Piperazine inhibitors of bacterial gyrase and topoisomerase iv

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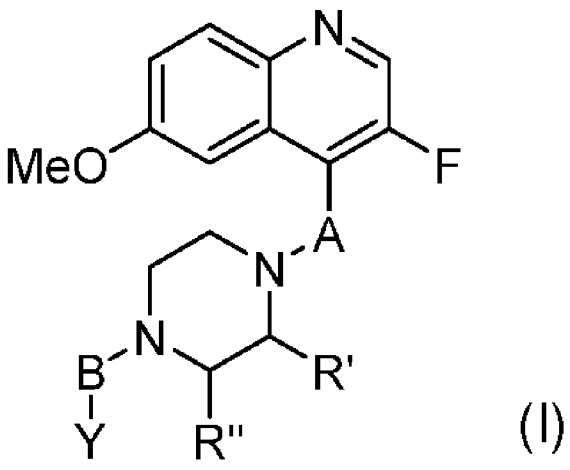
(54) Title: PIPERAZINE INHIBITORS OF BACTERIAL GYRASE AND TOPOISOMERASE IV



(I)

– CH_2-≡– (a)

– CH_2-=– (b)

(57) Abstract: This invention relates to a piperazine derivative having the formula (I), wherein R' is selected from -H, -COOH and -$CONH_2$; Ft" is selected from -H, -COOH and -$CONH_2$ with the proviso that when R' is -COOH or -$CONH_2$ then R" is not -COOH or -$CONH_2$, and when R" is -COOH or -$CONH_2$ then R' is not -COOH or -$CONH_2$; A is selected from -$(CH_2)_3$-, -$(CH_2)_2CH(OH)$-, -CH_2-CH=CH- (cis and trans), (a); B is selected from -$(CH_2)_n$-, -$(CH_2)_nO$-, -$(CH_2)_nS$- and -$(CH_2)_n$-CH=CH- (cis and trans), (b); and wherein n = 1 -4; and Y is selected from C_1-C_7 alkyl (straight or branched), C_5-C_6 cycloalkyi optionally substituted with one or more halogens, thiophene or phenyl optionally substituted with one or more halogens or -$C(hal)_3$ wherein "hal" denotes a halogen, or a pharmaceutically acceptable salt thereof.

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Piperazine inhibitors of bacterial gyrase and topoisomerase IV

Field of the invention

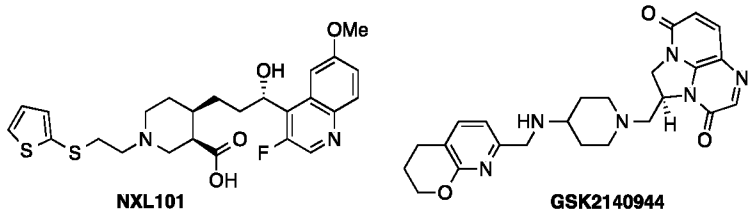
The present invention relates to a novel class of antibiotic compounds that are effective against methicillin-resistant *Staphylococcus aureus* (MRSA). The new class of antibiotics is constituted by a piperazine core that links to a fluoroquinoline and a hydrophobic moiety.

Background of the invention

Penicillin has been commercially available for half a century. However, the extensive use of penicillin has resulted in development in resistance among bacteria such as MRSA. The mortality rate for humans infected is 15-60% and in Europe 25,000 people die every year from infections caused by multidrug-resistant bacteria.

MRSA strains are resistant to the β-lactam antibiotics (penicillins), but resistance to tetracyclins, macrolides, lincosamides, aminoglycosides, trimethoprim, and in some cases also to fluoroquinolones is frequently observed. Vancomycin has for a long time been the drug of choice for MRSA infections, but this has now resulted in increasing vancomycin-resistance among MRSA.

Novexel and GSK have identified a new structural class of antibiotics, which consist of a quinolone and a partly aromatic heterocycle linked via a piperidine core. These antibiotics block the activity of bacterial topoisomerase and, accordingly, they are known as novel bacterial topoisomerase inhibitors (NBTIs). Novexel's lead compound NXL101 is a carboxy-piperidine based compound, whereas GSK progressed from the piperidine GSK2140944 compound (see below)



Structures of compounds NXL101 and GSK2140944

There are several advantages of topoisomerase inhibitors as antibiotics. Bacteria contain the two type IIA topoisomerases DNA gyrase (topoisomerase II) and topoisomerase IV. The active sites show a high degree of similarity, thus one antibiotic can potentially target those two distinct enzymes. Consequently, development of resistance would require mutations in both of the corresponding genes (*gyrA* for gyrase and *parC* for topoisomerase IV). Additionally, topoisomerase inhibitors might be effective against both Gram-positive and Gram-negative bacteria since the topoisomerase genes are highly conserved in both species. However, Gram-negative bacteria are typically harder to eradicate due to the outer membrane permeability barrier, multiple efflux pumps, as well as antibiotic- and target-modifying enzymes. Furthermore, DNA gyrase is not found in humans, and the human topoisomerases have distinct differences from the bacterial counterparts and are generally not affected by bacterial topoisomerase inhibitors.

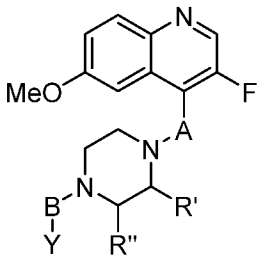
During the phase I clinical trial of NXL101, the compound was found to disturb the heart rhythm by prolongation of the QT interval. As this may lead to cardiac arrhythmia and sudden death, NXL101 was immediately discontinued. The typical cause of QT prolongation is blocking of the potassium channel in the heart encoded by the human ether-à-go-go related gene (hERG), commonly referred to as the hERG channel. The binding affinity for the hERG channel inhibitors is now always evaluated in pre-clinical studies of new drug candidates.

Thus, there is a medical need for new type of antibiotics that are effective towards pathogenic resistant bacterial strains and which have a safer profile than NXL101 regarding hERG.

Detailed description of the invention

The present invention provides a new class of antibiotics. The antibiotics target bacterial type II topoisomerase with a novel mode of action, which is distinct from the one of currently approved drugs. The antibiotics inhibit bacterial gyrase and topoisomerase IV and hamper DNA transcription and replication in living bacterial cells. Furthermore, this new class of antibiotics possesses a simple chemical structure, which facilitates its rapid preparation via chemical synthesis.

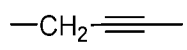
The present invention relates to a piperazine derivative having the formula (I)

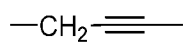


Formula (I),

wherein

R' is selected from –H, -COOH and $–CONH_2$;
R'' is selected from –H, -COOH and $–CONH_2$ with the proviso that when R' is –COOH or $–CONH_2$ then R'' is not –COOH or $–CONH_2$, and when R'' is –COOH or $–CONH_2$ then R' is not –COOH or $–CONH_2$;

A is selected from $–(CH_2)_3$-, $-(CH_2)_2CH(OH)$-, $-CH_2$-CH=CH- (cis and trans),  ;

B is selected from $–(CH_2)_n$-, $–(CH_2)_nO$-, $–(CH_2)_nS$- and $–(CH_2)_n$-CH=CH- (cis and trans),  and wherein n = 1-4; and

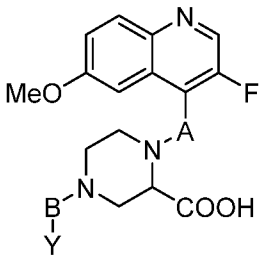
Y is selected from C_1-C_7 alkyl (straight or branched), C_5-C_6 cycloalkyl optionally substituted with one or more halogens, thiophene or phenyl optionally substituted with one or more halogens or $–C(hal)_3$ wherein "hal" denotes a halogen.

All cis-trans, R or S forms are encompassed in the above-mentioned formula (I) as well as all stereroisomers, enantiomers, racemic forms and mixtures thereof.

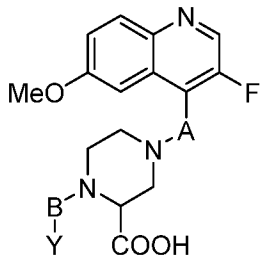
Compared with NXL101 the compounds of the present invention contain a piperazine core and not a piperidine core. The present inventors have found that changing the pi-

peridine core with a piperazine core in general does not have negative effect on the antibiotic activity, but the linker A as well as the substituent R' or R'' and the group B seem to have effect on reduction in hERG activity. Moreover, as seen from the examples herein, the fluor group in the quinoline moiety seems to be important for obtaining compounds with excellent antibiotic properties.

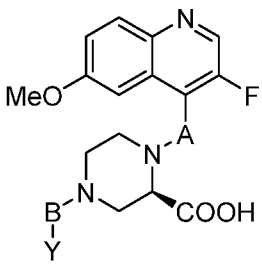
The R-configuration in the 2-position of the piperidine moiety seems to lead to more potent antibiotics, but compounds with S-configuration are still active and have suitable *in vitro* hERG characteristics. The R' group may be –H, -COOH or $–CONH_2$. From the experiments reported herein it is seen that changing R' from –COOH to $–CONH_2$ (all other structural elements being the same; see eg compound **53a** and **54**) does not affect the antibiotic activity, but had a 10-fold impact on hERG affinity. From the examples it is also seen that when R'' is –COOH then both antibiotic activity is suitable and hERG affinity is acceptable. Accordingly, compounds are preferred, wherein R' is –COOH. Accordingly, preferred compounds have the following structure:

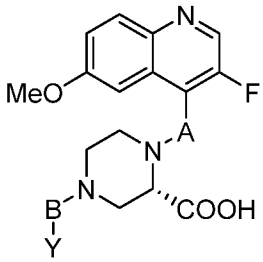


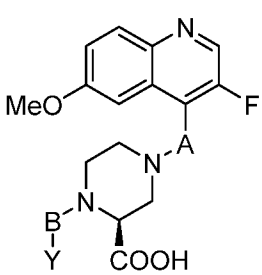
or

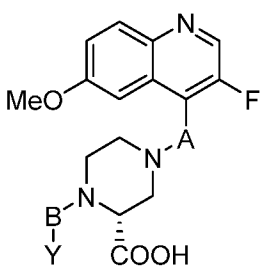


including the R- and the S-forms

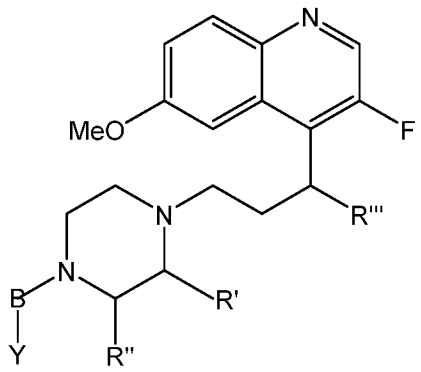






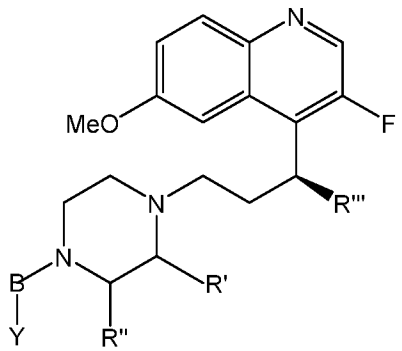


With respect to the linker A suitable results have been obtained with all the linkers mentioned above. It seems as if the antibiotic activity decreases going from an alkanyl group to an alkenyl or an alkynyl group, but on the other hand the results with respect to hERG affinity are improved. Thus, all the linkers seem to either contribute to a potent antibacterial response or to a suitable hERG affinity, or both. Especially some of the linkers seem to contribute to excellent antibiotic and hERG effect, namely $–CH_2-CH_2-CH_2-$ and $–CH_2-CH_2-CHOH-$:

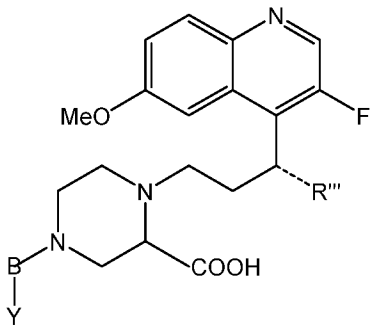
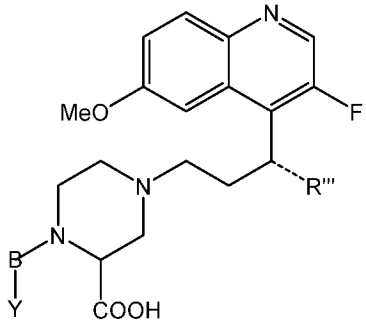
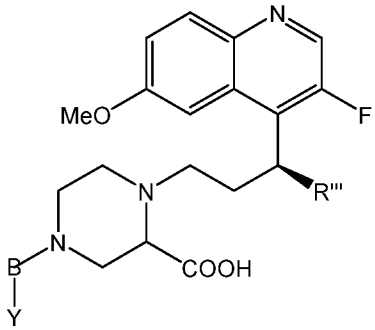
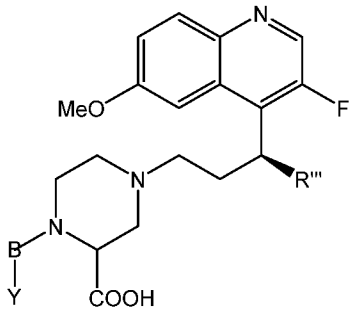


Where R', R'', B and Y are as defined herein and R''' is H or OH.

All configurations are included in the above formula. As it appears from the examples herein a suitable configuration is:

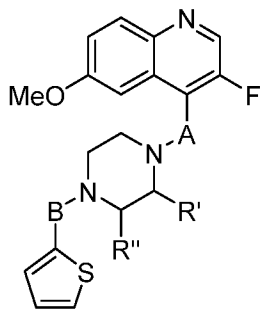
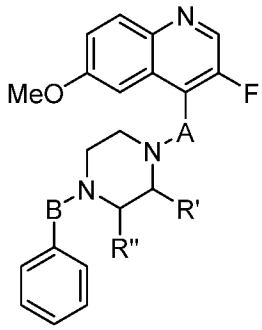


Combining the information obtained from linker A as well as from R' and R'' gives the following interesting structures:

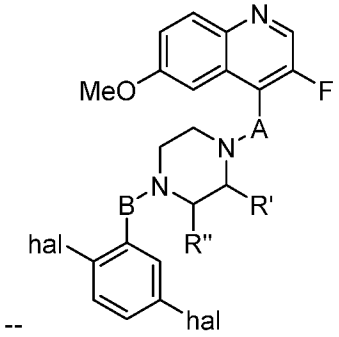





wherein R''', B and Y are as defined above and the –COOH group in the 2- or 3-position of the piperazine ring can be in the R- or S-forms as described above.

With respect the hydrophobic moiety –B-Y, the experiments reported herein show that Y groups like thiophene and phenyl are suitable optionally substituted with one or two halogens, especially fluorine, but also cycloalkanyl or straight or branched alkanyl groups are of interest (see eg compounds **58p** and **58r**):

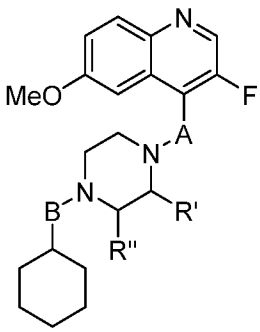



wherein the phenyl-group may be substituted with one or two halogens:

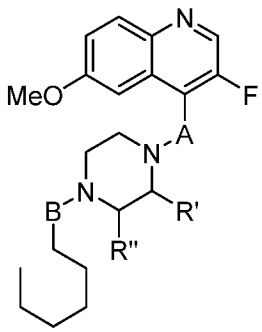


especially one or two fluorine atoms.

Other suitable Y groups are:

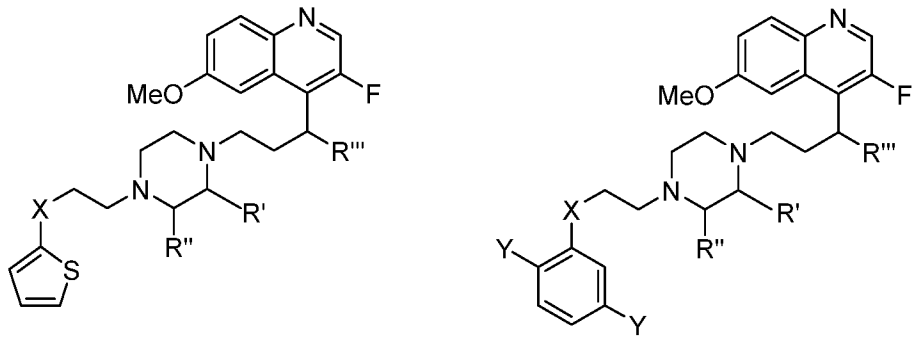


or



B is selected from $-(CH_2)_n-$, $-(CH_2)_nO-$, $-(CH_2)_nS-$ and $-(CH_2)_n-CH=CH-$ (cis and trans), $-CH_2-C\equiv C-$ and wherein n = 1-4. In the position closest to Y C, O and S lead to potent antibiotic compounds. It seems as if the compounds with O have a slightly better profile with respect to hERG and that disubstitution with F of the phenyl ring lead to compounds with good antibacterial effect and fine profile regarding hERG. Preferred linkers B are: $-CH_2-CH_2-CH_2-$, $-O-CH_2-CH_2-$, and $-S-CH_2-CH_2-$, where the –O- and the –S- part are coupled to Y and the $-CH_2-$ part is coupled to the piperazine moiety. However, as it appears from the results given herein suitable results are also obtained with any of the other mentioned B linkers.

In accordance with the above, the following structures are of interest:



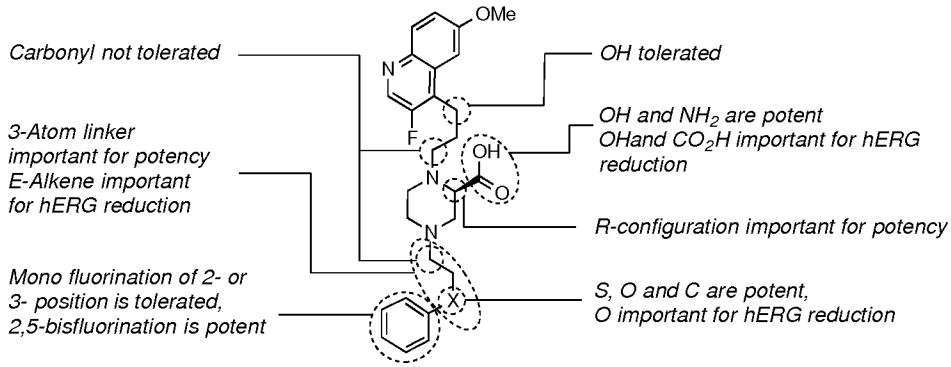
wherein R', R'', R''' are as defined above, X is C, O or S, and Y is H or halogen selected from F, Br, I, preferably F. As seen from the examples the phenyl ring may also be monosubstituted in the 3-position with a halogen.

Encompassed are also pharmaceutically acceptable salts of the compounds of the invention. Thus, when R' or R'' is –COOH the suitable pharmaceutically acceptable salts include alkali salt, alkaline earth salts. Salts can also be obtained by reaction with ammonia or other types of amines. The hydrated version of the carboxylic acid is also acceptable. Suitable salts may be the sodium, potassium, lithium, magnesium, calcium, zink, aluminium salts. Other suitable salts include ammonium salt or salts of amine bases (ethanolamine, diethanolamine, trimethylamine, triethylamine, methylamine, propylamine, diisopropylamine, *N*,*N*-dimethylethanolamine, benzylamine, dicyclohexylamine, *N*-benzyl-β-phenethylamine, *N*,*N'*-dibenzylethylenediamine, diphenylenediamine, benzhydrylamine, quinine, choline, arginine, lysine, leucine, dibenzylamine).
Pharmaceutically acceptable derivatives of the amine functions include the free base form or their acid addition or quaternary ammonium salts, for example their salts with mineral acids e.g. hydrochloric, hydrobromic, sulphuric nitric or phosphoric acids, or organic acids, e.g. acetic, fumaric, succinic, maleic, citric, benzoic, *p*-toluenesulphonic, methanesulphonic, naphthalenesulphonic acid, camphorsulfonic or tartaric acids. Compounds may also be prepared as the *N*-oxide.

The inventors have shown that the compounds of formula (I) have antibiotic activity, they act as topoisomerase inhibitors and they have suitable properties regarding hERG channel, i.e. they have sufficient low hERG inhibition.

Compounds of particular interest in the present context are included in Tables 1-5.

