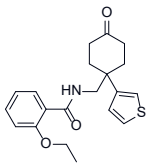
sequently treated with various primary amines to yield novel carbamate derivatives *trans*-**15**, *trans*-**16**, *trans*-**17**, *trans*-**18**, *trans*-**19**, *trans*-**20**, and *cis*-**21**.

Determination of K_V1.3 inhibition

To expand the library of 2-methoxybenzamides, a series of new K_V1.3 inhibitors was synthesised and evaluated for their inhibitory activity at 1 and 10 μmol L^{-1} using whole-cell patch-clamp electrophysiology (Tables I–III). Replacement of the 2-methoxyphenyl moiety in compound **B** (Fig. 2) with a 2-methoxycyclohexyl, as in **11b**, resulted in loss of inhibitory activity, while compound **11a** with a 3-methoxythiophen-4-yl group showed full inhibition of K_V1.3 at 10 μmol L^{-1} (Table I). Within the ketone series, compound **13a**, featuring a 5-fluoro substituent on the 2-methoxyphenyl ring, exhibited the highest potency, achieving 49 % inhibition at 1 μmol L^{-1} and complete block at 10 μmol L^{-1}. Substitution with either a 4-methyl (**13c**) or 4-methoxy (**13f**) group on the 2-methoxyphenyl ring was better tolerated than a 5-methyl substituent (**13b**), which showed reduced activity. Strong inhibition was also observed when the 2-methoxyphenyl group was replaced with a 3-methoxythiophen-4-yl (**13d**) or a 2-ethoxyphenyl group (**13h**). In contrast, compounds **13e** (bearing a methoxycyclohexyl group) and **13g** (with a furan-3-yl substituent) only weakly inhibited K_V1.3 at 10 μmol L^{-1} (Table I).

*Table I. K_V1.3 inhibitory activity of new analogues **11a**, **11b** and **13a–h**, manually patch-clamped to determine the percentage of inhibition at 1 and 10 μmol L^{-1}*

Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
11a		60	100
11b		0	22
13a		49	100
13b		9	63

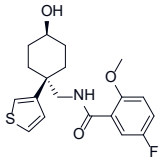
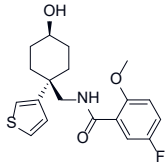
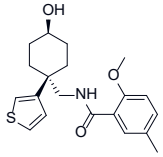
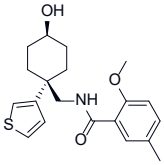
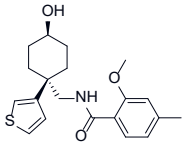
Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
13c		32	89
13d		25	92
13e		4	25
13f		27	85
13g		0	20
13h		29	88

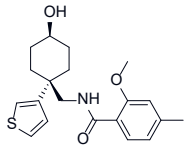
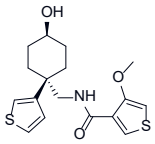
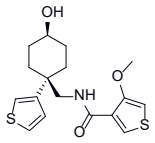
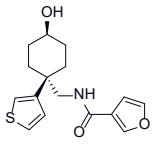
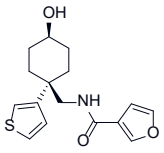
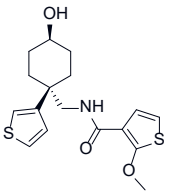
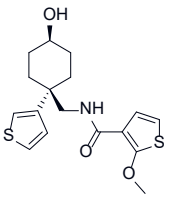
n = 3

In the hydroxy series (**14a–d**,**g**,**i**), an SAR pattern similar to that observed for the ketones (**13a–h**) was evident. Notably, the *cis*-isomers consistently exhibited more potent $K_v1.3$ inhibition than their *trans* counterparts, regardless of the substitution on the 2-methoxyphenyl ring. Among the hydroxy derivatives, the most potent compounds were *cis*-**14c**, *cis*-**14d**, and *cis*-**14i**, bearing 4-methyl-2-methoxyphenyl, 3-methoxythiophen-4-yl, and 2-methoxythiophen-3-yl substituents, respectively. Each of these compounds achieved complete $K_v1.3$ inhibition at 1 μmol L^{-1} (Table II). In the carbamate series (Table III), the 3-methoxypropyl analog of compound **C** (*trans*-**15**) also demonstrated full $K_v1.3$ inhibition

at 1 μmol L^{-1}. Consistent with findings from our previous study (16), the *trans*-carbamates generally exhibited stronger inhibitory activity than their *cis* counterparts. For example, *trans*-**17** inhibited $K_V1.3$ by 87 % at 1 μmol L^{-1}, whereas *cis*-**21** showed only 21 % inhibition at the same concentration. Other potent inhibitors included the propylcarbamates *trans*-**16** and *trans*-**18**, analogues of **14d** and **14a**, respectively, both of which showed complete inhibition at 1 μmol L^{-1} (Table III). Based on this preliminary screening, the most promising compounds, *cis*-**14c**, *cis*-**14d**, *cis*-**14i**, *trans*-**15**, *trans*-**16**, *trans*-**17**, and *trans*-**18**, were selected for further evaluation in concentration-response experiments (Table IV).

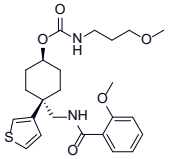
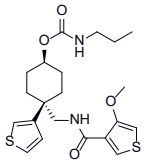
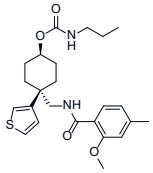
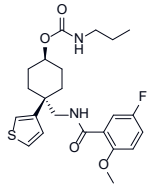
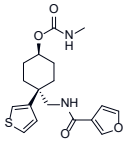
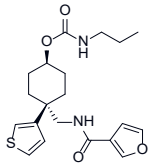
*Table II. $K_V1.3$ inhibitory activity of new analogues **14a-d,g,i**, manually patch-clamped to determine the percentage of inhibition at 1 and 10 μmol L^{-1}*

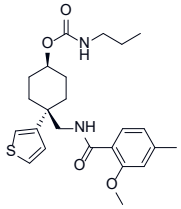
Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
trans-**14a**		31	80
cis-**14a**		84	100
trans-**14b**		11	40
cis-**14b**		49	100
trans-**14c**		0	32

Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
cis-**14c**		100	n.t.
trans-**14d**		12	52
cis-**14d**		100	n.t.
trans-**14g**		0	0
cis-**14g**		10	40
trans-**14i**		19	77
cis-**14i**		100	n.t.

n = 3

*Table III. $K_V1.3$ inhibitory activity of new analogues **15–21**, manually patch-clamped to determine the percentage of inhibition at 1 and 10 μmol L^{-1}*

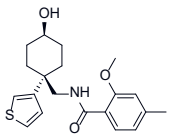
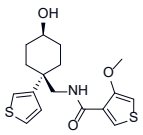
Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
trans-**15**		100	n.t.
trans-**16**		100	n.t.
trans-**17**		87	n.t.
trans-**18**		100	n.t.
trans-**19**		7	66
trans-**20**		0	21

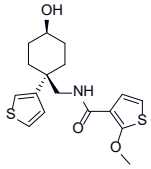
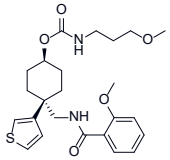
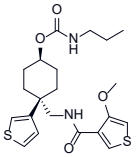
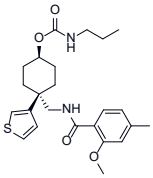
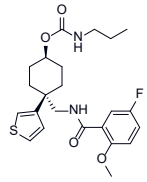
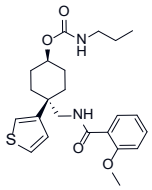
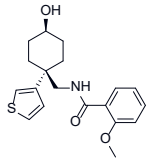
Compd.	Structure	Average block at 1 μmol L^{-1} (%)	Average block at 10 μmol L^{-1} (%)
cis-**21**		21	83

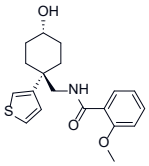
n = 3; n.t. – not tested

The potency of compounds *cis*-**14c**, *cis*-**14d**, and *cis*-**14i** was assessed by determining their IC_{50} values for K_V1.3 inhibition and compared to the reference compounds *cis*-**D** (IC_{50} = 226 nmol L^{-1} and *trans*-**D** (IC_{50} = 2.2 μmol L^{-1}). Among the tested compounds, *cis*-**14i** showed the highest potency, with an IC_{50} of 326 nmol L^{-1}, followed closely by *cis*-**14d** (IC_{50} = 346 nmol L^{-1}) and *cis*-**14c** (IC_{50} = 505 nmol L^{-1}). Although all three compounds displayed submicromolar IC_{50} values, they were less potent than *cis*-**D**. The potency of compounds *trans*-**15**, *trans*-**16**, *trans*-**17**, and *trans*-**18** was compared to the parent compound *trans*-**C** (IC_{50} = 0.23 μmol L^{-1}). Among these, *trans*-**18** exhibited the highest potency, with an IC_{50} of 122 nmol L^{-1}, followed by *trans*-**16** with an IC_{50} of 166 nmol L^{-1}. While both compounds were less potent than *trans*-**C**, they still retained significant inhibitory activity. *trans*-**15** and *trans*-**17** were less potent than *trans*-**16** and *trans*-**18**, though their inhibitory potency remained within the submicromolar range. These results suggest that the 2-methoxyphenyl ring, as present in compound *trans*-**C**, represents an optimal substituent for K_V1.3 inhibition at this position. However, small modifications, such as those present in *trans*-**16** and *trans*-**18**, are well tolerated in maintaining strong inhibitory potency.

Table IV. IC_{50} values determined on K_V1.3 channels

Compd.	Structure	IC_{50}
cis-**14c**		505 nmol L^{-1} (95 CI: 445–561 nmol L^{-1})
cis-**14d**		346 nmol L^{-1} (95 CI: 317–377 nmol L^{-1})

Compd.	Structure	IC_{50}
cis-**14i**		326 nmol L^{-1} (95 CI: 298–357 nmol L^{-1})
trans-**15**		342 nmol L^{-1} (95 CI: 319–367 nmol L^{-1})
trans-**16**		166 nmol L^{-1} (95 CI: 154–179 nmol L^{-1})
trans-**17**		438 nmol L^{-1} (95 CI: 411–466 nmol L^{-1})
trans-**18**		122 nmol L^{-1} (95 CI: 102–144 nmol L^{-1})
trans-**C**		74 nmol L^{-1} (95 CI: 65–84 nmol L^{-1})
cis-**D**		234 nmol L^{-1} (95 CI: 220–242 nmol L^{-1})

Compd.	Structure	IC_{50}
trans-**D**		2.6 μmol L^{-1} (95 CI: 2.0–3.2 μmol L^{-1})

CONCLUSIONS

In this study, a ligand-based design approach was used for the optimisation of novel thiophene-based $K_v1.3$ inhibitors, building on a previously reported benzamide scaffold. Structural modifications focused on the 2-methoxybenzamide moiety and the core tetrahydropyran or cyclohexane ring, while retaining the 3-thienyl group, enabled the identification of several potent inhibitors. Structure-activity relationship analysis revealed that *cis*-isomers in the hydroxy series consistently exhibited stronger $K_v1.3$ inhibition than their *trans* counterparts, with *cis*-**14i**, *cis*-**14d**, and *cis*-**14c** emerging as the most effective (IC_{50} = 326–505 nmol L^{-1}). In the carbamate series, *trans*-isomers showed superior activity, with *trans*-**18** and *trans*-**16** achieving IC_{50} values of 122 and 166 nmol L^{-1}, respectively. While none of the new compounds outperformed the most potent reference inhibitors, several analogues exhibited submicromolar potency. These findings provide valuable insights into the SAR of $K_v1.3$ inhibitors and highlight promising candidates for further development.

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Conflicts of interest. – The authors declare no conflict of interest.

Authors contributions. – Conceptualization, L.P.M. and T.T.; methodology, M.F., Š.P., and J.A.N.; analysis M.F., Š.P., and J.A.N.; investigation, M.F., Š.P., and J.A.N.; writing, original draft preparation, M.F. and T.T.; writing, review and editing, Š.P., J.A.N., H.W., L.P.M., and T.T. All authors have read and agreed to the published version of the manuscript.