Based on structure-activity studies the following elements are important:



Structure-activity relationships for piperazine-based antibiotic agents

As mentioned above, the piperazine derivatives of the present invention have been shown to act as MRSA antibiotics. Most of the compounds have been tested to identify the minimal inhibitory concentration against *S. aureus*; one β-lactam sensitive strain have been used, namely *S. aureus* MSSA (RV37) and one β-lactam resistant *S. aureus* MRSA (CC398). Moreover, the compounds have been tested for inhibition of the bacterial enzymes gyrase and topoisomerase IV indicating that the compounds act as topoisomerase inhibitors. Finally, the compounds have been tested in an *in vitro* assay for hERG affinity. The results appear from the experimental section herein.

The criteria to divide piperazine derivatives in groups of active versus non-active are based on results with the two conventional antibiotics ciprofloxaxin and vancomycin against *S. aureus* and *E. faecalis*.

The following tables show the MIC values of ciprofloxacin and vancomycin against *S. aureus* and *E. faecalis* according to the FDA. The data are divided according to the following criteria: susceptible, intermediate and resistant.

Organism	**Minimum Inhibitory Concentration (µg/mL)**					
	Ciprofloxacin			Vancomycin		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
S. aureus	≤1	2	≥4	≤2	4-8	≥16
E. faecalis	≤1	2	≥4	≤4	8-16	≥32

According to FDA standard vancomycin and ciprofloxacin powder should provide MIC values provided in the following table:

Organism	Minimum Inhibitory Concentration (µg/mL)	
	Ciprofloxacin	Vancomycin
S. aureus ATCC 29213	0.12 - 0.5	1.0 – 2.0
E. faecalis ATCC 29212	0.25 – 2.0	0.5 – 4.0

In the present context, the compounds of the invention are regarded as antibiotics if the MIC values for MSSA RV37 and/or MRSA CC398 are at the most 16 µg/mL. The most potent compounds are those having MIC values for MSSA RV37 and/or MRSA CC398 of at the most 1 µg/mL. The intermediate active compounds have MIC values from 1 to 10 µg/mL.

As seen from the examples herein compounds are provided, which have excellent antibiotic properties. Most of the exemplified and tested compounds have MIC values of 10 µg/mL or less and many of the compounds have MIC values of 5 µg/mL or less. Together with the excellent antibiotic properties, the compounds of the invention also seem to have suitable properties with respect to hERG inhibition.

With respect to hERG affinity it is generally assumed that the hERG affinity has to be less than 50% inhibition at 30 µM, i.e. the EC_{50} has to be higher than 30 µM for replacement of the substrates (in the *in vitro* test kit) in the hERG channel protein. As seen from the tables herein, in some cases the hERG affinity is determined by % inhibition at 30 µM and in other cases by EC_{50} for replacement of a substrate in a hERG test. To enable comparison of the two different assessments, the % inhibition at 30 µM will be represented by >30 µM or <30 µM in tables with a majority of compounds characterized by EC_{50}, and EC_{50} will be represented as >50% inhibition or <50% inhibition in tables with a majority of compounds characterized by % inhibition at 30 µM.

The tests performed are *in vitro* tests and only give a rough indication. The hERG channel inhibition assay is regarded as a highly sensitive measurement which will identify compounds exhibiting cardiotoxicity related to hERG inhibition *in vivo*. However, it is important to note that not all compounds which inhibit hERG activity *in vitro* will proceed to cause cardiotoxicity *in vivo*. The relevance of the *in vitro* data will depend on other factors such as the plasma concentrations reached *in vivo*. Moreover, some compounds may pass the *in vitro* test, but still cause cardiotoxicity *in vivo*. Accordingly, it is

important to supplement the *in vitro* tests with other tests, preferably an *in vivo* test in a suitable test animal.

The hERG tests must be supplemented by other test such as manual or automated patch clamp assays, which are optional to use as preclinical cardiac risk indicators.

As mentioned above, the hERG test performed (as described in the experimental section) gives only an indication of the ability of the compound to inhibit the hERG channel *in vitro*. The inhibition should be as low as possible, but the test only gives indicative results on which a selection may take place. In order to have a more conclusive evaluation of hERG inhibition a so-called patch-clamp test should be performed. In the present context, a compound of the invention is regarded as of interest, if the compound has excellent antibacterial effect. Preferably, the compound also have suitably low hERG inhibition. Preferably, when the compound is tested in the hERG test, the test results in an EC_{50}- value of 24 µM or more. However, a person skilled in the art will know that the values obtained from the hERG test are indicative and that further tests are necessary to ensure low cardiotoxicity of the compound *in vivo.*
In some cases, a compound is regarded as of interest with respect to a suitable hERG profile if the EC_{50} is higher than 30 µM, which corresponds to less than 50% inhibition at 30 µM, but as explained above, the *in vitro* results may differ markedly from *in vivo* results relating to cardiotoxicity.

The compounds are intended for use in the treatment of infections caused by pathogenic bacteria. Treatment includes a range of bacteria including Gram-positive and Gram-negative bacteria and mycobacteria. The infection may be on any part of the mammal body. Treatment of humans as well as household, farm and live-stock animals is within the scope of the present invention.

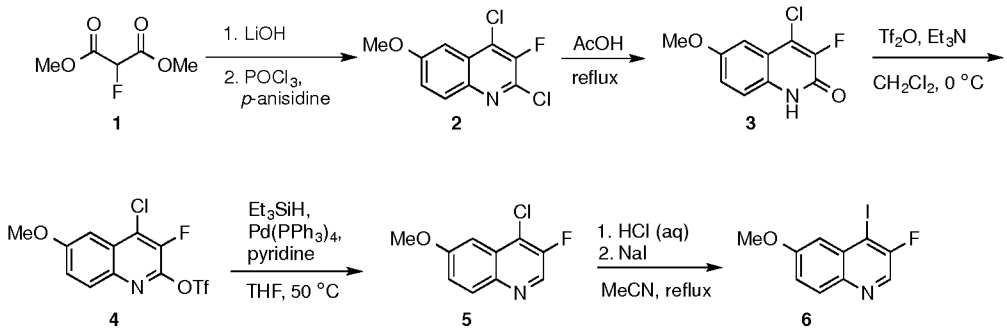
The compounds may be administered to a subject in need thereof in the form of a pharmaceutical composition comprising the compound together with one or more pharmaceutically acceptable excipients. The formulation may be designed to oral, parenteral or topical application. It may be in the form of a dosage form such as a solid dosage form and may contain an effective dose of the compound. A person skilled in the art will find guidance of how to formulate pharmaceutical composition in Remington's Pharmaceutical Sciences (newest edition) and a person skilled in the art will know how a suitable

dosage regime can be determined based on pharmacokinetic data and pre-clinical studies.

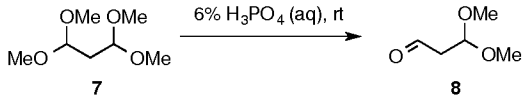
General description of methods for preparing compounds according to the invention

In the following schemes are given details regarding the preparation of the compounds of the invention and intermediates:

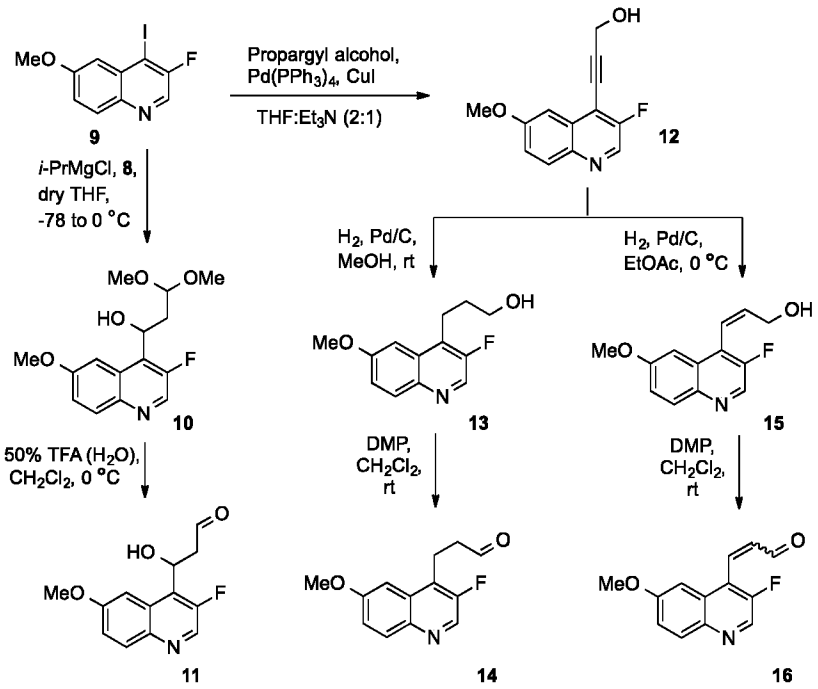
Scheme 1. Synthesis of quinoline building block **6**



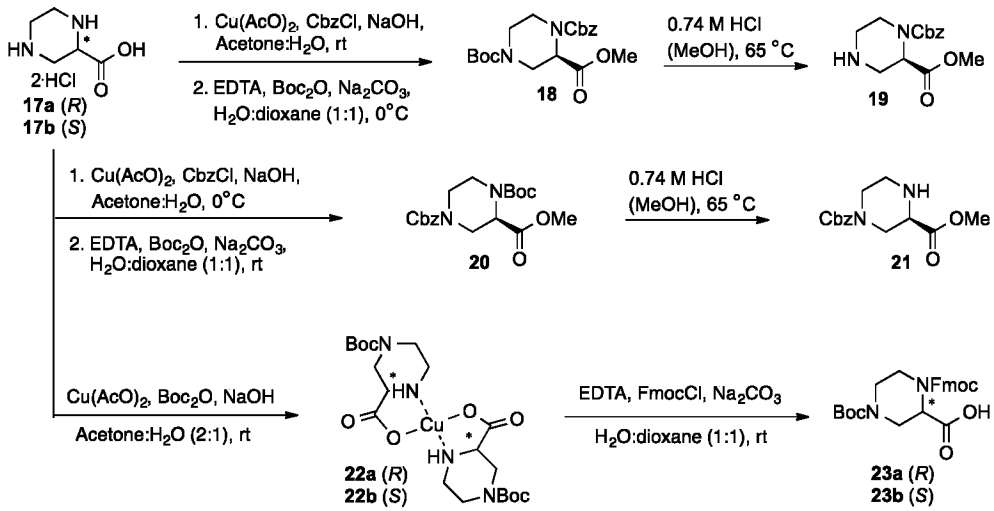
Scheme 2. Synthesis of aldehyde building block **8**