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Supplementary material

Exploration of the chemical space of benzamide-based voltage-gated potassium channel $K_V1.3$ inhibitors

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Chemistry - Syntheses

The obtained compounds 4-(thiophen-3-yl)tetrahydro-2*H*-pyran-4-carbonitrile (**4**), dimethyl 4-cyano-4-(thiophen-3-yl)heptanedioate (**5**), methyl 5-cyano-2-oxo-5-(thiophen-3-yl)cyclohexane-1-carboxylate (**6**), 4-oxo-1-(thiophen-3-yl)cyclohexane-1-carbonitrile (**7**), 8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**8**), (4-(thiophen-3-yl)tetrahydro-2*H*-pyran-4-yl)methanamine (**9**), (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine, (**10**) were prepared as previously reported.[1,2]

General Procedure A: Synthesis of benzamide analogues (**11a/11b, 12a-i**). – Carboxylic acid derivative (26 mmol, 1.0 equiv) was dissolved in dichloromethane (100 mL) with ice cooling. Oxalyl chloride (78 mmol, 3.0 equiv) was added dropwise, followed by 5 drops of DMF. The batch was stirred at room temperature overnight and next day the solvent was evaporated under reduced pressure. Appropriate amine (26 mmol, 1.0 equiv) and Et_3N (78 mmol, 3.0 equiv) were dissolved in dichloromethane (75 mL) with ice cooling, followed by addition of benzoyl chloride intermediate (26 mmol, 1.0 equiv), dissolved in dichloromethane (75 mL). Reaction mixture was stirred at room temperature overnight. Organic phase was then diluted with 75 mL of dichloromethane and washed with saturated aqueous $NaHCO_3$ solution (2 × 50 mL), 1 M HCl (2 × 50 mL), water (2 × 50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and organic phase was then removed under reduced pressure. The product was used in the next step without further purification unless stated otherwise.

General Procedure B: Removal of protecting group from ketone (**13a-i**). – Benzamide analogue (23 mmol, 1.0 equiv) was dissolved in acetone (150 mL), followed by the addition of pyridinium *p*-toluenesulfonate (PPTS) (2.3 mmol, 0.1 equiv) and water (20 mL). The reaction mixture was stirred at reflux for 48 h, and then the solvent was evaporated. The residue was dissolved in

dichloromethane (200 mL) and washed with aqueous $NaHCO_3$ solution (50 mL), 1 M aqueous HCl solution (50 mL), water (2 × 50 mL), and saturated brine solution (50 mL). Organic phase was dried over Na_2SO_4 and removed under reduced pressure. The product was purified by flash column chromatography.

General Procedure C: Reduction of ketone group to hydroxyl group (*trans*-**14a-d,** *trans*-**14g,** *trans*-**14i,** *cis*-**14a-d,** *cis*-**14g,** *cis*-**14i**). – Benzamide derivative (17 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL) under an argon atmosphere with ice cooling. $NaBH_4$ (34 mmol, 2.0 equiv) was then added in portions with ice cooling and reaction mixture stirred at room temperature overnight. Next day 1 M HCl (100 mL) was added to reaction mixture with ice cooling and extracted with dichloromethane (2 × 100 mL). Combined organic phases were then washed with water (50 mL), dried over Na_2SO_4, filtered and the solvent removed under reduced pressure. Product was purified by flash column chromatography. *trans* and *cis* derivatives were separated by flash column chromatography.

General Procedure D: Synthesis of carbamate derivatives from alcohols (*trans*-**15-20** and *cis*-**21**). – Hydroxyl analogue (0.6 mmol or 1.2 mmol, 1.0 equiv) was dissolved in dichloromethane (50 mL) and then Et_3N (3 mmol or 6 mmol, 5.0 equiv) was slowly added. The flask was stirred at room temperature for 5 minutes and then 4-nitrophenyl chloroformate (1.2 mmol or 2.4 mmol, 2.0 equiv) was added in portions. Reaction mixture was stirred at room temperature overnight and then washed with water (25 mL), 1 M HCl (25 mL), and brine (25 mL). Organic phase was dried over Na_2SO_4, filtered and removed under reduced pressure. Intermediate (0.3 mmol or 0.6 mmol, 1.0 equiv) was dissolved in dichloromethane (50 mL) and then amine (3 mmol or 6 mmol, 10.0 equiv) was added at room temperature. The flask was stirred at room temperature overnight and next day washed with water (25 mL), 1 M HCl (25 mL), and brine (25 mL). Organic phase was dried over Na_2SO_4, filtered and removed under reduced pressure. Product was additionally purified by flash column chromatography.

*Synthesis of 4-(thiophen-3-yl)tetrahydro-2H-pyran-4-carbonitrile (**4**).* – 2-(Thiophen-3-yl)acetonitrile (5 mL, 43.8 mmol, 1.0 equiv) was slowly added to a stirred solution of NaH (60 % dispersion in mineral oil) (3.5 g, 87.6 mmol, 2.0 equiv) in anhydrous DMF (100 mL) while ice cooling under argon atmosphere. The batch was stirred for 15 minutes and then solution of 1-chloro-2-(2-chloroethoxy)ethane (5.14 mL, 43.8 mmol, 1.0 equiv) in anhydrous DMF (30 mL) was added dropwise while ice cooling. The batch was stirred at room temperature overnight. Next day water (50 mL) was added to the reaction mixture and the reaction mixture was washed with diethyl ether (3 × 100 mL). Combined organic phases were washed with saturated brine solution (2 × 100 mL), dried over Na_2SO_4, filtered and then solvent was removed under reduced pressure. Product was purified by flash column chromatography. Column chromatography, EtOAc/*n*-hex = 1/4 (v/v). Yield: 93 % (7.9 g); yellow oil.

*Synthesis of (4-(thiophen-3-yl)tetrahydro-2H-pyran-4-yl)methanamine (**9**).* – 4-(Thiophen-3-yl)tetrahydro-2*H*-pyran-4-carbonitrile (**4**) (7.9 g, 40.95 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL) under argon atmosphere with ice cooling. $LiAlH_4$ (3.26 g, 81.9 mmol,

2.0 equiv) was added in portions on ice bath and batch was stirred at room temperature overnight. For workup, diethyl ether (300 mL) was added to flask with ice cooling and then saturated brine solution (5-10 mL) was slowly added while the batch was stirred on ice bath. Residual water was removed by addition of Na_2SO_4. Precipitate was filtered off and additionally washed with diethyl ether. Organic solvent was removed under reduced pressure and the product was used without further purification unless stated otherwise. Yield: 55.4 % (4.48 g); yellow oil.

*Synthesis of 4-methoxy-N-((4-(thiophen-3-yl)tetrahydro-2H-pyran-4-yl)methyl)thiophene-3-carboxamide (**11a**).* – Synthesized from 4-methoxythiophene-3-carboxylic acid (250 mg, 1.58 mmol, 1.0 equiv), oxalyl chloride (0.41 mL, 4.74 mmol, 3.0 equiv) and then from (4-(thiophen-3-yl)tetrahydro-2*H*-pyran-4-yl)methanamine (**9**) (312 mg, 1.58 mmol, 1.0 equiv), 4-methoxythiophene-3-carbonyl chloride (1.58 mmol, 1.0 equiv) and Et_3N (0.66 mL, 4.74 mmol, 3.0 equiv) *via* general procedure A. Yield: 19.4 % (310 mg); white solid.

*Synthesis of 2-methoxy-N-((4-(thiophen-3-yl)tetrahydro-2H-pyran-4-yl)methyl)cyclohexane-1-carboxamide (**11b**).* – Synthesized from 2-methoxycyclohexane-1-carboxylic acid (100 mg, 0.66 mmol, 1.0 equiv), oxalyl chloride (0.165 mL, 1.9 mmol, 3.0 equiv) and then from (4-(thiophen-3-yl)tetrahydro-2*H*-pyran-4-yl)methanamine (**9**) (124 mg, 0.63 mmol, 1.0 equiv), 2-methoxycyclohexane-1-carbonyl chloride (0.66 mmol, 1.0 equiv) and Et_3N (0.265 mL, 1.9 mmol, 3.0 equiv) via general procedure A. Column chromatography, EtOAc/*n*-hex = 1:1 (v/v). Yield: 23.6 % (31 mg); white solid.

*Table S1. Spectral data of compounds **4** and **9***

	^{1}H NMR (δ, ppm)
4	(400 MHz, $CDCl_3$) δ 7.39 (dd, J_1 = 5.1 Hz, J_2 = 3.0 Hz, 1H), 7.31 (dd, J_1 = 3.0 Hz, J_2 = 1.5 Hz, 1H), 7.14 (dd, J_1 = 5.1 Hz, J_2= 1.5 Hz, 1H), 4.05 (dt, J_1 = 12.1 Hz, J_2 = 3.2 Hz, 2H), 3.86 (ddd, J_1 = 12.4 Hz, J_2 = 9.2 Hz, J_3 = 5.0 Hz, 2H), 2.12 – 2.07 (m, 4H).
9	(400 MHz, DMSO) δ 7.50 (dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, 1H), 7.22 (dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, 1H), 7.07 (dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, 1H), 3.67 (dt, J_1 = 11.5 Hz, J_2 = 4.2 Hz, 2H), 3.36 – 3.30 (m, 2H), 2.56 (s, 2H), 1.98 – 1.91 (m, 2H), 1.71 (ddd, J_1 = 17.8 Hz, J_2 = 9.4 Hz, J_3 = 4.4 Hz, 2H), 0.95 (brs, 2H).

Compound ID
4
9

*Table S2. Spectral and analytical data of compounds **11a** and **11b***

^{1}H NMR (400 MHz, DMSO-d_6, TMS) (δ, ppm)	^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm)	HRMS (ESI+)	HPLC purity at 254 nm
δ 8.02 (1H, d, J = 3.6 Hz, H-11), 7.61 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.37 (1H, dd, J_1 = 2.8 Hz, J_2 = 1.3 Hz, H-15), 7.18 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-13), 7.12 (1H, t, J = 5.7 Hz, CONHCH$_2$), 6.73 (1H, d, J = 3.6 Hz, H-10), 3.73 (3H, s, H-12', H-12'', H-12'''), 3.74 – 3.65 (2H, m, H$_e$-3,4), 3.49 (2H, d, J = 5.9 Hz, H-7', H-7''), 3.46 – 3.35 (2H, m, H$_a$-3,4), 2.03 – 1.93 (2H, m, H$_e$-2,5), 1.79 – 1.68 (2H, m, H$_a$-2,5).	δ 160.53 (C-7), 154.18 (C-9), 145.55 (C-14), 131.58 (C-11), 126.63 (C-16), 126.46 (C-13), 126.35 (C-8), 121.83 (C-15), 99.93 (C-10), 63.33 (C-3,4), 58.11 (C-12), 48.18 (C-6), 38.97 (C-1), 34.04 (C-2,5).	338.0879 338.0879	99.88 %(t_R = 4.863 min)
δ 7.54 (1H, dd, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-18), 7.28 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-17), 7.11 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-15), 7.08 (1H, t, J = 6.1 Hz, CONHCH$_2$), 3.73 – 3.62 (2H, m, H$_e$-3,4), 3.55 – 3.49 (1H, m, H-9), 3.36 (2H, dd, J_1 = 9.6 Hz, J_2 = 2.1 Hz, H$_a$-3,4), 3.35 – 3.28 (1H, m, H-6'), 3.16 (1H, d, J = 5.8 Hz, H-6''), 3.12 (3H, s, H-14', H-14'', H-14'''), 2.32 (1H, dt, J_1 = 10.2 Hz, J_2 = 3.4 Hz, H-8), 1.93 – 1.79 (3H, m, H$_e$-10, H$_e$-2,5), 1.78 – 1.62 (3H, m, H$_e$-13, H$_a$-2,5), 1.59 – 1.47 (1H, m, H$_e$-12), 1.47 – 1.35 (2H, m, H$_a$-13, H$_e$-11), 1.35 – 1.26 (2H, m, H$_a$-10, H$_a$-11), 1.26 – 1.13 (1H, m, H$_a$-12).	δ 172.77 (C-7), 145.98 (C-16), 126.63 (C-15), 126.17 (C-18), 121.40 (C-17), 77.15 (C-9), 63.41 (C-3,4), 55.41 (C-14), 48.08 (C-6), 46.15 (C-8), 40.19 (C-1), 33.73 (C-2,5), 33.66 (C-2,5), 27.04 (C-10), 24.03 (C-13), 23.85 (C-12), 20.50 (C-11)	338.1784 338.1780	98.88 % (t_R = 5.200 min)

Cmpd.	11a	11b

*Synthesis of Dimethyl 4-cyano-4-(thiophen-3-yl)heptanedioate (**5**)*

2-(Thiophen-3-yl)acetonitrile (9.98 mL, 75 mmol, 1.0 equiv) and methyl acrylate (34.00 mL, 375 mmol, 5.0 equiv) were dissolved in *tert*-butanol (45 mL) at room temperature and heated to boiling point. The heating source was then removed and benzyltrimethylammonium hydroxide (Triton B) (13.20 mL, 75 mmol, 1.0 equiv), dissolved in *tert*-butanol (10 mL), was added dropwise at room temperature. The reaction mixture was stirred under reflux for 4 h and then cooled to room temperature overnight. Then toluene (100 mL) and water (70 mL) were added to reaction mixture. The organic phase was separated and washed with water (2 × 70 mL), brine (50 mL), dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. The product was used in the next step without further purification. Yield: 81 % (18.00 g); pale yellow oil.

*Synthesis of methyl 5-cyano-2-oxo-5-(thiophen-3-yl)cyclohexane-1-carboxylate (**6**)*

Dimethyl 4-cyano-4-(thiophen-3-yl)heptanedioate (**5**) (18.00 g, 61 mmol, 1.0 equiv) was dissolved in anhydrous THF (250 mL) under argon atmosphere. Potassium *tert*-butoxide (13.69 g, 122 mmol, 2 equiv) was added in portions with ice cooling. The reaction mixture was stirred under reflux for 5 h and cooled to room temperature overnight. Next day 2.5 M acetic acid (220 mL) was added dropwise with ice cooling. The batch was mixed with toluene (150 mL). Organic phase was separated and washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL), water (3 × 100 mL) and brine (75 mL). After drying over Na_2SO_4, the solvent was evaporated. The product was used without further purification unless stated otherwise. Yield: 77 % (12.40 g); pale yellow solid.

*Synthesis of 4-oxo-1-(thiophen-3-yl)cyclohexane-1-carbonitrile (**7**)*

Methyl 5-cyano-2-oxo-5-(thiophen-3-yl)cyclohexane-1-carboxylate (**6**) (12.40 g, 47 mmol, 1.0 equiv) was dissolved in 10 % sulfuric acid (170 mL) and glacial acetic acid (380 mL). The reaction mixture was heated at 100 °C for 24 hours. The batch was then cooled to room temperature and diluted with water (500 mL) on ice bath. The water phase was extracted with ethyl acetate (3 × 150 mL) and combined organic phases were thoroughly washed with saturated aqueous $NaHCO_3$ solution (5 × 100 mL), water (5 × 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and evaporated. When ethyl acetate (25 mL) was added to crude product, white precipitate was formed. White precipitate was removed by filtration and dried. The product was additionally purified by flash column chromatography. Column chromatography, EtOAc/*n*-hex = 1/3 (v/v). Yield: 62 % (6.00 g); pale yellow solid.

*Synthesis of 8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**8**)*

4-Oxo-1-(thiophen-3-yl)cyclohexane-1-carbonitrile (**7**) (5.95 g, 29 mmol, 1.0 equiv) was dissolved in toluene (300 mL). Ethane-1,2-diol (16.2 mL, 290 mmol, 10.0 equiv) and *p*-

toluenesulfonic acid (TsOH) (86.10 mg, 0.58 mmol, 0.02 equiv) were added to reaction mixture. The flask was boiled at 140 °C in Dean-Stark apparatus overnight. Next day the flask was cooled to room temperature and the solvent was evaporated. Product was dissolved in ethyl acetate (400 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 150 mL), water (2 × 150 mL) and brine (150 mL). Organic phase was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The product was additionally purified by flash column chromatography. Column chromatography, EtOAc/*n*-hex = 1/3 (v/v). Yield: 96 % (6.70 g); white solid.

*Synthesis of (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**)*

8-(Thiophen-3-yl)-1,4-dioxaspiro[4.5]decane-8-carbonitrile (**8**) (6.70 g, 27 mmol, 1.0 equiv) was dissolved in anhydrous THF (100 mL) under argon atmosphere with ice cooling. $LiAlH_4$ (2.05 g, 54 mmol, 2.0 equiv) was added in portions on ice bath and batch was stirred at room temperature overnight. For workup, diethyl ether (300 mL) was added to flask with ice cooling and then saturated brine solution (5-10 mL) was slowly added while the batch was stirred on ice bath. Residual water was removed by addition of Na_2SO_4. Precipitate was filtered off and additionally washed with diethyl ether. Organic solvent was removed under reduced pressure and the product was used without further purification unless stated otherwise. Yield: 96 % (6.60 g); pale yellow oil.

*Synthesis of 5-fluoro-2-methoxy-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl) benzamide (**12a**)*

Synthesized from 5-fluoro-2-methoxybenzoic acid (350 mg, 2 mmol, 1.0 equiv), oxalyl chloride (0.51 mL, 6 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (521 mg, 2 mmol, 1.0 equiv), 5-fluoro-2-methoxybenzoyl chloride (2 mmol, 1.0 equiv.) and Et_3N (0.84 mL, 6 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 89 % (722 mg); white solid.

*Synthesis of 2-methoxy-5-methyl-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12b**)*

Synthesized from 2-methoxy-5-methylbenzoic acid (332 mg, 2 mmol, 1.0 equiv), oxalyl chloride (0.51 mL, 6 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (507 mg, 2 mmol, 1.0 equiv), 2-methoxy-5-methylbenzoyl chloride (369 mg, 2.0 mmol, 1.0 equiv) and Et_3N (0.84 mL, 6 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 93 % (747 mg); white solid.

*Synthesis of 2-methoxy-4-methyl-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12c**)*

Synthesized from 2-methoxy-4-methylbenzoic acid (332 mg, 2 mmol, 1.0 equiv), oxalyl chloride (0.51 mL, 6 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-

dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (507 mg, 2 mmol, 1.0 equiv), 2-methoxy-4-methylbenzoyl chloride (369 mg, 2.0 mmol, 1.0 equiv) and Et_3N (0.84 mL, 6 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 91 % (731 mg); white solid.

*Synthesis of 4-methoxy-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)thiophene-3-carboxamide (**12d**)*

Synthesized from 4-methoxythiophene-3-carboxylic acid (250 mg, 1.58 mmol, 1.0 equiv), oxalyl chloride (0.41 mL, 4.74 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (400 mg, 1.58 mmol, 1.0 equiv), 4-methoxythiophene-3-carbonyl chloride (1.58 mmol, 1.0 equiv) and Et_3N (0.66 mL, 4.74 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 91 % (731 mg); white solid.

*Synthesis of 2-methoxy-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)cyclohexane-1-carboxamide (**12e**)*

Synthesized from 2-methoxycyclohexane-1-carboxylic acid (62 mg, 0.39 mmol, 1.0 equiv), oxalyl chloride (0.1 mL, 1.17 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (100 mg, 0.39 mmol, 1.0 equiv), 2-methoxycyclohexane-1-carbonyl chloride (0.39 mmol, 1.0 equiv) and Et_3N (0.16 mL, 1.17 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 98 % (150 mg); white solid.

*Synthesis of 2,4-dimethoxy-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12f**)*

Synthesized from 2,4-dimethoxybenzoic acid (148 mg, 0.81 mmol, 1.0 equiv), oxalyl chloride (0.21 mL, 2.43 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (205 mg, 0.81 mmol, 1.0 equiv), 2-methoxycyclohexane-1-carbonyl chloride (0.81 mmol, 1.0 equiv) and Et_3N (0.34 mL, 2.43 mmol, 3.0 equiv) via general procedure A. The product was used without further purification. Yield: 89 % (300 mg); white solid.

*Synthesis of N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)furan-3-carboxamide (**12g**)*

Synthesized from furan-3-carboxylic acid (224 mg, 2 mmol, 1.0 equiv), oxalyl chloride (0.52 mL, 6 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (507 mg, 2 mmol, 1.0 equiv), Et_3N (2.09 mL, 6 mmol, 3 equiv) and furan-3-carbonyl chloride (2 mmol, 1.0 equiv) via general procedure A. The product was used without further purification. Yield: 79 % (549 mg); white solid.

*Synthesis of 2-ethoxy-N-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12h**)*

Synthesized from 2-ethoxybenzoic acid (131 mg, 0.79 mmol, 1.0 equiv), oxalyl chloride (0.21 mL, 2.37 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-

yl)methanamine (**10**) (200 mg, 0.79 mmol, 1.0 equiv), Et_3N (0.33 mL, 2.37 mmol, 3 equiv) and 2-ethoxybenzoyl chloride (0.79 mmol, 1.0 equiv) via general procedure A. The product was used without further purification. Yield: 88 % (280 mg); white solid.

*Synthesis of 5-methoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)thiophene-3-carboxamide (**12i**)*
Synthesized from 2-methoxythiophene-3-carboxylic acid (500 mg, 3.16 mmol, 1.0 equiv), oxalyl chloride (0.83 mL, 9.48 mmol, 3.0 equiv) and then from (8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methanamine (**10**) (800 mg, 3.16 mmol, 1.0 equiv), Et_3N (1.32 mL, 9.48 mmol, 3 equiv) and 2-ethoxybenzoyl chloride (3.16 mmol, 1.0 equiv) via general procedure A. The product was used without further purification. Yield: 76 % (940 mg); white solid.

*Synthesis of 5-fluoro-2-methoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)benzamide (**13a**)*
Synthesized from 5-fluoro-2-methoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12a**) (722 mg, 1.78 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (45 mg, 0.18 mmol, 0.1 equiv) and water (10 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/1 (v/v). Yield: 58 % (370 mg); white solid.

*Synthesis of 2-methoxy-5-methyl-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)benzamide (**13b**)*
Synthesized from 2-methoxy-5-methyl-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12b**) (747 mg, 1.86 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (47 mg, 0.19 mmol, 0.1 equiv) and water (10 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/1 (v/v). Yield: 59 % (390 mg); white solid.

*Synthesis of 2-methoxy-4-methyl-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)benzamide (**13c**)*
Synthesized from 2-methoxy-4-methyl-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12c**) (731 mg, 1.82 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (46 mg, 0.18 mmol, 0.1 equiv) and water (10 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/1 (v/v). Yield: 59 % (386 mg); white solid.

*Synthesis of 4-methoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)thiophene-3-carboxamide (**13d**)*
Synthesized from 4-methoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)thiophene-3-carboxamide (**12d**) (731 mg, 1.82 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (46 mg, 0.18 mmol, 0.1 equiv) and water (10 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/1 (v/v). Yield: 58 % (370 mg); white solid.

*Synthesis of 2-methoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)cyclohexane-1-carboxamide (**13e**)*
Synthesized from 2-methoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)cyclohexane-1-carboxamide (**12e**) (150 mg, 0.38 mmol, 1.0 equiv), water (2 mL) and

pyridinium *p*-toluenesulfonate (10 mg, 0.038 mmol, 0.1 equiv) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1:1 (v/v). Yield: 22.6 %; colorless oil (30 mg).

*Synthesis of 2,4-dimethoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)benzamide (**13f**)*

Synthesized from 2,4-dimethoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12f**) (300 mg, 0.72 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (18 mg, 0.07 mmol, 0.1 equiv) and water (8 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/1 (v/v). Yield 40 % (108 mg); white solid.

*Synthesis of N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (**13g**)*

Synthesized from *N*-((8-(thiophen-2-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)furan-3-carboxamide (**12g**) (549 mg, 1.58 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (40 mg, 0.16 mmol, 0.1 equiv) and water (8 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/2 (v/v). Yield: 63 % (302 mg); white solid.