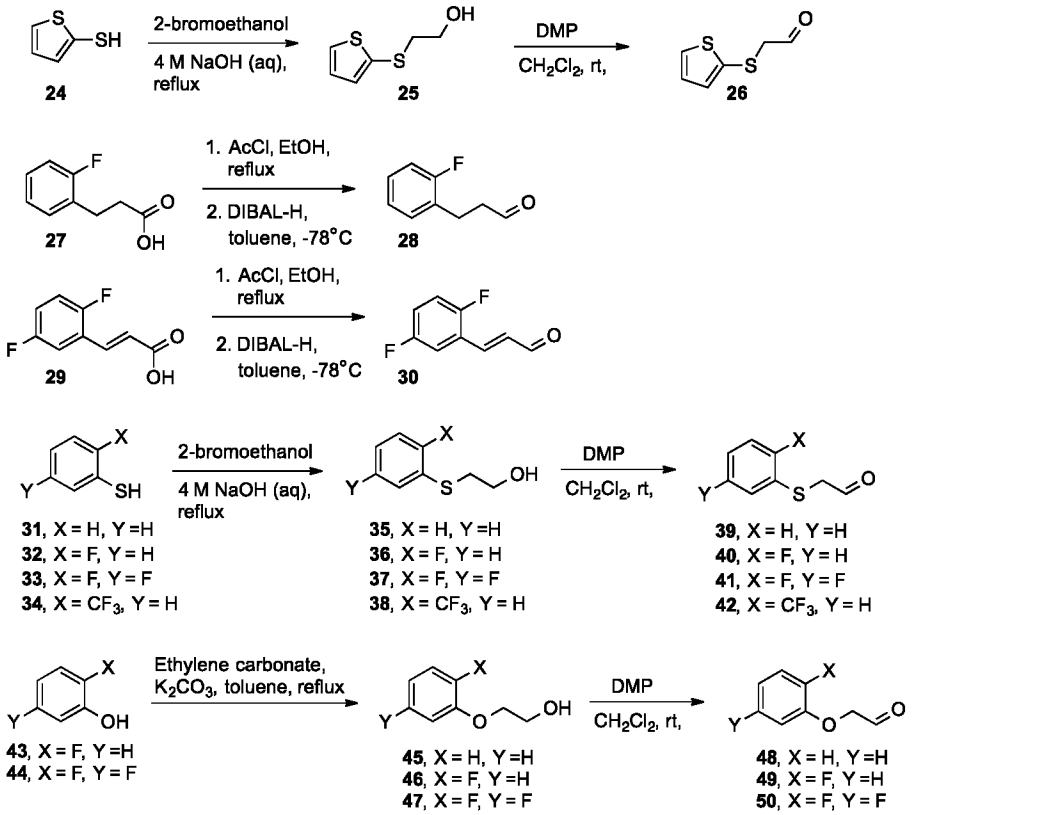
Scheme 3. Synthesis of quinoline-aldehyde building blocks **11**, **14**, and **16**



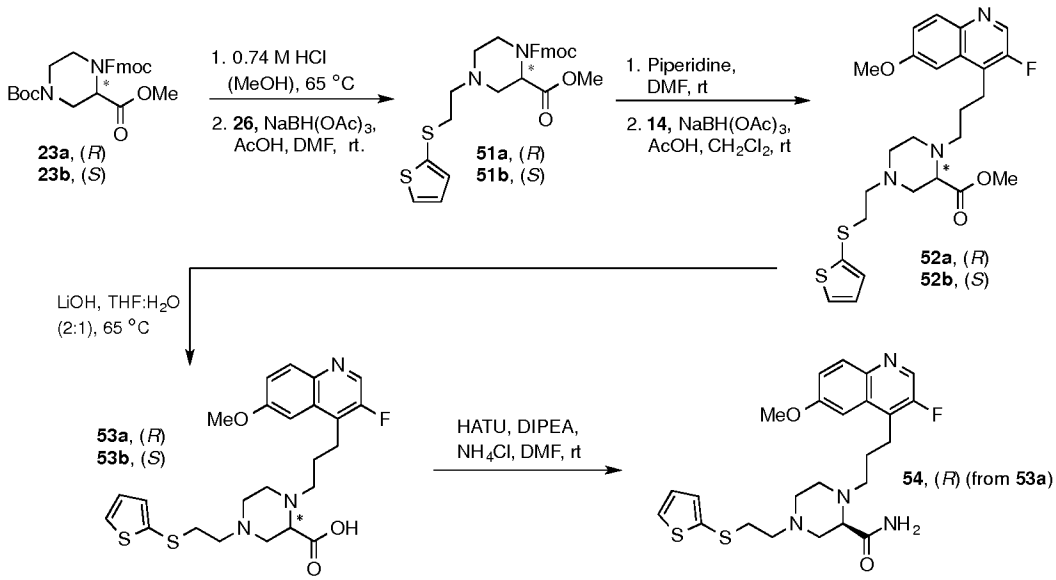
Scheme 4. Synthesis of *N*-protected piperazine building blocks



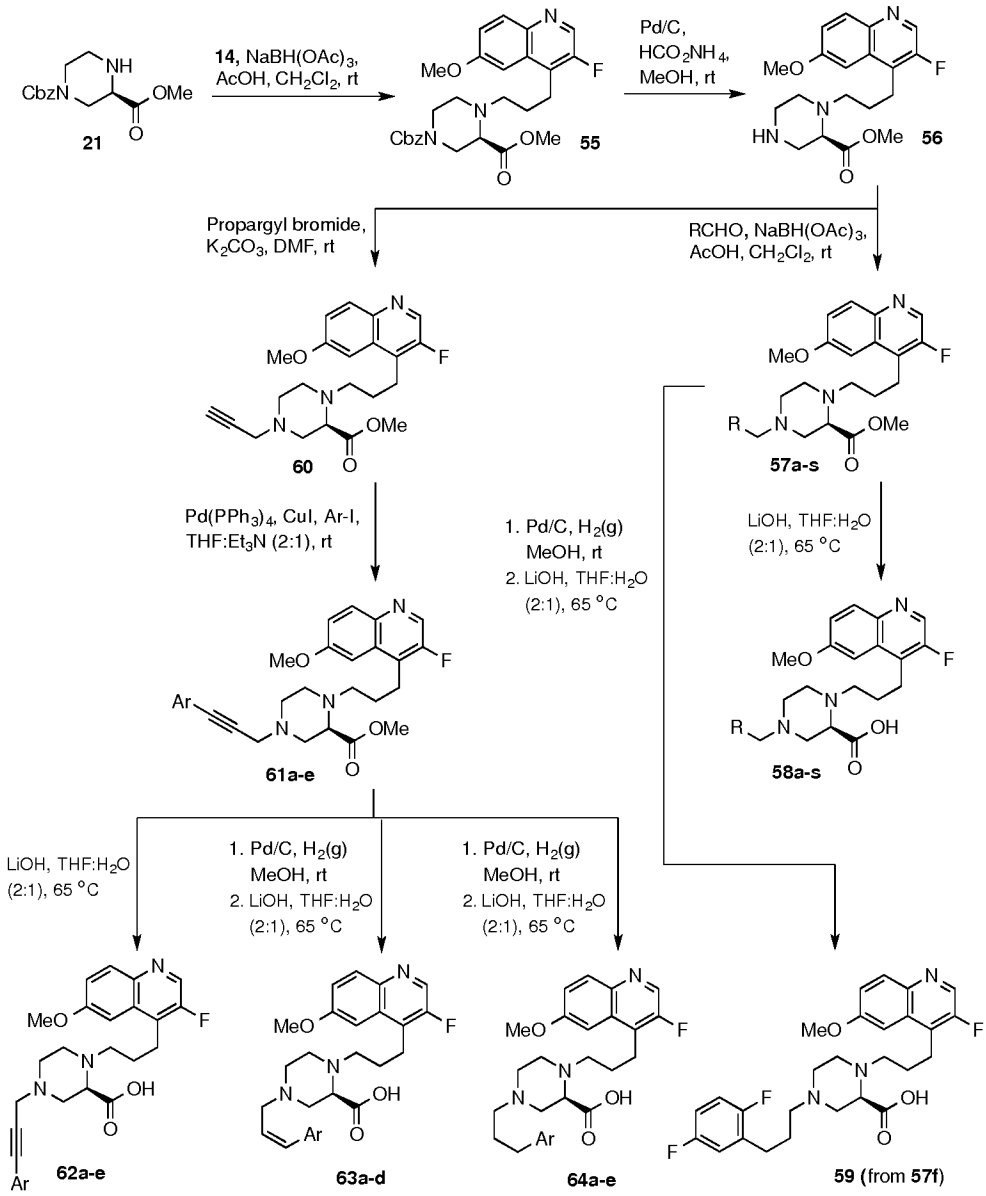
Scheme 5. Synthesis of aldehyde building blocks