*Synthesis of 2-ethoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)benzamide (**13h**)*

Synthesized from 2-ethoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)benzamide (**12h**) (280 mg, 0.70 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (17 mg, 0.07 mmol, 0.1 equiv) and water (8 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/2 (v/v). Yield: 50 % (124 mg); white solid.

*Synthesis of 5-methoxy-N-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)thiophene-3-carboxamide (**13i**)*

Synthesized from 5-methoxy-*N*-((8-(thiophen-3-yl)-1,4-dioxaspiro[4.5]decan-8-yl)methyl)thiophene-3-carboxamide (**12i**) (310 mg, 0.79 mmol, 1.0 equiv), pyridinium *p*-toluenesulfonate (20 mg, 0.079 mmol, 0.1 equiv) and water (10 mL) via general procedure B. Column chromatography, EtOAc/*n*-hex = 1/2 (v/v). Yield: 60 % (165 mg); white solid.

*Synthesis of 5-fluoro-N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxybenzamide (trans-**14a**) and 5-fluoro-N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxybenzamide (cis-**14a**)*

Synthesized from 5-fluoro-2-methoxy-*N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl) benzamide (**13a**) (370 mg, 1.02 mmol, 1.0 equiv) and $NaBH_4$ (77.46 mg, 2.05 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent was used to separate *trans*-**14a** and *cis*-**14a**. *trans*-**14a:** yield: 41 % (155 mg); white solid; *cis*-**14a**: yield: 57 % (213 mg); white solid.

*Synthesis of N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-5-methylbenzamide (trans-**14b**) and N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-5-methylbenzamide (cis-**14b**)*

Synthesized from 2-methoxy-5-methyl-*N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl) benzamide (**13b**) (390 mg, 1.09 mmol, 1.0 equiv) and $NaBH_4$ (82.55 mg, 2.18 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent was used to separate *trans***-14b** and *cis***-14b**. *trans***-14b**: yield: 39 % (153 mg); white solid; *cis***-14b**: yield: 58 % (224 mg); white solid.

*Synthesis of N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-4-methylbenzamide (trans**-14c**) and N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-4-methylbenzamide (cis**-14c**)*

Synthesized from 2-methoxy-4-methyl-*N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl) benzamide (**13c**) (386 mg, 1.08 mmol, 1.0 equiv) and $NaBH_4$ (81.70 mg, 2.16 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent was used to separate *trans***-14c** and *cis***-14c**. *trans***-14c**: yield: 40 % (156 mg); white solid; *cis***-14**: yield: 60 % (234 mg); white solid.

*Synthesis of N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-4-methoxythiophene-3-carboxamide (trans**-14d**) and N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-4-methoxythiophene-3-carboxamide (cis**-14d**)*

Synthesized from 4-methoxy-*N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)thiophene-3-carboxamide (**13d**) (370 mg, 1.06 mmol, 1.0 equiv) and $NaBH_4$ (80.11 mg, 2.12 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent was used to separate *trans***-14d** and *cis***-14d**. *trans***-14d**: yield: 35 % (132 mg); white solid; *cis***-14d**: yield: 59 % (219 mg); white solid.

*Synthesis of N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (trans**-14g**) and N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (cis**-14g**)*

Synthesized from *N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (**13g**) (302 mg, 1.00 mmol, 1.0 equiv) and $NaBH_4$ (75.81 mg, 2.00 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent was used to separate *trans***-14g** and *cis***-14g**. *trans***-14g**: yield: 38 % (117 mg); white solid; *cis***-14g**: yield: 63 % (191 mg); white solid.

*Synthesis of N-(((1R,4R)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxythiophene-3-carboxamide (trans**-14i**) and N-(((1S,4S)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxythiophene-3-carboxamide (cis**-14i**)*

Synthesized from 2-methoxy-*N*-((4-oxo-1-(thiophen-3-yl)cyclohexyl)methyl)thiophene-3-carboxamide (**13i**) (165 mg, 0.472mmol, 1.0 equiv) and $NaBH_4$ (36 mg, 0.944 mmol, 2.0 equiv) via general procedure C. Column chromatography using DCM/MTBE = 3/1 (v/v) as eluent

was used to separate *trans*-**14i** and *cis*-**14i**. *trans*-**14i**: yield: 41 % (68 mg); white solid; *cis*-**14i**: yield: 61 % (102 mg); white solid.

*Synthesis of (1R,4R)-4-((2-Methoxybenzamido)methyl)-4-(thiophen-3-yl)cyclohexyl (3-methoxypropyl)carbamate (trans-**15**)*

Synthesized from *N*-(((1*R*,4*R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxybenzamide (103 mg, 0.30 mmol, 1 equiv), 4-nitrophenyl chloroformate (121 mg, 0.60 mmol, 2 equiv), Et_3N (0.13 mL, 0.90 mmol, 3 equiv) and 3-methoxypropylamine (0.31 mL, 3.0 mmol, 10.0 equiv) via general procedure D. Column chromatography, EtOAc/*n*-hexane = 1/1 (v/v). Yield: 47 % (58 mg); white solid.

*Synthesis of (1R,4R)-4-((4-Methoxythiophene-3-carboxamido)methyl)-4-(thiophen-3-yl)cyclohexyl propylcarbamate (trans-**16**)*

Synthesized from *N*-(((*1R,4R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-4-methoxythiophene-3-carboxamide (*trans*-**14d**) (84 mg, 0.24 mmol, 1 equiv), 4-nitrophenyl chloroformate (96 mg, 0.78 mmol, 2 equiv), Et_3N (0.10 mL, 0.72 mmol, 3 equiv) and propylamine (0.2 mL, 2.4 mmol, 10.0 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v).Yield: 49 % (52 mg); white solid.

*Synthesis of (1R,4R)-4-((2-methoxy-4-methylbenzamido)methyl)-4-(thiophen-3-yl)cyclohexyl propylcarbamate (trans-**17**)*

Synthesized from *N*-(((*1R,4R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-4-methylbenzamide (*trans*-**14c**) (200 mg, 0.45 mmol, 1 equiv), 4-nitrophenyl chloroformate (167 mg, 0.9 mmol, 2 equiv), Et_3N (0.19 mL, 1.35 mmol, 3 equiv) and propylamine (1.0 mL, 9 mmol, 20.0 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v). 1Yield: 60 % (120 mg); white solid.

*Synthesis of (1R,4R)-4-((5-fluoro-2-methoxybenzamido)methyl)-4-(thiophen-3-yl)cyclohexyl propylcarbamate (trans-**18**)*

Synthesized from 5-fluoro-*N*-(((*1R,4R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxybenzamide (*trans*-**14a**) (90 mg, 0.248 mmol, 1 equiv), 4-nitrophenyl chloroformate (75 mg, 0.37 mmol, 1.5 equiv), Et_3N (0.10 mL, 0.74 mmol, 3 equiv) and propylamine (0.41 mL, 4.96 mmol, 20.0 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v). Yield: 49 % (44 mg); white solid.

*Synthesis of (1R,4R)-4-((furan-3-carboxamido)methyl)-4-(thiophen-3-yl)cyclohexyl methylcarbamate (trans-**19**)*

Synthesized from *N*-(((*1R,4R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (*trans*-**14g**) (141 mg, 0.46 mmol, 1 equiv), 4-nitrophenyl chloroformate (171 mg, 0.92 mmol, 2 equiv), Et_3N (0.19 mL, 1.39 mmol, 3 equiv) and methylamine (143.40 mg, 4.62

mmol, 10 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v). Yield: 40 % (67 mg); white solid.

*Synthesis of (1R,4R)-4-((furan-3-carboxamido)methyl)-4-(thiophen-3-yl)cyclohexyl propylcarbamate (trans-**20**)*

Synthesized from *N*-(((*1R,4R*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)furan-3-carboxamide (*trans*-**14g**) (270 mg, 0.69 mmol, 1 equiv), 4-nitrophenyl chloroformate (256 mg, 1.38 mmol, 2 equiv), Et_3N (0.17 mL, 2.07 mmol, 3 equiv) and propylamine (0.97 mL, 6.91 mmol, 10 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v). Yield: 54 % (147 mg); white solid.

*Synthesis of (1S,4S)-4-((2-methoxy-4-methylbenzamido)methyl)-4-(thiophen-3-yl)cyclohexyl propylcarbamate (cis-**21**)*

Synthesized from *N*-(((*1S,4S*)-4-hydroxy-1-(thiophen-3-yl)cyclohexyl)methyl)-2-methoxy-4-methylbenzamide (*cis*-**14c**) (164 mg, 0.37 mmol, 1 equiv), 4-nitrophenyl chloroformate (137 mg, 0.75 mmol, 2 equiv), Et_3N (0.089 mL, 1.11 mmol, 3 equiv) and propylamine (1.04 mL, 7.4 mmol, 20.0 equiv) via general procedure D. Column chromatography, DCM/MeOH = 50/1 (v/v). Yield: 59 % (97 mg); white solid.

Compound ID	^{1}H NMR (δ, ppm)
5	(400 MHz, $CDCl_3$): δ 2.15 – 2.37 (m, 6H), 2.41 – 2.61 (m, 2H), 3.63 (s, 6H), 6.97 (dd, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 1H), 7.33 (dd, J_1 = 3.0 Hz, J_2 = 1.5 Hz, 1H), 7.40 (dd, J_1 = 5.1 Hz, J_2 = 3.0 Hz, 1H)
6	(400 MHz, DMSO): δ 2.17 – 2.27 (m, 1H), 2.29 – 2.37 (m, 1H), 2.42 – 2.48 (m, 1H), 2.55 – 2.65 (m, 2H), 2.71 (dd, J_1 = 15.8 Hz, J_2 = 1.0 Hz, 1H), 2.94 (d, J = 15.8 Hz, 1H), 3.75 (s, 3H), 7.31 (dd, J_1 = 5.0 Hz, J_2 = 1.5 Hz, 1H), 7.63 (dd, J_1 = 2.9 Hz, J_2 = 1.5 Hz, 1H), 7.65 (dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 1H).
7	(400 MHz, $CDCl_3$): δ 2.20 – 2.31 (m, 2H), 2.51 – 2.61 (m, 4H), 2.80 – 2.93 (m, 2H), 7.16 (dd, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 1H), 7.36 (dd, J_1 = 3.0 Hz, J_2 = 1.5 Hz, 1H), 7.42 (dd, J_1 = 5.1 Hz, J_2 = 3.0 Hz, 1H).
8	(400 MHz, $CDCl_3$): δ 1.80 – 1.89 (m, 2H), 2.01 – 2.18 (m, 4H), 2.18 – 2.26 (m, 2H), 3.93 – 3.98 (m, 2H), 3.98 – 4.03 (m, 2H), 7.15 (dd, J_1 = 5.1 Hz, J_2 = 1.5 Hz, 1H), 7.30 (dd, J_1 = 3.0 Hz, J_2 = 1.5 Hz, 1H), 7.35 (dd, J_1 = 5.1 Hz, J_2 = 3.0 Hz, 1H).
10	(400 MHz, $CDCl_3$): δ 0.96 (brs, 2H), 1.55 – 1.70 (m, 4H), 1.70 – 1.79 (m, 2H), 2.09 – 2.16 (m, 2H), 2.68 (s, 2H), 3.88 – 3.97 (m, 4H), 7.01 (dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, 1H), 7.03 (dd, J_1 = 3.0 Hz, J_2 = 1.4 Hz, 1H), 7.31 (dd, J_1 = 5.0 Hz, J_2 = 3.0 Hz, 1H).
12a	(400 MHz, DMSO): δ 7.80 (1H, t, J = 5.8 Hz), 7.59 (1H, dd, J = 5.0, 2.9 Hz), 7.55 (1H, dd, J = 9.5, 3.4 Hz), 7.40 (1H, dd, J = 2.9, 1.4 Hz,), 7.33 (1H, ddd, J = 9.1, 7.8, 3.4 Hz), 7.20 (1H, dd, J = 5.0, 1.3 Hz), 7.15 (1H, dd, J = 9.2, 4.3 Hz), 3.88 – 3.79 (4H, m), 3.76 (3H, s), 3.47 (2H, d, J = 5.9 Hz), 2.08 – 2.00 (2H, m,), 1.83 – 1.74 (2H, m), 1.68 – 1.57 (2H, m), 1.48 – 1.39 (2H, m).