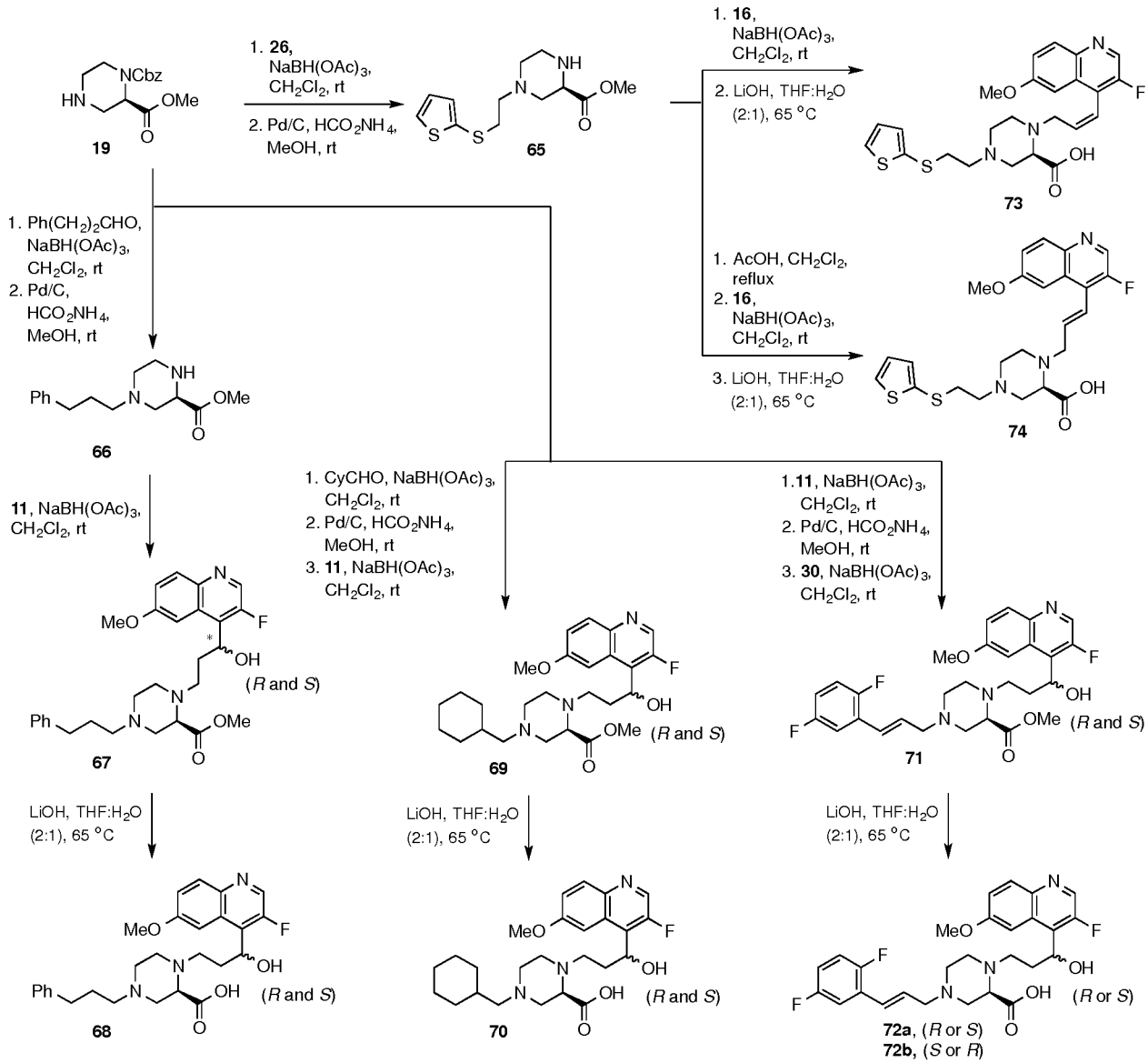
Scheme 6. Synthesis of compounds **53a**, **53b** and **54**



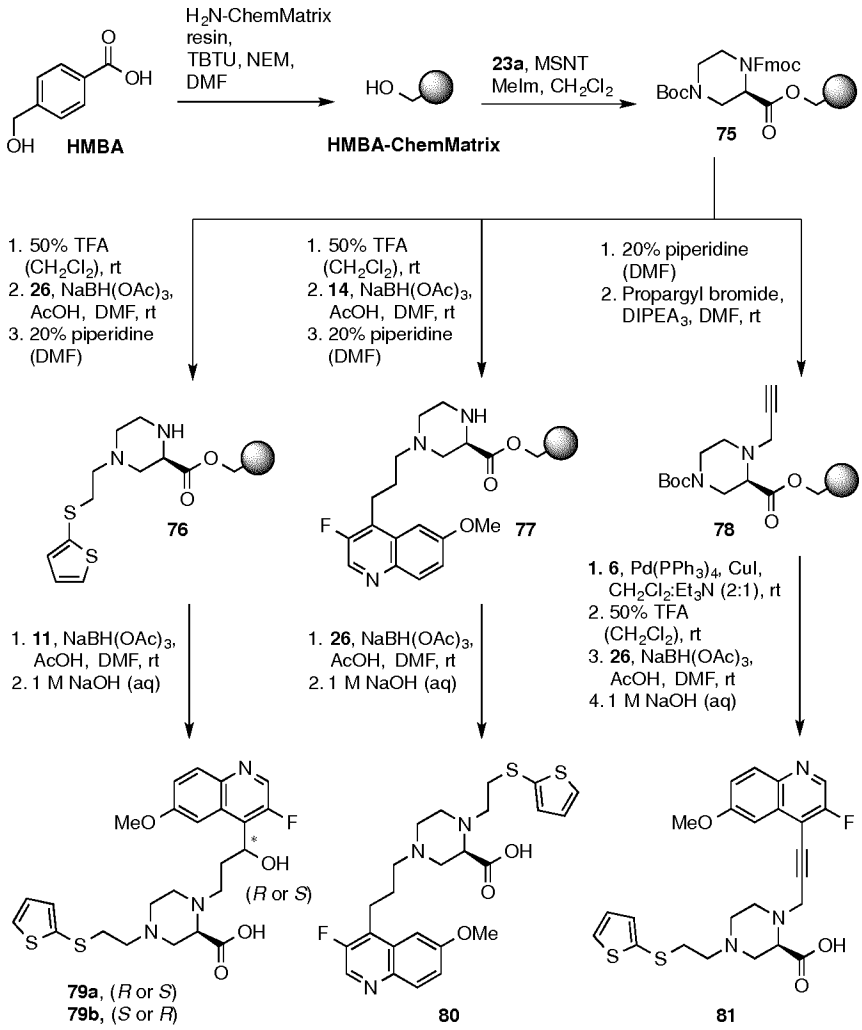
Scheme 7. Synthesis of final compounds **58a-s**, **59**, **62a-e**, **63a-f** and **64a-e**



Scheme 8. Synthesis of final compounds **68**, **70**, **72a-b**, **73** and **74**



Scheme 9. Solid-phase synthesis of final compounds **79a-b**, **80** and **81**



Legends to figures

Figure 1. Gels showing inhibition of *S. aureus* gyrase supercoiling enzymatic activity. Ciprofloxacin tested in dosing range 0.05-50 µM and NXL101 and 58f tested in dosing range 0.05-10 µM.

Figure 2. Gels showing inhibition of *S. aureus* topoisomerase IV relaxation enzymatic activity. Ciprofloxacin. NXL101 and 58f tested in concentrations 50-0.05 µM.

The invention is further illustrated in the following non-limiting examples.

Materials and methods

Procedures and characterization

All reagents and solvents were purchased from commercial suppliers and used without further purification. All solvents used were of HPLC-grade, which predominantly were used without further drying. Dry DMF was obtained from an Innovative Technology Pure Solv MD 7 Solvent Purification System. The glassware for dry reactions was dried over a Bunsen flame under vacuum before contact with solvent or reagents. Unless otherwise stated, reactions were run as open-system reactions, using only a loosely-fitted plastic plug in order to avoid contamination of the reaction mixture. Reaction products have been purified using flash column chromatography or preparative high-performance liquid chromatography (prep-HPLC). Reactions were routinely monitored using thin layer chromatography (TLC), ultra-performance liquid-chromatography mass-spectrometry (UPLC-MS) and/or high-performance liquid-chromatography with UV detection (HPLC-UV).

Analytical TLC was performed using Merck aluminium sheets covered with silica (C60). The plates were visualized using UV light and/or a $KMnO_4$ staining solution (3 g in water (300 mL), K_2CO_3 (20 g) and 5% NaOH (aq) (5 mL)) followed by heating.

Analytical HPLC-UV was accomplished on a Waters Alliance reversed phase (RP) HPLC system, employing a Waters 2695 Separations Module and a Waters 2998 Photodiode Array Detector. The column used was a Symmetry® C18 column (*d* 3.5 µm, 4.6 x 75 mm; column temp: 25 °C; flow: 1 mL/min) with routine detection at 215 nm and 254 nm. Eluents A (0.1% TFA in H_2O) and B (0.1% TFA in MeCN) were used in a linear gradient (100% A to 100% B) in a total run time of 13 min.

Analytical UPLC-MS (ESI) was performed on a S2 Waters ACQUITY RP-UPLC system equipped with a diode array detector using an ACQUITY UPLC BEH C18 column (*d* 1.7 µm, 2.1 x 50mm; column temp: 65 °C; flow: 0.6 mL/min), as well as a SQD ESI MS detector. Eluents A1 (0.1% HCOOH in H_2O), A2 (0.1% NH_4COOCH_3), B1 (0.1% HCOOH in MeCN) and B2 (0.1% NH_4COOCH_3 in MeCN) were used in a linear gradient 5% B1/B2 to 100% B1/B2 in a total run time of 2.6 min.

Analytical LC-HRMS (ESI) analysis was performed on an Agilent 1100 RP-LC system equipped with a diode array detector using a Phenomenex Luna C18 column (*d* 3 µm, 2.1 x 50 mm; column temp: 40 °C; flow: 0.4 mL/min). Eluents A (0.1% HCOOH in H_2O) and B (0.1% HCOOH in MeCN) were used in a linear gradient (20% B to 100% B) in a total run time of 15 min. The LC system was coupled to a Micromass LCT orthogonal

time-of-flight mass spectrometer equipped with a Lock Mass probe operation in positive electrospray mode.

Flash column chromatography was achieved using a glass column packed with Merck Geduran® 60 silica gel (40-63 µm particles) as stationary phase, and liquid phase as specified in the individual experimental procedures.

Preparative RP-HPLC was carried out on a Waters Alliance RP-HPLC system consisting of a Waters 2545 Binary Gradient Module equipped with an xBridgeTM Prep BEH130 C18 column OBDTM (*d* 5 µm, 19 x 100mm; column temp: 25 °C; flow: 20 mL/min), a Waters Photodiode Array Detector (detecting at 210-600 nm), a Waters UV Fraction Manager and a Waters 2767 Sample Manager. Elution was carried out in a linear reversed phase gradient, combining H_2O and MeCN (buffered with 0.1% HCOOH or NH_4COOCH_3). Freeze drying was accomplished via a Thermo Scientific Heto PowerDry® LL 1500 freeze dryer.

All purified compounds have been routinely characterized by ^{1}H NMR, ^{13}C NMR, IR, RP-UPLC-MS and RP-HPLC-UV, as well as melting point and optical rotation where applicable. Novel compounds were further characterized via HRMS. For diastereomeric mixtures, only ^{1}H NMR was obtained, as well as HRMS for acid analogs.

NMR spectra were recorded on a Bruker Ascend spectrometer with a Prodigy cryoprobe (operating at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR), and analyzed via the NMR software MestReNova (version 6.2.1-7569) released by Mestrelab Research S.L. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) in Hz. The majority of the spectra have been recorded in $CDCl_3$, and the signals were adjusted relative to this position (δ 7.26 ppm for ^{1}H NMR and δ 77.2 ppm for ^{13}C NMR). For spectra recorded in DMSO-d_6, the signals were adjusted relative to the DMSO signal (δ 2.5 ppm for ^{1}H NMR and δ 39.5 ppm for ^{13}C NMR). In some of the spectra of acid analogs, a residue of formic acid can be seen (δ 8.3 ppm for ^{1}H NMR and δ 165.5 ppm for ^{13}C NMR), which originates from the purification using preparative HPLC.