Compound ID	^{1}H NMR (δ, ppm)
12b	(400 MHz, DMSO) δ 7.74 – 7.69 (1H, m), 7.66 (1H, d, *J* = 1.9 Hz,), 7.58 (1H, dd, *J* = 4.9, 2.9 Hz), 7.39 (1H, d, *J* = 1.5 Hz), 7.26 (1H, dd, *J* = 8.3, 2.0 Hz), 7.20 (1H, d, *J* = 5.0 Hz), 7.00 (1H, d, *J* = 8.4 H), 3.87 – 3.80 (4H, m), 3.72 (3H, s), 3.47 (2H, d, *J* = 5.8 Hz), 2.25 (3H, s), 2.07 – 1.99 (2H, m), 1.83 – 1.74 (2H, m), 1.68 – 1.60 (2H, m), 1.51 – 1.39 (2H, m).
12c	(400 MHz, DMSO) δ 7.77 (1H, d, *J* = 7.9 Hz), 7.64 (1H, brs), 7.58 (1H, d, *J* = 2.9 Hz), 7.39 (1H, brs), 7.20 (1H, d, *J* = 4.6 Hz), 6.93 (1H, brs), 6.85 (1H, d, *J* = 7.9 Hz), 3.89 – 3.79 (4H, m), 3.74 (3H, s), 3.47 (2H, d, *J* = 5.1 Hz), 2.32 (3H, s), 2.07 – 1.98 (2H, m), 1.84 – 1.72 (2H, m), 1.69 – 1.58 (2H, m), 1.53 – 1.38 (2H, m).
12d	(400 MHz, DMSO) δ 8.02 (1H, d, *J* = 3.6 Hz), 7.59 (1H, dd, *J* = 5.0, 2.9 Hz), 7.38 (1H, dd, *J* = 2.9, 1.3 Hz), 7.18 (1H, dd, *J* = 5.0, 1.3 Hz), 7.13 (1H, t, *J* = 5.8 Hz), 6.75 (1H, d, *J* = 3.6 Hz), 3.87 – 3.80 (4H, m), 3.74 (3H, s), 3.42 (2H, d, *J* = 5.9 Hz), 2.07 – 1.99 (2H, m), 1.79 – 1.69 (2H, m), 1.67 – 1.59 (2H, m), 1.47 – 1.38 (2H, m).
12e	(400 MHz, DMSO) δ 7.51 (1H, dd, *J* = 5.0, 2.9 Hz), 7.28 (1H, dd, *J* = 2.9, 1.3 Hz), 7.11 (1H, dd, *J* = 5.0, 1.3 Hz), 7.04 (1H, t, *J* = 6.0 Hz), 3.82 (4H, dd, *J* = 14.3, 5.1 Hz), 3.34 (2H, d, *J* = 5.5 Hz), 3.13 (3H, s), 1.99 – 1.90 (2H, m), 1.77 – 1.65 (4H, m), 1.62 – 1.51 (4H, m), 1.44 – 1.37 (6H, m).
12f	(400 MHz, DMSO) δ 7.86 (1H, d, *J* = 8.8 Hz), 7.59 (1H, dd, *J* = 5.0, 2.9 Hz), 7.54 (1H, t, *J* = 5.6 Hz), 7.39 (1H, dd, *J* = 2.8, 1.3 Hz), 7.20 (1H, dd, *J* = 5.0, 1.2 Hz), 6.63 (1H, d, *J* = 2.3 Hz), 6.55 (1H, dd, *J* = 8.3, 2.3 Hz), 3.85 (4H, dd, *J* = 12.9, 7.9 Hz), 3.80 (3H, s), 3.75 (3H, s), 3.47 (2H, d, *J* = 5.7 Hz), 2.07 – 1.99 (2H, m), 1.81 – 1.72 (2H, m), 1.68 – 1.61 (2H, m), 1.48 – 1.39 (2H, m).

Table S3. Spectral data of compounds **5-8**, **10** and **12a-i**

Compound ID	^{1}H NMR (δ, ppm)
12g	(400 MHz, DMSO) δ 8.15 (1H, dd, J = 1.5, 0.7 Hz), 7.95 (1H, brs), 7.85 (1H, t, J = 6.4 Hz), 7.69 (1H, t, J = 1.7 Hz), 7.49 (1H, dd, J = 5.0, 2.9 Hz), 7.31 (1H, dd, J = 2.9, 1.3 Hz), 7.11 (1H, dd, J = 5.0, 1.3 Hz), 6.82 (1H, dd, J = 1.8, 0.7 Hz), 3.81 (4H, dd, J = 15.5, 5.3 Hz), 3.23 (2H, d, J = 6.4 Hz), 2.09 – 1.98 (2H, m), 1.84 – 1.72 (2H, m), 1.64 – 1.53 (2H, m), 1.42 – 1.32 (2H,m).
12h	(400 MHz, DMSO) δ 7.93 – 7.82 (2H, m), 7.70 – 7.62 (1H, m), 7.54 (1H, dd, J = 4.8, 2.9 Hz), 7.20 (2H, dd, J = 11.7, 6.7 Hz), 7.09 (2H, t, J = 7.8 Hz), 4.16 – 4.05 (5H, m), 3.89 – 3.78 (4H, m), 3.52 (2H, d, J = 6.0 Hz), 2.10 – 1.95 (2H,m), 1.86 – 1.74 (2H, m), 1.71 – 1.62 (2H, m), 1.49 – 1.39 (2H, m).
12i	(400 MHz, DMSO) δ 8.02 (1H, d, J = 3.6 Hz), 7.59 (1H, dd, J = 5.0, 2.9 Hz), 7.38 (1H, dd, J = 2.9, 1.3 Hz), 7.18 (1H, dd, J = 5.0, 1.3 Hz), 7.13 (1H, t, J = 5.8 Hz), 6.75 (1H, d, J = 3.6 Hz), 3.88 – 3.84 (2H, m), 3.84 – 3.79 (2H, m), 3.74 (3H, s), 3.42 (2H, d, J = 5.9 Hz), 2.07 – 1.99 (2H, m), 1.79 – 1.69 (2H, m), 1.68 – 1.59 (2H, m), 1.48 – 1.38 (2H, m).

Compound ID	^{1}H NMR (400 MHz, DMSO-d_6, TMS) (δ, ppm)	^{13}C NMR (100 MHz, DMSO-d_6) (δ, ppm)	HRMS (ESI+)	HPLC purity at
13a	δ 7.88 (1H, t, J = 5.9 Hz, CONHCH$_2$), 7.63 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.54 (1H, dd, J_1 = 2.7 Hz, J_2 = 1.0 Hz, H-18), 7.51 (1H, d, J = 3.3 Hz, H-14), 7.36 – 7.30 (1H, m, H-12), 7.30 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-16), 7.14 (dd, J_1 = 9.1 Hz, J_2 = 4.2 Hz, H-11), 3.75 (3H, s, H-15', H-15'', H-15'''), 3.59 (2H, d, J = 6.0 Hz, H-7', H-7''), 2.42 – 2.27 (4H, m, H$_e$-2,6, H$_e$-3,5), 2.26 – 2.13 (2H, m, H$_a$-3,5), 2.09 – 1.92 (2H, m, H$_a$-2,6).	δ 210.14 (C-4), 163.36 (d, J = 1.6 Hz, C-8), 156.06 (d, J = 237.0 Hz, C-13), 153.38 (d, J = 1.5 Hz, C-10), 144.65 (C-17), 126.72 (C-19), 126.60 (C-16), 123.24 (d, J = 6.5 Hz, C-9), 121.97 (C-18), 118.73 (d, J = 23.1 Hz, C-12), 116.67 (d, J = 24.8 Hz. C-14), 113.91 (d, J = 7.7 Hz, C-11), 56.47 (C-15),	calcd 362.1221 found 362.1218	95.31 % (t_R = 4.833 min)
13b	δ 7.80 (1H, t, J = 5.9 Hz, CONHCH$_2$), 7.63 (2H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-14, H-19), 7.52 (1H, dd, J_1 = 2.9, J_2 = 1.4 Hz, H-18), 7.29 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-16), 7.28 – 7.23 (1H, m, H-12), 6.99 (1H, d, J = 8.5 Hz, H-11), 3.72 (3H, s, H-15', H-15'', H-15'''), 3.61 (2H, d, J = 6.0 Hz, H-7', H-7''), 2.40 – 2.26 (4H, m, H$_e$-3,5, H$_e$-2,6), 2.25 (3H, s, H-20', H-20'', H-20'''), 2.23 – 2.14 (2H, m, H$_a$-3,5), 2.08 – 1.91 (2H, m, H$_a$-2,6).	δ 210.20 (C-4), 164.53 (C-8), 155.07 (C-10), 144.85 (C-17), 132.85 (C-12), 131.16 (C-14), 129.45 (C-13), 126.71 (C-19), 126.59 (C-16), 121.89 (C-18), 121.24 (C-9), 112.04 (C-11), 55.86 (C-15), 48.28 (C-7), 40.59 (C-1), 37.36 (C-3,5), 33.27 (C-2,6), 19.91 (C-20)	calcd 358.1471; found 358.1468	99.50 %(tR = 5.153 min)
13c	δ 7.76 (1H, d, J = 7.9 Hz, H-14), 7.72 (1H, t, J = 5.8 Hz, CONHCH2), 7.64 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.52 (1H, dd, J_1 = 2.8 Hz, J_2 = 1.4 Hz, H-18), 7.29 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-16), 6.93 (1H, s, H-11), 6.87 – 6.79 (1H, m, H-13), 3.74 (3H, s, H-15', H-15'', H-15'''), 3.61 (2H, d, J = 5.9 Hz, H-7', H-7''), 2.32 (3H, s, H-20', H-20'', H-20'''), 2.41 – 2.26 (4H, m, He-2,6, He-3,5), 2.25 – 2.14 (2H, m, Ha-3,5), 2.08 – 1.94 (2H, m, Ha-2,6).	δ 210.21 (C-4), 164.36 (C-8), 157.06 (C-10), 144.87 (C-17), 143.02 (C-12), 131.00 (C-14), 126.74 (C-19), 126.60 (C-16), 121.90 (C-18), 121.40 (C-13), 118.69 (C-9), 112.61 (C-11), 55.78 (C-15), 48.26 (C-7), 40.55 (C-1), 37.35 (C-3,5), 33.28 (C-2,6), 21.19 (C-20).	calcd 358.1471; found 358.1468	99.50 %(tR = 5.153 min)

13d	δ 8.02 (1H, d, J = 3.6 Hz, H-12), 7.64 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-17), 7.52 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-16), 7.28 (dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-14), 7.21 (1H, t, J = 5.7 Hz, CONHCH$_2$), 6.75 (1H, d, J = 3.6 Hz, H-11), 3.74 (3H, s, H-13', H-13'', H-13'''), 3.56 (2H, d, J = 6.0 Hz, H-7', H-7''), 2.38 – 2.25 (4H, m, H$_e$-2,6, H$_e$-3,5), 2.24 – 2.13 (2H, m, H$_a$-3,5), 2.05 – 1.93 (2H, m, H$_a$-2,6).	δ 210.11 (C-4), 160.56 (C-8), 154.21 (C-10), 144.48 (C-15), 131.60 (C-12), 126.80 (C-17), 126.52 (C-14), 126.35 (C-9), 122.06 (C-16), 99.93 (C-11), 58.13 (C-13), 47.72 (C-7), 40.44 (C-1), 37.30 (C-3,5), 33.20 (C-2,6)	Calcd 350.0879; found 350.0877	98.20 % (t_R = 4.637 min)
13e	δ 7.57 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.44 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-18), 7.22 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-16), 7.19 (1H, t, J = 6.2 Hz, CONHCH$_2$), 3.57 – 3.51 (1H, m, H-10), 3.40 (1H, dd, J_1 = 13.3 Hz, J_2 = 6.6 Hz, H-7'), 3.20 (1H, dd, J_1 =13.3 Hz, J_2 = 5.9 Hz, H-7''), 3.10 (3H, s, H-15', H-15'', H-15'''), 2.36 – 2.31 (1H, m, H-9), 2.31 – 2.10 (6H, m, H$_e$-2,6, H$_a$-3,5, H$_e$-3,5), 2.02 – 1.90 (2H, m, H$_a$-2,6), 1.91 – 1.80 (1H, m, H-11$_e$), 1.72 – 1.61 (1H, m, H-14$_e$), 1.60 – 1.49 (1H, m, H$_e$-13), 1.45 – 1.34 (2H, m, H-12$_e$, H$_a$-14), 1.34 – 1.24 (2H, m, H$_a$-11, H$_a$-12), 1.24 – 1.13 (1H, m,	δ 210.36 (C-4), 172.86 (C-8), 144.92 (C-17), 126.61 (C-16), 126.40 (C-19), 121.62 (C-18), 77.18 (C-10), 55.40 (C-15), 47.60 (C-7), 46.19 (C-9), 41.09 (C-1), 37.47 (C-3,5), 33.05 (C-2,6), 27.00 (C-11), 23.91 (C-14), 23.87 (C-13), 20.44 (C-12).	calcd 350.1784; found 350.1783	98.90 % (t_R = 4.890 min)
13f	δ 7.86 (1H, d, J = 8.7 Hz, H-14), 7.66 – 7.62 (1H, m, H-19), 7.61 (1H, t, J = 5.8 Hz, CONHCH2), 7.52 (1H, dd, J_1 = 2.7 Hz, J_2 = 1.4 Hz, H-18), 7.29 (1H, dd, J_1 = 4.9 Hz, J_2 = 1.4 Hz, H-16), 6.62 (1H, d, J = 7.5 Hz, H-13), 6.60 (1H, s, H-11), 3.79 (3H, s, H-15', H-15'', H-15'''), 3.74 (3H, s, H-20', H-20'', H-20'''), 3.61 (2H, d, J = 5.7 Hz, H-7', H-7''), 2.42 – 2.25 (4H, m, He-3,5, He-2,6), 2.25 – 2.09 (2H, m, Ha-3,5), 2.07 – 1.92 (2H, m, Ha-2,6).	δ 210.19 (C-4), 164.04 (C-8), 162.92 (C-10), 158.58 (C-12), 144.92 (C-17), 132.69 (C-14), 126.76 (C-19), 126.57 (C-16), 121.88 (C-18), 113.93 (C-9), 105.83 (C-13), 98.47 (C-11), 55.96 (C-20), 55.50 (C-15), 48.19 (C-7), 40.50 (C-1), 37.35 (C-3,5), 33.30 (C-2,6).	calcd 374.1421; found 374.1421.	99.68 % (t_R = 4.910 min).

13g	δ 8.15 (1H, dd, J_1 = 1.5 Hz, J_2 = 0.7 Hz, H-12), 7.91 (1H, t, J = 6.4 Hz, CONH), 7.69 (1H, t, J = 1.7 Hz, H-11), 7.54 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.47 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-13), 7.22 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-15), 6.81 (1H, dd, J_1 = 1.8 Hz, J_2 = 0.7 Hz, H-10), 3.37 (2H, d, J = 6.4 Hz, H-7', H-7''), 2.40 – 2.29 (2H, m, He-2,6), 2.29 – 2.10 (4H, m, Ha-3,5, He-3,5), 2.04 – 1.92 (2H, m, Ha-2,6).	δ 210.30 (C-4), 161.87 (C-8), 145.05 (C-12), 144.32 (C-11), 143.78 (C-14), 126.76 (C-15), 126.23 (C-16), 122.67 (C-9), 121.81 (C-13), 109.17 (C-10), 48.43 (C-7), 41.55 (C-1), 37.50 (C-3,5), 33.14 (C-2,6).	calcd 304.1002 found 304.0998	96.03 % (t_R = 3.547 min).
13h	δ 7.96 (1H, t, J = 6.1 Hz, CONH), 7.82 (1H, dd, J_1 = 7.7 Hz, J_2 = 1.8 Hz, H-14), 7.60 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.50 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-16), 7.44 (1H, ddd, J_1 = 8.4 Hz, J_2 = 7.3 Hz, J_3 = 1.9 Hz, H-12), 7.28 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-18), 7.10 (1H, d, J = 8.0 Hz, H-11), 7.05 – 6.97 (1H, m, H-13), 4.07 (1H, q, J = 7.0 Hz, H-15', H-15''), 3.63 (2H, d, J = 6.2 Hz, H-7', H-7''), 2.41 – 2.25 (4H, m, He-2,6, He-3,5), 2.25 – 2.15 (2H, m, Ha-3,5), 2.12 – 1.99 (2H, m, Ha-2,6), 1.16 (1H, t, J = 7.0 Hz, H-20', H-20'', H-20''')	δ 210.17 (C-4), 164.80 (C-8), 156.23 (C-10), 145.04 (C-17), 132.47 (C-12), 130.90 (C-14), 126.64 (C-18), 126.57 (C-19), 122.06 (C-9), 121.75 (C-16), 120.55 (C-13), 112.88 (C-11), 64.20 (C-15), 47.91 (C-7), 40.89 (C-1), 37.38 (C-3,5), 33.20 (C-2,6), 14.26 (C-20).	calcd 358.1471 found 358.1467	96.29 % (t_R = 5.103 min)
13i	δ 8.02 (1H, d, J = 3.6 Hz, H-12), 7.64 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-17), 7.52 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-16), 7.28 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-14), 7.21 (1H, t, J = 5.7 Hz, CONHCH$_2$), 6.75 (1H, d, J = 3.6 Hz, H-11), 3.74 (3H, s, H-13', H-13'', H-13'''), 3.56 (2H, d, J = 6.0 Hz, H-7', H-7''), 2.38 – 2.25 (4H, m, H$_e$-2,6, H$_e$-3,5), 2.24 – 2.13 (2H, m, H$_a$-3,5), 2.05 – 1.93 (2H, m, H$_a$-2,6).	δ 210.11 (C-4), 160.56 (C-8), 154.21 (C-10), 144.48 (C-15), 131.60 (C-12), 126.80 (C-17), 126.52 (C-14), 126.35 (C-9), 122.06 (C-16), 99.93 (C-11), 58.13 (C-13), 47.72 (C-7), 40.44 (C-1), 37.30 (C-3,5), 33.20 (C-2,6).	calcd 350.0879 found 350.0877	98.20 % (t_R = 4.637 min)

trans-**14a**	δ 7.76 (1H, t, *J* = 5.7 Hz, CONHCH2), 7.57 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.54 (1H, dd, J_1 = 9.5 Hz, J_2 = 3.4 Hz, H-14), 7.37 (1H, dd, J_1 = 2.8 Hz, J_2 = 1.3 Hz, H-18), 7.35 – 7.26 (1H, m, H-12), 7.16 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-16), 7.13 (1H, dd, J_1 = 4.3 Hz, J_2 = 2.0 Hz, H-11), 4.41 (1H, d, *J* = 4.5 Hz, OH), 3.77 (3H, s, H-15', H-15'', H-15'''), 3.51 – 3.41 (1H, m, H-4), 3.37 (2H, d, *J* = 5.8 Hz, H-7'. H-7''), 2.15 (2H, d, J = 13.6 Hz, He-2,6), 1.73 – 1.62 (2H, m, He-3,5), 1.56 – 1.43 (2H, m, Ha-2,6), 1.26 – 1.13 (2H, m, Ha-3,5)	δ 163.09 (d, *J* = 1.8 Hz, C-8), 156.05 (d, *J* = 236.9 Hz, C-13), 153.40 (d, *J* = 1.8 Hz, C-10), 145.64 (C-17), 126.76 (C-16), 126.24 (C-19), 123.18 (d, *J* = 6.6 Hz, C-9), 121.71 (C-18), 118.74 (d, *J* = 23.1 Hz, C-12), 116.67 (d, *J* = 24.7 Hz, C-14), 113.98 (d, *J* = 7.8 Hz, C-11), 68.40 (C-4), 56.54 (C-15), 50.62 (C-7), 40.76 (C-1), 31.65 (C-2,6), 31.01 (C-3,5)	calcd 364.1377 found 364.1374	95.13 % (t_R = 4.543 min)
cis-**14a**	δ 7.69 (1H, t, *J* = 5.6 Hz, CONHCH2), 7.59 (1H, dd, J_1 = 8.9 Hz, J_2 = 2.7 Hz, H-14), 7.56 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.3 Hz, H-19), 7.36 – 7.28 (2H, m, H-12, H-18), 7.20 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-16), 7.13 (dd, J_1 = 9.2 Hz, J_2 = 4.3 Hz, H-11), 4.50 (1H, d, *J* = 4.0 Hz, OH), 3.70 (3H, s, H-15', H-15'', H-15'''), 3.58 (2H, d, *J* = 5.7 Hz, H-7', H-7''), 3.55 – 3.46 (1H, m, H-4), 2.02 – 1.85 (2H, m, H_e-2,6), 1.73 – 1.62 (2H, m, H_a-2,6), 1.61 – 1.44 (4H, m, H_a-3,5,	δ 162.90 (d, *J* = 1.4 Hz, C-8), 156.10 (d, *J* = 237.0 Hz, C-13), 153.47 (d, *J* = 1.4 Hz, C-10), 147.66 (C-17), 126.52 (C-16), 126.19 (C-19), 122.76 (d, *J* = 6.4 Hz, C-9), 120.77 (C-18), 118.92 (d, *J* = 23.1 Hz, C-12), 116.79 (d, *J* = 24.8 Hz, C-14), 114.06 (d, *J* = 7.8 Hz, C-11), 66.67 (C-4), 56.47 (C-15), 46.95 (C-7),	calcd 364.1377 found 364.1370	95.11 % (tR = 4.890 min)
trans-**14b**	δ 7.68 (1H, t, *J* = 5.7 Hz, CONH), 7.65 (1H, d, *J* = 2.1 Hz, H-14), 7.57 (1H, dd, *J*1 = 5.0 Hz, *J*2 = 2.9 Hz, H-19), 7.36 (1H, dd, *J*1 = 2.9 Hz, *J*2 = 1.4 Hz, H-16), 7.27 – 7.23 (1H, m, H-12), 7.16 (1H, dd, *J*1 = 5.0 Hz, *J*2 = 1.3 Hz, H-18), 7.00 (1H, d, *J* = 8.5 Hz, H-11), 4.40 (1H, d, *J* = 4.5 Hz, OH), 3.74 (3H, s, OCH3), 3.52 – 3.41 (1H, m, H-4), 3.37 (2H, d, *J* = 5.8 Hz, H-7', H-7''), 2.25 (3H, s, H-20', H-20'', H-20'''), 2.14 (2H, d, *J* = 13.6 Hz, He-2,6), 1.73 – 1.63 (2H, m, He-3,5), 1.57 – 1.42 (2H, m, Ha-2,6), 1.25 – 1.11 (2H,	δ 164.30 (C-8), 155.09 (C-10), 145.80 (C-17), 132.84 (C-12), 131.21 (C-14), 129.44 (C-13), 126.76 (C-18), 126.23 (C-19), 121.65 (C-16), 121.18 (C-9), 112.07 (C-11), 68.40 (C-4), 55.92 (C-15), 50.54 (C-7), 40.73 (C-1), 31.65 (C-2,6), 31.00 (C-3,5), 19.93 (C-20).	calcd 360.1628 found 360.1622	99.78 % (tR = 4.860 min)