IR analyses were performed on a Bruker Alpha FT-IR spectrometer. Melting points were measured using a Stuart SMP30 melting point apparatus, and specified as an in-

terval of melting temperatures (°C), or as a point from where the compound decomposed (dec.). Optical rotation was measured on a Perkin-Elmer 341 polarimeter (polarimeter cell 1.0 mL, 100 mm), with a sodium source lamp (589.3 nm, 23 °C). Compounds have been drawn and named through use of the visualization software ChemDraw Ultra 14.0 released by PerkinElmer Informatics. Molecular- and exact masses have been calculated via this program as well.

Biological methods

Gyrase Supercoiling Assay

The assay was performed using *S. aureus* Gyrase Supercoiling Assay Kit (Inspiralis, Norwich, UK, Cat No. SAS4001). The assay was carried out according to the instructions from the supplier. Supercoiled pBR322 plasmid DNA was incubated with gyrase in the assay buffer supplied by the manufacturer. Different concentrations of the compounds were tested. Reactions were carried out for 30 minutes at 37 °C and terminated by addition of stop buffer (STEP) and chloroform/isoamyl alcohol. Samples were vortexed, centrifuged and run through a 1% agarose gel for 2 h at 80 V. Gels were stained with ethidium bromide and visualized under UV light.

Gyrase Supercoilling High Throughput Plate Assay

The assay was performed using *S. aureus* Gyrase Supercoiling High/Medium-Throughput Assay Kit (Inspiralis, Norwich, UK, Cat No. SATRG01). Black streptavidin-coated 96-well microplates were rehydrated by using Wash buffer followed by immobilize biotinylated oligo (TF01) onto the wells[1]. Excess of oligo was removed by using Wash buffer. Enzyme assay was carried out by using pNO1 followed by addition of enzyme and compounds. The plate was incubated for 30 minutes at 37 °C followed by addition of TE buffer and then 30 minutes incubation at room temperature. Unbound plasmid was washed off with TE buffer. DNA stain was added and fluorescence was measured in plate reader (Excitation: 495 nm; Emission 537 nm).

Topoisomerase IV High Throughput Plate Assay

The assay was performed using *S. aureus* Topoisomerase IV High / Medium-Throughput Assay Kit (Inspiralis, Norwich, UK, Cat No. SATRIV01). Black streptavidin-coated 96-well microplates were rehydrated by using Wash buffer followed by immobilize biotinylated oligo (TF01) onto the wells[1]. Excess of oligo was removed by using Wash buffer. Enzyme assay was carried out by using pNO1 followed by addition of enzyme and compounds. The plate is incubated for 30 minutes at 37°C followed by addition of

TE buffer and then 30 minutes incubation at room temperature. Unbound plasmid was washed off with TE buffer. DNA stain was added and fluorescence was measured in plate reader (Excitation: 495 nm; Emission 537 nm).

hERG inhibition

The hERG channel inhibition was measured by the Predictor™ hERG Fluorescence Polarization Assay test kit (catalog no. PV5365) from Invitrogen (Carlsbad, CA). The binding assay was carried out according to the kit instructions[2]. The Predictor™ hERG kit from Invitrogen is a homogeneous fluorescent assay that uses a simple add-and-read format. The assay is based on the principle of fluorescence polarization where a red fluorescent tracer is displaced from the hERG channel by compounds that bind to the channel. Assay performance was validated by using established hERG channel blockers.

MIC determination by broth microdilution

The MIC values of the different compounds were determined by standard broth micro-dilution assay in 96-well sterile microplates[3]. The following two bacterial strains were used, *S. aureus* MSSA (RV37), DSM4910, ATCC35556 and *S. aureus* MRSA (CC398, SSI). The bacteria were grown for 24 h. at 37°C in Mueller Hinton media supplemented with 1 % glucose when appropriate. The compounds were tested in 11 different concentrations ranging from 50 µg/mL to 0.05 µg/mL. The MIC endpoint was determined as the lowest concentration of antibiotic at which there was no visible growth.

References for biological protocols

[1]Maxwell A, Burton NP and O'Hagan N High-throughput assays for DNA gyrase and other topoisomerases. *Nucl. Acids Res.* (2006) *34 (15): e104.*

[2]Invitrogen. Predictor™ hERG Fluorescence Polarization Assay test kits. Protocol part no. PV5365.pps. Rev. date: 28 October 2009

[3]*Andrews JM. J.* Determination of minimum inhibitory concentrations. *Antimicrob. Chemother.* (2001) 48 (suppl 1): 5-16.

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[1] Li, B.; Zhang, Z.; Mangano, M. *Org. Process Res. Dev.* **2008**, *12*, 1273-1275.
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[1] Mieczkowski, A.; Kozminski, W.; Jurczak, J. *Synthesis* **2009**, **2010**, 221–232.
[1] Ranganathan, S.; Ranganathan, D.; Singh, S. K., *Tetrahedron Lett.* **1987**, *28*, 2893-2894.
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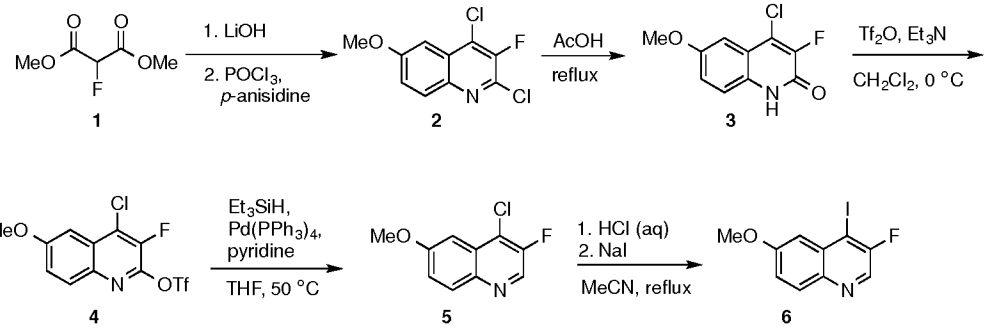
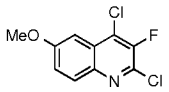
[1] Peng, H.; Cheng, Y.; Ni, N.; Li, M.; Choudhary, G.; Chou, H. T.; Lu, C.-D.; Tai, P. C.; Wang, B. *ChemMedChem* **2009**, *4*, 1457-1468
[1] Wu, J.-J.; Cheng, J.-H.; Zhang, J.; Shen, L.; Qian, X.-H.; Cao, S. *Tetrahedron* **2011**, *67*, 285-288.

Experimental and Examples

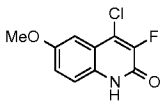
Scheme 10. Synthesis of quinoline building block **6**[i]



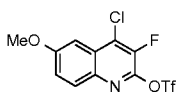


2,4-Dichloro-3-fluoro-6-methoxyquinoline (2).[ii] Dimethyl 2-fluoromalonate (**1**) (20.0 g, 134 mmol) and LiOH (6.89 g, 287 mmol) were dissolved in a mixture of water (20 mL) and MeOH (300 mL) and the reaction mixture was stirred for 22 h at rt. The reaction mixture was concentrated *in vacuo* and the residue was suspended in water (30 mL) and MTBE (200 mL). The suspension was cooled to 0 °C and conc. HCl (30 mL) was slowly added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with MTBE (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give 2-fluoromalonic acid as a white solid (15.4 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.48 (d, J_{HF} = 48.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.9 (d, J_{CF} = 23.7 Hz), 85.4 (d, J_{CF} = 189.2 Hz); IR (neat) cm^{-1}: 2945, 1707, 1407, 1268, 1127,

901, 693; m.p.: 134.8 - 139.2 °C. 2-Fluoromalonic acid (15.4 g, 126 mmol) was added portion wise to $POCl_3$ (91.7 mL, 989 mmol) under an argon atmosphere and the solution was stirred for 35 min at reflux. The solution was then cooled to 60 °C and *p*-anisidine (15.5 g, 126 mmol) was added portion wise whereupon the reaction mixture was stirred for 2 h at reflux. Evolved HCl gas was trapped with 1 M NaOH. Excess $POCl_3$ was removed by distillation and the residue was cooled to rt, poured over crushed ice, and the mixture was stirred overnight. 25% NH_4OH (aq.) was then added until pH 10 (210 mL) and the mixture was stirred for 1 h 30 min at rt. The mixture was filtered and the filter cake was washed with water and purified by flash column chromatography on silica gel (EtOAc:heptane (1:19 to 1:14), R_f = 0.4 in 1:9 EtOAc:heptane) to give the title compound as an off-white solid (11.5 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.2 Hz, 1H), 7.38 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.33 (d, *J* = 2.7 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 148.5 (d, J_{CF} = 261.2 Hz), 139.8 (d, J_{CF} = 4.4 Hz), 137.0 (d, J_{CF} = 21.9 Hz), 130.6 , 127.9, 126.0 (d, J_{CF} = 16.1 Hz), 123.1 (d, J_{CF} = 3.0 Hz), 101.7 (d, J_{CF} = 5.3 Hz), 55.8; IR (neat) cm^{-1}: 1620, 1586, 1494, 1376, 1347, 1234, 826, 787; m.p.: 140.2 - 141.1 °C. All spectroscopic data were consistent with those in the literature.

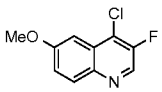


4-Chloro-3-fluoro-6-methoxyquinolin-2-ol (3).[i] Dichloroquinoline **2** (30.4 g, 124 mmol) was dissolved in AcOH (400 mL) and the reaction mixture was stirred for 42 h at reflux. Then water (280 mL) was added and the mixture was cooled to rt and filtered. The filter cake was washed with water and dried *in vacuo* to give the title compound as a white solid (27.4 g, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.48 (br s, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.27 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.24 (d, *J* = 2.7 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 155.7, 154.1 (d, J_{CF} = 26.0 Hz), 148.7 (d, J_{CF} = 250.9 Hz), 129.5 (d, J_{CF} = 2.5 Hz), 125.4 (d, J_{CF} = 15.5 Hz), 120.4 (d, J_{CF} = 3.0 Hz), 118.0, 117.7, 106.1 (d, J_{CF} = 6.3 Hz), 56.1; IR (neat) cm^{-1}: 2812, 1650, 1610, 1577, 1497, 1455, 1424, 1292, 1199; m.p.: 254.6 - 259.1 °C.