cis-**14b**	δ 7.71 (1H, d, *J* = 2.3 Hz, H-14), 7.62 (1H, t, *J* = 5.6 Hz, CONH), 7.56 (1H, dd, *J*1 = 5.0 Hz, *J*2 = 2.9 Hz, H-19), 7.32 (1H, dd, *J*1 = 2.9 Hz, *J*2 = 1.3 Hz, H-16), 7.28 – 7.23 (1H, m, H-12), 7.20 (1H, dd, *J*1 = 5.0 Hz, *J*2 = 1.3 Hz, H-18), 6.98 (1H, d, *J* = 8.4 Hz, H-11), 4.50 (1H, d, *J* = 4.0 Hz, OH), 3.67 (3H, s, OCH3), 3.58 (2H, d, *J* = 5.6 Hz, H-7', H-7''), 3.55 – 3.45 (1H, m, H-4), 2.25 (3H, s, H-20', H-20'', H-20'''), 1.97 – 1.87 (2H, m, He-2,6), 1.71 – 1.62 (2H, m, Ha-2,6), 1.61 – 1.44 (4H, m, Ha-	δ 164.08 (C-8), 155.14 (C-10), 147.85 (C-17), 132.97 (C-12), 131.35 (C-14), 129.50 (C-13), 126.50 (C-18), 126.16 (C-19), 120.74 (C-16), 120.67 (C-9), 112.11 (C-11), 66.79 (C-4), 55.84 (C-15), 46.72 (C-7), 40.73 (C-1), 30.54 (C-2,6), 30.24 (C-3,5), 19.93	calcd 360.1628 found 360.1623.	95.31 % (tR = 5.257 min)
trans-**14c**	δ 7.76 (1H, d, J = 7.9 Hz, H-14), 7.61 (1H, t, J = 5.6 Hz, CONHCH2), 7.58 (1H, dd, J1 = 5.0 Hz, J2 = 2.8 Hz, H-19), 7.36 (1H, dd, J1 = 2.9 Hz, J2 = 1.4 Hz, H-18), 7.16 (1H, dd, J1 = 5.0 Hz, J2 = 1.4 Hz, H-16), 6.93 (1H, d, J = 1.4 Hz, H-11), 6.84 (1H, d, J = 7.9 Hz, H-13), 4.40 (1H, d, J = 4.5 Hz, OH), 3.76 (3H, s, H-15', H-15'', H-15'''), 3.52 – 3.42 (1H, m, H-4), 3.17 (2H, d, J = 5.2 Hz, H-7', H-7''), 2.32 (3H, s, H-20', H-20'', H-20'''), 2.14 (2H, d, J = 13.7 Hz, He-2,6), 1.67 (2H, dd, J1 = 12.7 Hz, J2 = 3.4 Hz, He-3,5), 1.57 – 1.37 (2H, m, Ha-2,6), 1.24 –	δ 164.13 (C-8), 157.06 (C-10), 145.80 (C-17), 142.96 (C-12), 131.04 (C-14), 126.74 (C-16), 126.24 (C-19), 121.64 (C-18), 121.39 (C-13), 118.66 (C-9), 112.60 (C-11), 68.38 (C-4), 55.81 (C-15), 50.54 (C-7), 40.68 (C-1), 31.67 (C-2,6), 30.99 (C-3,5), 21.18 (C-20)	calcd 360.1628; found 360.1625	100 % (t_R =4.853 min)
cis-**14c**	δ 7.80 (1H, d, J = 7.9 Hz, H-14), 7.57 (1H, dd, J1 = 5.0 Hz, J2 = 2.9 Hz, H-19), 7.55 (1H, t, J = 5.6 Hz, CONHCH2), 7.32 (1H, dd, J1 = 2.9 Hz, J2 = 1.3 Hz, H-18), 7.20 (1H, dd, J1 = 5.0 Hz, J2 = 1.3 Hz, H-16), 6.91 (1H, s, H-11), 6.88 – 6.78 (1H, m, H-13), 4.50 (1H, d, J = 4.0 Hz, OH), 3.69 (3H, s, H-15', H-15'', H-15'''), 3.58 (2H, d, J = 5.6 Hz, H-7', H-7''), 3.54 – 3.45 (1H, m, H-4), 2.31 (3H, s, H-20', H-20'', H-20'''), 1.97 – 1.86 (2H, m, He-2,6), 1.70 – 1.61 (2H, m, Ha-2,6), 1.61 – 1.43 (4H, m, Ha-	δ 163.96 (C-8), 157.08 (C-10), 147.89 (C-17), 143.08 (C-12), 131.16 (C-14), 126.49 (C-16), 126.17 (C-19), 121.44 (C-13), 120.66 (C-18), 118.34 (C-9), 112.62 (C-11), 66.81 (C-4), 55.72 (C-15), 46.62 (C-7), 39.85 (C-1), 30.56 (C-2,6), 30.25 (C-3,5), 21.17	calcd 360.1628; found 360.1624	95.42 % (t_R = 5.283 min)

trans-**14d**	δ 8.00 (1H, d, J = 3.6 Hz, H-12), 7.58 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-17), 7.35 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.3 Hz, H-16), 7.15 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-14), 7.10 (1H, t, J = 5.7 Hz, CONHCH$_2$), 6.74 (1H, d, J = 3.6 Hz, H-11), 4.40 (1H, d, J = 4.2 Hz, OH), 3.76 (3H, s, OCH$_3$), 3.51 – 3.41 (1H, m, H-4), 3.32 (2H, d, J = 5.9 Hz, H-7'. H-7''), 2.14 (2H, d, J = 13.6 Hz, H$_e$-2,6), 1.75 – 1.62 (2H, m, H$_e$-3,5), 1.53 – 1.40 (2H, m, H$_a$-2,6), 1.25 – 1.09	δ 160.42 (C-8), 154.20 (C-10), 145.44 (C-15), 131.49 (C-12), 126.66 (C-14), 126.47 (C-17), 126.30 (C-9), 121.77 (C-16), 99.91 (C-11), 68.36 (C-4), 58.14 (C-13), 49.90 (C-7), 40.60 (C-1), 31.64 (C-2,6), 30.95 (C-3,5)	calcd 352.1036 found 352.1032	99.85 % (t_R = 4.323 min)
cis-**14d**	δ 8.02 (1H, d, J = 3.6 Hz, H-12), 7.57 (1H, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-17), 7.31 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.3 Hz, H-16), (1H, dd, J_1 = 5.0, J_2 = 1.4 Hz, H-14), 7.04 (1H, t, J = 5.6 Hz, CONHCH$_2$), 6.73 (1H, d, J = 3.6 Hz, H-11), 4.61 – 4.41 (1H, m, OH), 3.69 (3H, s, H-13', H-13'', H-13'''), 3.52 (2H, d, J = 5.7 Hz, H-7'. H-7''), 3.53 – 3.44 (1H, m, H-4), 1.97 – 1.84 (2H, m, H$_e$-2,6), 1.71 – 1.60 (2H, m, H$_a$-2,6), 1.62 – 1.43 (4H, m, H$_a$-3,5, H$_e$-3,5)	δ 160.34 (C-8), 154.12 (C-10), 147.51 (C-15), 131.61 (C-12), 126.41 (C-14), 126.34 (C-17), 126.22 (C-9), 120.81 (C-16), 99.96 (C-11), 66.77 (C-4), 58.07 (C-13), 46.11 (C-7), 39.82 (C-1), 30.44 (C-2,6), 30.19 (C-3,5).	calcd 352.1036 found 352.1031	95.78 % (t_R = 4.793 min)
trans-**14g**	δ 1.06 – 1.19 (2H, m, H$_a$-3,5), 1.52 (2H, td, J_1 = 13.6 Hz, J_2 = 2.8 Hz, H$_a$-2,6), 1.62 – 1.69 (2H, m, H$_e$-3,5), 2.11 (2H, d, J = 13.1 Hz, H$_e$-2,6), 3.18 (2H, d, J = 6.4 Hz, H-7', H-7''), 3.32 – 3.41 (1H, m, H-4), 4.37 (1H, brs, OH), 6.81 (1H, dd, J_1 = 1.8 Hz, J_2 = 0.7 Hz, H-10), 7.09 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.3 Hz, H-15), 7.27 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.3 Hz, H-13), 7.47 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.68 (1H, t, J = 1.7 Hz, H-11), 7.79 (1H, t, J = 6.3 Hz, CONH), 8.15 (1H,	δ 31.32 (C-3,5), 31.70 (C-2,6), 41.89 (C-1), 50.03 (C-7), 68.90 (C-4), 109.19 (C-10), 121.36 (C-13), 122.82 (C-9), 125.67 (C-16), 126.90 (C-15), 143.75 (C-11), 144.94 (C-12), 145.63 (C-14), 161.72 (C-8).	calcd 306.1158 found 306.1152	98.58 % (t_R = 2.873 min)

cis-**14g**	δ 1.39 – 1.59 (4H, m, H_a-3,5, H_e-3,5), 1.63 – 1.74 (2H, m, H_a-2,6), 1.90 – 2.00 (2H, m, H_e-2,6), 3.31 (2H, d, *J* = 6.3 Hz, H-7', H-7''), 3.56 (1H, brs, H-4), 4.36 (1H, brs, OH), 6.76 – 6.79 (1H, m, H-10), 7.06 – 7.11 (1H, m, H-15), 7.20 – 7.22 (1H, m, H-13), 7.43 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.61 (1H, t, *J* = 6.0 Hz, H-11), 7.67 (1H, t, *J* = 1.6 Hz, CONH), 8.12 (1H, s, H-12).	δ 29.27 (C-2,6), 29.76 (C-3,5), 41.24 (C-1), 47.96 (C-7), 65.41 (C-4), 109.20 (C-10), 120.64 (C-13), 122.84 (C-9), 125.32 (C-16), 126.85 (C-15), 143.70 (C-11), 144.89 (C-12), 146.90 (C-14), 161.64 (C-8)	calcd 306.1158 found 306.1154	95.08 % (t_R = 3.423 min)
trans-**14i**	δ 7.37 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.28 (1H, d, *J* = 5.9 Hz, H-11), 7.10 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-13), 7.08 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.4 Hz, H-15), 6.65 (1H, t, *J* = 5.0 Hz, CONHCH$_2$), 6.48 (1H, d, *J* = 5.9 Hz, H-12), 3.89 (3H, s, H-17', H-17'', H-17'''), 3.72 (1H, tq, J_1 = 7.4 Hz, J_2 = 4.1 Hz, H-4), 3.47 (2H, d, *J* = 6.1 Hz, H-7', H-7''), 2.23 (2H, d, *J* = 13.8 Hz, H_e-2,6), 1.91 – 1.83 (2H, m, H_e-3,5), 1.68 – 1.56 (2H, m, H_a-2,6), 1.44 – 1.31 (2H, m, H_a-3,5)	δ 166.06 (C-10), 162.47 (C-8), 145.50 (C-14), 127.87 (C-11), 126.55 (C-15), 126.12 (C-16), 121.62 (C-13), 116.18 (C-9), 109.62 (C-12), 70.41 (C-4), 61.92 (C-17), 50.35 (C-7), 41.35 (C-1), 32.21 (C-2,6), 31.12 (C-3,5)	calcd 352.1036 found 352.1031	97.33 % (t_R = 4.280 min)
cis-**14i**	δ 7.36 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-16), 7.28 (1H, d, *J* = 5.9 Hz, H-11), 7.10 (1H, dd, J_1 = 5.1, J_2 = 1.4 Hz, H-15), 7.08 (1H, dd, J_1 = 2.9 Hz, J_2 = 1.4 Hz, H-13), 6.62 (1H, t, *J* = 4.7 Hz, CONHCH$_2$), 6.48 (1H, d, *J* = 5.9 Hz, H-12), 3.85 (3H, s, H-17', H-17'', H-17'''), 3.74 (1H, brs, H-4), 3.64 (2H, d, *J* = 6.0 Hz, H-7', H-7''), 2.10 – 2.00 (2H, m, H_e-2,6), 1.85 – 1.64 (6H, m, H_a-2,6, H_a-3,5, H_e-3,5)	δ 166.04 (C-10), 162.41 (C-8), 147.50 (C-14), 127.86 (C-11), 126.36 (C-15), 125.93 (C-16), 120.68 (C-13), 116.25 (C-9), 109.62 (C-12), 68.77 (C-4), 61.90 (C-17), 47.20 (C-7), 40.57 (C-1), 30.77 (C-2,6), 30.48 (C-3,5)	calcd 352.1036 found 352.1032	100 % (t_R = 4,757 min