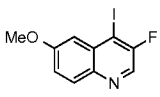


4-Chloro-3-fluoro-6-methoxyquinolin-2-yl trifluoromethanesulfonate (4).[i] Quinolone **3** (27.4 g, 120 mmol) was suspended in CH_2Cl_2 (350 mL) and Et_3N (21.7 mL, 156 mmol) and cooled to 0 °C under an argon atmosphere. Tf_2O (24.5 mL, 145 mmol) was added drop wise over 1 h, whereupon the mixture was stirred for 1 h at 0 °C. Then additional Et_3N (2.20 mL, 15.6 mmol) and Tf_2O

(2.4 mL, 14.5 mmol) were added at 0 °C and the mixture was stirred for 15 min. The reaction mixture was quenched with water (150 mL) and transferred to a separatory funnel where the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 230 mL) and the combined organic layers were dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.61). The product was washed with heptane to give an off-white solid (36.7 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 9.2 Hz, 1H), 7.44 (dd, J = 9.2, 2.7 Hz, 1H), 7.38 (d, J = 2.7 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 143.9 (d, J_{CF} = 264.5 Hz), 140.8 (d, J_{CF} = 17.2 Hz), 137.2 (d, J_{CF} = 4.4 Hz), 131.1 (d, J_{CF} = 1.6 Hz), 129.0 (d, J_{CF} = 1.5 Hz), 128.1 (d, J_{CF} = 14.2 Hz), 124.0 (d, J_{CF} = 2.9 Hz), 118.7 (q, J_{CF} = 320.6 Hz), 102.0 (d, J_{CF} = 5.2 Hz), 56.1; IR (neat) cm^{-1}: 3092, 2948, 1621, 1505, 1423, 1391, 1359, 1205, 1131, 1104, 922, 808; m.p.: 67.7 - 69.6 °C.

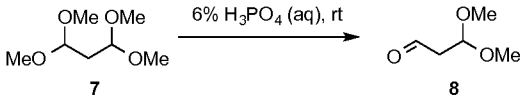


4-Chloro-3-fluoro-6-methoxyquinoline (5).[iii] A solution of triflate **4** (34.6 g, 96.2 mmol) and $Pd(PPh_3)_4$ (1.83 g, 1.59 mmol) in THF (480 mL) was charged with a magnetic stirring bar and heated to 50-60 °C in flame dried flask under an argon atmosphere. Pyridine (77.5 mL, 962 mmol) and Et_3SiH (153 mL, 140 mmol) were then added and the mixture was stirred for 2 h. The temperature was raised to 65 - 70 °C and the mixture was stirred for another 1 h 20 min. The reaction was then quenched with sat. $NaHCO_3$ (20 mL) and concentrated *in vacuo*. EtOAc (100 mL) and sat. $NaHCO_3$ (280 mL) were added and the layers were separated. The organic layer was washed with sat. NH_4Cl (3 x 185 mL), dried over $MgSO_4$, concentrated *in vacuo*, and then purified by flash column chromatography (EtOAc:heptane (1:9 to 1:4), R_f = 0.42 in 1:4 EtOAc:heptane) to give the title compound as a white solid (12.3 g, 61%). Fractions where product was contaminated with impurities were unsuccessfully purified by flash column chromatography to give the title compound as an off-white solid (8.7 g, 43%, purity by RP-UPLC-MS = 92%). The two crops of product were combined and used directly in the next step. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.45 (dd, J = 9.2, 2.7 Hz, 1H), 7.32 (d, J = 2.7 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.3, 152.3 (d, J_{CF} = 255.9 Hz), 141.2 (d, J_{CF} = 2.9 Hz), 138.1 (d, J_{CF} = 26.4 Hz), 131.4, 127.3, 122.8 (d, J_{CF} = 15.1 Hz), 122.1 (d, J_{CF} = 2.9 Hz), 101.2 (d, J_{CF} = 5.4 Hz), 55.8; IR (neat) cm^{-1}: 3016, 2966, 1621, 1495, 1460, 1354, 1306, 1223, 1018, 910, 824, 788; m.p.: 92.5 - 94.4 °C. All spectroscopic data were consistent with those in the literature.

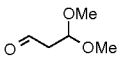


3-Fluoro-4-iodo-6-methoxyquinoline (6).[iii] Chloroquinoline **5** (20.3 g, 92.2 mmol) was dissolved in CH_2Cl_2 (160 mL) and treated with 1 M HCl in ether (105 mL), whereupon the solvents were removed *in vacuo* to give a yellow solid. The salt was suspended in MeCN (480 mL) together with NaI (144 g, 959 mmol) and stirred for 22 h at reflux. A solution containing 5% $Na_2S_2O_3$ (aq) and 10% K_2CO_3 (aq) (350 mL) was then added and the solution was stirred for 10 min. MeCN was removed *in vacuo* and the remaining aqueous phase was filtered. The filter cake was washed with CH_2Cl_2 to give the title compound as a white solid (21.0 g, 72% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.97 (d, J = 9.1 Hz, 1H), 7.33 (dd, J = 9.1, 2.7 Hz, 1H), 7.27 (d, J = 2.7 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3, 157.6 (d, J_{CF} = 253.9 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 137.1 (d, J_{CF} = 30.3 Hz), 132.4, 131.7, 122.0 (d, J_{CF} = 3.1 Hz), 109.2 (d, J_{CF} = 5.1 Hz), 93.9 (d, J_{CF} = 22.4 Hz), 55.9; IR (neat) cm^{-1}: 3012, 2959, 2827, 1616, 1496, 1463, 1400, 1348, 1304, 1223, 1126, 1017, 904, 822, 789; m.p.: 172.2-174.2 °C. All spectroscopic data were consistent with those in the literature.

Scheme 2. Synthesis of aldehyde building block **8**[iv]

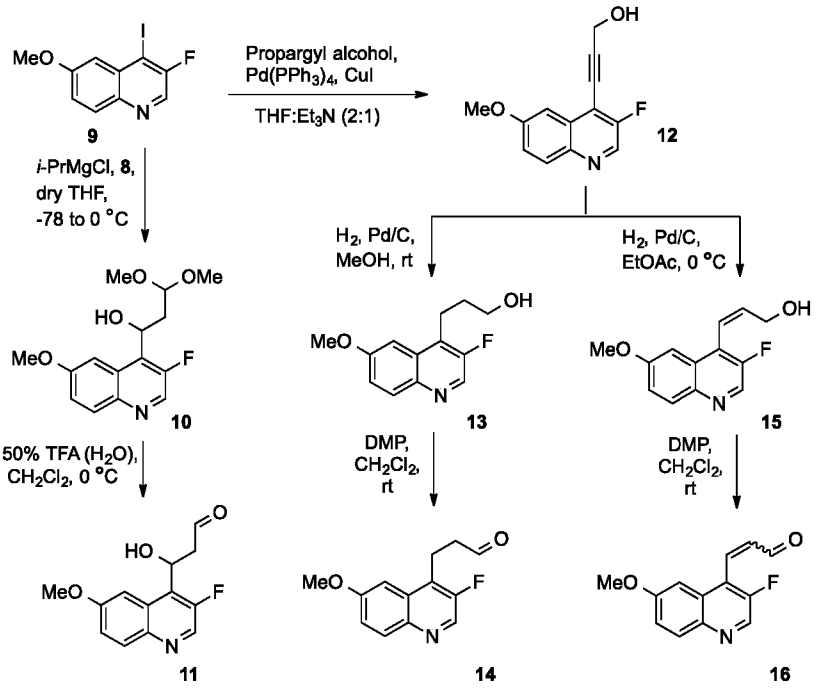


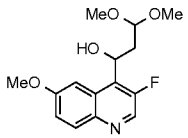
7 8



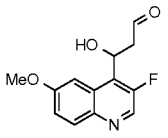
3,3-Dimethoxypropanal (8).[iv] A 250 mL flask was charged with a magnetic stirring bar, 1,1,3,3-tetramethoxypropane (40 g, 0.243 mol), 6% H_3PO_4 (20 mL) and the mixture was stirred for 5 days at rt. Then Et_2O (300 mL) was added and the mixture was cooled in an ice bath. $CaCO_3$ (20 g) was added and after 5 min stirring the mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (Et_2O:pentane (3:7), R_f = 0.2) to give the title compound as a colorless liquid (8.57 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.32 (s, 1H), 4.42 (t, J = 3.9 Hz, 1H), 2.97-2.94 (m, 6H), 2.40-2.09 (m, 2H). All spectroscopic data were consistent with those in the literature.

Scheme 3. Synthesis of quinoline-aldehyde building blocks **11**, **14**, and **16**

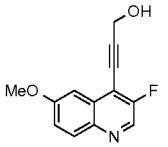




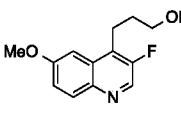
1-(3-Fluoro-6-methoxyquinolin-4-yl)-3,3-dimethoxypropan-1-ol (10). A 50 mL flask was charged with a magnetic stirring bar, iodoquinoline **6** (0.500 g, 1.65 mmol), THF (8 mL) and the mixture was cooled to -78 °C. 2 M *i*-PrMgCl in THF (1.07 mL, 2.14 mmol) was then added and the mixture was stirred for 10 min, whereupon 3,3-dimethoxypropanal **8** (0.292 g, 2.47 mmol) was added and the external cooling was removed. After stirring for 10 min NH_4Cl (aq) was added and the mixture was concentrated to remove the volatiles. The mixture was then taken up in water, extracted with CH_2Cl_2 (3 x 50 mL) and the combined organic layers were concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give the title compound as a colorless oil (195 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 1.9 Hz, 1H), 7.93 (d, *J* = 9.2 Hz, 1H), 7.76 (d, *J* = 2.7 Hz, 1H), 7.27 (dd, *J* = 9.5, 2.4 Hz, 1H), 5.70 (dd, *J* = 9.5, 3.7 Hz, 1H), 4.63 (t, *J* = 5.4 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.51 (ddd, *J* = 14.5, 9.4, 5.4 Hz, 1H), 2.07 (ddd, *J* = 14.5, 5.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 154.0 (d, J_{CF} = 253.7 Hz), 142.1 (d, J_{CF} = 2.5 Hz), 138.4 (d, J_{CF} = 30.1 Hz), 131.5, 130.0 (d, J_{CF} = 8.3 Hz), 127.9 (d, J_{CF} = 2.9 Hz), 120.8 (d, J_{CF} = 2.5 Hz), 103.4 (d, J_{CF} = 5.3 Hz), 103.2, 64.5 (d, J_{CF} = 4.6 Hz), 55.6, 54.0, 53.4, 39.1; IR (neat) cm^{-1}: 2938, 2832, 1621, 1508, 1467, 1427, 1354, 1227, 1123, 1053; HRMS (ESI) calcd for $C_{15}H_{19}FNO_4$ $[M + H]^+$ 296.1293, found 296.1298.