trans-**15**	(CDCl$_3$): δ_H δ 8.20 (1H, dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, H-14), 7.65 (1H, t, J = 5.7 Hz, CONHCH$_2$), 7.44 – 7.37 (2H, m, H-12, H-19), 7.13 – 7.09 (2H, m, H-16, H-18), 7.08 – 7.01 (1H, m, H-13), 6.92 – 6.87 (1H, m, H-11), 4.93 – 4.83 (1H, m, OCONHCH$_2$), 4.76 – 4.64 (1H, m, H-4), 3.74 (3H, s, OCH$_3$), 3.60 (2H, d, J = 5.9 Hz, H-7', H-7''), 3.41 (2H, t, J = 5.8 Hz, H-23', H-23''), 3.30 (3H, s, H-24', H-24'', H-24'''), 3.24 (2H, q, J = 6.1 Hz, H-21', H-21''), 2.20 (2H, d, J = 14.2 Hz, H$_e$-2,6), 1.98 – 1.87 (2H, m, H$_e$-3,5), 1.80 – 1.66 (4H, m, H-22', H-22'', H$_a$-2,6), 1.49 (2H, q, J = 10.2 Hz, H$_a$-3,5)	(CDCl$_3$) for both confomers: δ_C 165.23 (C-8), 157.47 (C-10), 156.17 (C-20), 146.10 (C-17), 132.75 (C-12), 132.48 (C-14), 126.48 (C-18), 126.06 (C-19), 121.29 (C-9), 121.25 (C-16), 121.22 (C-13), 111.17 (C-11), 72.50 (C-4), 71.22 (C-23), 58.79 (C-24), 55.65 (C-15), 50.28 (C-7), 41.03 (C-1), 39.07 (C-21), 31.74 (C-2,6), 29.69 (C-22), 27.58 (C-3,5)	calcd 461.2105 found 461.2097	97.48 % (t_R = 5.477 min)
trans-**16**	(CDCl$_3$): δ 8.05 (1H, d, J = 3.7 Hz, H-10), 7.38 (1H, dd, J = 4.8, 3.0 Hz, H-16), 7.13 – 7.05 (3H, m, H-13, H-15, CONHCH$_2$), 6.26 (1H, d, J = 3.7 Hz, H-11), 4.76 – 4.65 (1H, m, H-4), 4.52 (1H, brs, OCONH), 3.76 (3H, s, H-21', H-21'', H-21'''), 3.52 (2H, d, J = 6.1 Hz, H-7', H-7''), 3.09 (2H, q, J = 6.6 Hz, H-18', H-18''), 2.19 (2H, d, J = 14.1 Hz, H$_e$-2,6), 1.92 (2H, d, J = 12.7 Hz, H$_e$-3,5), 1.70 (2H, t, J = 12.4 Hz, H$_a$-2,6), 1.46 (4H, dt, J_1 = 13.7 Hz, J_2 = 6.7 Hz, H$_a$-3,5, H-19', H-19''), 0.93 – 0.82 (3H, m, H-20', H-20'', H-	(CDCl$_3$) δ 161.6 (C-8), 156.18 (C-17), 154.65 (C-12), 145.74 (C-14), 132.04 (C-10), 126.57 (C-15), 126.39 (C-16), 126.08 (C-9), 121.41 (C-13), 98.49 (C-11), 72.46 (C-4), 57.90 (C-21), 49.55 (C-7), 42.66 (C-18), 41.01 (C-1), 31.67 (C-2,6), 27.57 (C-3,5), 23.28 (C-19), 11.29 (C-20)	calcd 437.1563 found 437.1556	95.39 % (t_R = 5.753 min)
trans-**17**	(CDCl$_3$): δ 8.07 (1H, d, J = 8.0 Hz, H-14), 7.61 (1H, t, J = 5.6 Hz, CONH), 7.40 – 7.34 (1H, m, H-19), 7.12 – 7.05 (2H, m, H-16, H-18), 6.88 – 6.81 (1H, m, H-13), 6.69 (1H, s, H-11), 4.79 – 4.65 (1H, m, H-4), 4.56 (1H, brs, OCONH), 3.72 (3H, s, H-15', H-15'', H-15'''), 3.58 (2H, d, J = 5.9 Hz, H-7', H-7''), 3.08 (2H, q, J = 6.5 Hz, H-22', H-22''), 2.35 (3H, s, H-20', H-20'', H-20'''), 2.18 (2H, d, J = 14.0 Hz, H$_e$-2,6), 1.99 – 1.85 (2H, m, H$_e$-3,5), 1.77 – 1.65 (2H, m, H$_a$-2,6), 1.55 – 1.37 (4H, m, H$_a$-3,5, H-23', H-23''), 0.87 (3H, t, J = 7.4 Hz, H-24', H-24'')	CDCl$_3$) δ 165.35 (C-8), 157.44 (C-21), 156.20 (C-10), 146.28 (C-17), 143.58 (C-12), 132.49 (C-14), 126.53 (C-16), 126.03 (C-19), 122.12 (C-13), 121.27 (C-18), 118.58 (C-9), 111.92 (C-11), 72.50 (C-4), 55.59 (C-15), 50.15 (C-7), 42.69 (C-22), 41.08 (C-1), 31.72 (C-2,6), 27.60 (C-3,5), 23.32 (C-23), 21.82 (C-20), 11.32 (C-24)	calcd 445.2156 found 445.2150	96.54 % (t_R = 6.110 min)

trans-**18**	(CDCl$_3$) δ 7.89 (1H, dd, J_1 = 9.6 Hz, J_2 = 3.3 Hz, H-14), 7.67 (1H, t, J = 5.6 Hz, CONH), 7.38 (1H, dd, J_1 = 4.7 Hz, J_2 = 3.0 Hz, H-19), 7.13 – 7.02 (3H, m, H-16, H-18, H-12), 6.83 (1H, dd, J_1 = 9.1 Hz, J_2 = 4.1 Hz, H-11), 4.77 – 4.65 (1H, m, H-4), 4.57 (1H, brs, OCONH), 3.71 (3H, s, H-15', H-15'', H-15'''), 3.58 (2H, d, J = 5.9 Hz, H-7', H-7''), 3.08 (2H, q, J = 6.5 Hz, H-21', H-21''), 2.18 (2H, d, J = 14.2 Hz, H$_e$-2,6), 1.96 – 1.86 (2H, m, H$_e$-3,5), 1.75 – 1.63 (2H, m, H$_a$-2,6), 1.55 – 1.38 (4H, m, H$_a$-3,5, H-22', H-22''), 0.87 (3H, t, J = 7.4 Hz, H-23', H-23'', H-23''').	(CDCl$_3$) δ 164.06 (d, J = 1.8 Hz, C-8), 157.17 (d, J = 239.8 Hz, C-13), 156.18 (C-20), 153.62 (d, J = 2.0 Hz, C-10), 146.04 (C-17), 126.44 (C-16), 126.19 (C-19), 122.74 (d, J = 6.7 Hz, C-9), 121.34 (C-18), 119.01 (d, J = 23.4 Hz, C-12), 118.77 (d, J = 25.0 Hz, C-14), 112.52 (d, J = 7.6 Hz, C-11), 72.40 (C-4), 56.28 (C-15), 50.34 (C-7), 42.69 (C-21), 40.99 (C-1), 31.74 (C-2,6), 27.56 (C-3,5), 23.31 (C-	calcd 449.1905 found 449.1900	96.53 % (t_R = 5.810 min)
trans-**19**	(CDCl$_3$) δ 1.38 – 1.52 (2H, m, H$_a$-3,5), 1.64 – 1.76 (2H, m, H$_a$-2,6), 1.86 – 1.95 (2H, m, H$_e$-3,5), 2.19 (2H, d, J = 14.0 Hz, H$_e$-2,6), 2.75 (3H, d, J = 4.7 Hz, H-18', H-18'', H-18'''), 3.45 (2H, d, J = 6.3 Hz, H-7', H-7''), 4.45 (1H, brs, OCONH), 4.66 – 4.78 (1H, m, H-4), 5.37 (1H, t, J = 6.0 Hz, CONH), 6.40 (1H, dd, J_1 = 1.9 Hz, J_2 = 0.8 Hz, H-10), 7.05 – 7.12 (2H, m, H-15, H-13), 7.37 – 7.43 (2H, m, H-16, H-11), 7.79 – 7.84 (1H, m, H-12).	(CDCl$_3$) δ 27.54 (C-3,5), 27.62 (C-18), 31.77 (C-2,6), 41.44 (C-1), 49.59 (C-7), 72.64 (C-4), 108.10 (C-10), 121.35 (C-13), 122.60 (C-9), 126.23 (C-15), 126.92 (C-16), 143.91 (C-11), 144.69 (C-12), 145.41 (C-14), 156.79 (C-17), 162.48 (C-8)	calcd 363.1373 found 363.1368	100 % (t_R = 3.863 min)
trans-**20**	(CDCl$_3$) δ 0.88 (3H, t, J = 7.4 Hz, H-20', H-20'', H-20'''), 1.41 – 1.52 (4H, m, H$_a$-3,5, H-19', H-19''), 1.62 – 1.75 (2H, m, H$_a$-2,6), 1.87 – 1.97 (2H, m, H$_e$-3,5), 2.18 (2H, d, J = 14.1 Hz, H$_e$-2,6), 3.09 (2H, q, J = 6.5 Hz, H-18', H-18''), 3.45 (2H, d, J = 6.3 Hz, H-7', H-7''), 4.53 (1H, brs, OCONH), 4.62 – 4.76 (1H, m, H-4), 5.39 (1H, t, J = 6.0 Hz, CONH), 6.41 (1H, dd, J_1 = 1.9 Hz, J_2 = 0.9 Hz, H-10), 7.04 – 7.11 (2H, m, H-15, H-13), 7.37 – 7.43 (2H, m, H-16, H-11), 7.78 – 7.83 (1H, m, H-12).	(CDCl$_3$) δ 11.28 (C-20), 23.26 (C-19), 27.58 (C-3,5), 31.73 (C-2,6), 41.43 (C-1), 42.66 (C-18), 49.61 (C-7), 72.49 (C-4), 108.11 (C-10), 121.32 (C-13), 122.54 (C-9), 126.22 (C-15), 126.81 (C-16), 143.84 (C-11), 144.67 (C-12), 145.34 (C-14), 156.16 (C-17), 162.50 (C-8)	calcd 391.1686 found 391.1679	98.90 % (t_R =4.747 min)

cis-**21**	($CDCl_3$) δ 8.09 (1H, d, J = 8.0 Hz, H-14), 7.61 (1H, t, J = 5.5 Hz, CONH), 7.37 (1H, dd, J_1 = 5.0 Hz, J_2 = 2.9 Hz, H-19), 7.10 (2H, t, J = 3.8 Hz, H-16, H-18), 6.89 – 6.83 (1H, m, H-13), 6.68 (1H, s, H-11), 4.77 – 4.69 (1H, m, H-4), 4.67 (1H, brs, OCONH), 3.68 (5H, d, J = 5.6 Hz, H-7', H-7'', H-15', H-15'', H-15'''), 3.13 (2H, q, J = 6.8 Hz, H-22', H-22''), 2.36 (3H, s, H-20', H-20'', H-20'''), 2.01 – 1.63 (6H, m, H_e-2,6), 1.52 (2H, p, J = 7.3 Hz, H-23', H-23''), 0.93 (3H, t, J = 7.4 Hz, H-24', H-24'', H-24''')	($CDCl_3$) δ 165.37 (C-8), 157.47 (C-21), 156.36 (C-10), 146.84 (C-17), 143.59 (C-12), 132.48 (C-14), 126.48 (C-16), 125.96 (C-19), 122.09 (C-13), 120.93 (C-18), 118.56 (C-9), 111.92 (C-11), 70.88 (C-4), 55.53 (C-15), 49.08 (C-7), 42.73 (C-22), 40.78 (C-1), 30.52 (C-2,6), 27.07 (C-3,5), 23.37 (C-23), 21.82 (C-20), 11.39 (C-24)	calcd 445.2156 found 445.2149	95.00 % (t_R = 5.917 min)

Table S4. Spectral and analytical data of compounds **13a-i,** *trans*-**14a-d,** *trans*-**14g,** *trans*-**14i** *cis*-**14a-d,** *cis*-**14g,** *cis*-**14i,** *trans*-**15-20** and *cis*-**21**

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