3-(3-Fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropanal (11). Acetal **10** (47 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (0.6 mL), cooled to 0 °C and added TFA:H_2O (1:1, 0.3 mL) and the mixture was stirred for 10 min at this temperature followed by 2 h at rt. CH_2Cl_2 (25 mL) and $NaHCO_3$ (sat, aq) (25 mL) were added and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were dried using Na_2SO_4 and concentrated *in vacuo* to give the title compound as a mixture of dimeric structures. Mixture used directly without further purification.



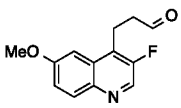
3-(3-Fluoro-6-methoxyquinolin-4-*yl*)prop-2-yn-1-ol (12). A suspension of iodoquinoline **6** (10.0 g, 33.0 mmol) in THF (200 mL) and Et_3N (130 mL) was degassed with argon for 1 h. $Pd(PPh_3)_4$ (1.14 g, 0.990 mmol) and CuI (0.315 g, 1.65 mmol) were added and the reaction mixture was degassed with argon for 1 h. Propargyl alcohol (2.15 mL, 39.6 mmol) was added via syringe and the reaction mixture was degassed for 30 min before stirring for 5 days at rt. Water (150 mL) and CH_2Cl_2 (200 mL) were then added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The remaining solids were washed with CH_2Cl_2 to give the title compound as a white solid, which was collected as crop 1 (5.80 g). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2) to give the title compound as an additional crop of white solid (1.70 g). Combined yield: 7.50 g, 98%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (s, 1H), 8.03 - 7.94 (m, 1H), 7.50 - 7.40 (m, 2H), 5.65 (t, J = 6.1 Hz, 1H), 4.54 (d, J = 6.1 Hz, 2H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.18, 156.3 (d, J_{CF} = 259.1 Hz), 140.7 (d, J_{CF} = 2.5 Hz), 138.0 (d, J_{CF} = 26.7 Hz), 131.3, 129.1, 121.5 (d, J_{CF} = 2.7 Hz), 111.9 (d, J_{CF} = 12.7 Hz), 105.1 (d, J_{CF} = 4.5 Hz), 103.4 (d, J_{CF} = 5.2 Hz), 73.0 (d, J_{CF} = 0.9 Hz), 55.7, 49.7; IR (neat) cm^{-1}: 3322, 3089, 2831, 2661, 1620, 1596, 1503, 1470, 1222, 1027; m.p.: 118.8-119.8 °C.



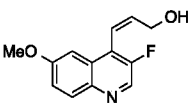
3-(3-Fluoro-6-methoxyquinolin-4-yl)propan-1-ol (13). Alkyne **12** (7.50 g, 32.4 mmol) and Pd/C (3.45 g, 3.24 mmol) were placed under an argon atmosphere. MeOH (325 mL) was added via syringe and the flask was evacuated, filled with hydrogen, and the reaction mixture was stirred for 2 days at rt. Then additional Pd/C (0.843 g, 0.792 mmol), (0.570 g, 0.139 mmol) and (1.87 g, 0.456 mmol) was added after 2 days, 5 days, and 8 days, respectively. After 9

days the reaction mixture was filtered through celite, washed with EtOAc, and concentrated *in vacuo*. The residue was washed with CH_2Cl_2 and the white solid was collected as crop 1 (3.44 g). The filtrate was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give a second crop of product (1.70 g) as a white solid. Combined yield: 5.14 g, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J_{HF} = 0.9 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 7.30 (dd, J = 9.0, 2.7 Hz, 1H), 7.28 (d, J = 2.5 Hz, 1H), 3.94 (s, 3H), 3.72 (t, J = 6.1 Hz, 2H), 3.20 - 3.09 (m, 2H), 2.21 - 1.84 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 155.1 (d, J_{CF} = 251.2 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.7, 129.8 (d, J_{CF} = 13.0 Hz), 129.4 (d, J_{CF} = 3.9 Hz), 120.5 (d, J_{CF} = 2.7 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 61.9, 55.7, 32.0, 20.5 (d, J_{CF} = 3.3 Hz); IR (neat) cm^{-1}: 3219, 2941, 2877, 2842, 1620, 1511, 1431, 1324, 1216, 1031, 828; m.p. = 116.2 - 117.5 °C.

General procedure I: Oxidation of alcohols to aldehydes with Dess-Martin periodinane

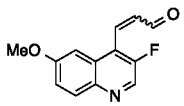


3-(3-Fluoro-6-methoxyquinolin-4-yl)propanal (14). 3-(3-Fluoro-6-methoxyquin-olin-4-yl)propan-1-ol (**13**) (135 mg, 0.574 mmol) and DMP (292 mg, 0.689 mmol) were dissolved in CH_2Cl_2 (3 mL) and stirred at rt. After 2 h the reaction mixture was quenched with a 2:1 solution of 10% $Na_2S_2O_3$ (aq) and sat. $NaHCO_3$ (aq) (3 mL) and stirred for 30 min, whereupon the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL) and the combined organic layers were washed with water containing a few drops of 2 M NaOH (aq) (10 mL), dried over Na_2SO_4, to afford the title compound as a white solid (131 mg, >95%), which was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.59 (s, J = 1.1 Hz, 1H), 8.01 (d J = 9.2 Hz, 1H), 7.32 (dd, J = 9.2, 2.7 Hz, 1H), 7.15 (d, J = 2.7 Hz, 1H), 3.95 (s, 3H), 3.35 (dt, J = 7.7, 1.8 Hz, 2H), 2.87 (t, J = 7.7 Hz, 2H); HRMS (ESI) calcd for $C_{13}H_{13}FNO_2$ $[M + H]^+$ 234.0925, found 234.0931.



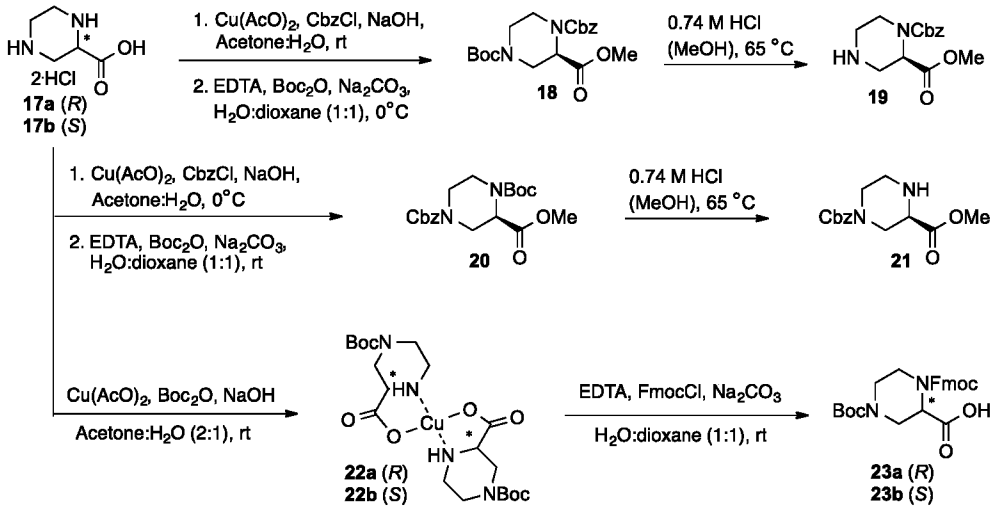
(*Z*)-3-(3-Fluoro-6-methoxyquinolin-4-yl)prop-2-en-1-ol (15). A 50 mL flask was charged with a magnetic stirring bar, a septum, 3-(3-fluoro-6-methoxyquinolin-4-yl)prop-2-yn-1-ol (**12**) (0.500 mg, 2.16 mmol), EtOAc (25 mL) and Pd/C (115 mg, 0.108 mmol) and cooled to 0 °C in an ice bath. An H_2-atmosphere was introduced via a balloon and the mixture was stirred for 4 h. The mixture was then filtered through celite, which was washed with EtOAc. The fil-

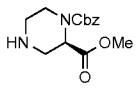
trate was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2) to give the title compound as a white solid (421 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J_{HF} = 0.7 Hz, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.29 (dd, J = 9.2, 2.7 Hz, 1H), 7.05 (d, J = 2.7 Hz, 1H), 6.56 (dd, J = 11.6, 1.3 Hz, 1H), 6.38 (dt, J = 11.6, 6.5 Hz, 1H), 4.13 (dt, J = 6.5, 1.3 Hz, 2H), 3.90 (s, 3H), 2.26 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 153.2 (d, J_{CF} = 253.4 Hz), 141.3 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.6 Hz), 137.7 (d, J J_{CF} = 1.0 Hz), 131.3, 128.7 (d, J_{CF} = 2.7 Hz), 124.9 (d, J_{CF} = 13.5 Hz), 121.2 (d, J_{CF} = 2.7 Hz), 118.8, 102.6 (d, J_{CF} = 5.5 Hz), 60.6 (d, J_{CF} = 4.6 Hz), 55.7; IR (neat) cm^{-1}: 3500-3300, 2937, 2834, 1620, 1507, 1426, 1358, 1227, 1026, 830; HRMS (ESI) calcd for $C_{13}H_{13}FNO_2$ $[M + H]^+$ 234.0930, found 234.0927; m.p.: 97 - 99 °C.



(Z)-3-(3-Fluoro-6-methoxyquinolin-4-yl)acrylaldehyde (16) Following ***general procedure I*** using (*Z*)-3-(3-fluoro-6-methoxyquinolin-4-yl)prop-2-en-1-ol (**15**) (85 mg, 0.36 mmol) and DMP (170 mg, 0.40 mmol) the title compound was obtained as a white solid (82 mg, >95%, *cis*:*trans* (3:1)) after extraction. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (dd, J = 7.4, 1.4 Hz, 1H), 9.60 (dd, J = 8.1, 2.0 Hz, 0.3H), 8.69 (s, 1H), 8.68 (s, 0.3H), 8.03 (d, J = 9.2 Hz, 1H), 8.03 (d, J = 9.1 Hz, 0.3H), 7.85 (dd, J = 16.3, 1.4 Hz, 0.3H), 7.60 (dd, J = 11.5, 2.0 Hz, 1H), 7.25 (d, J = 2.8 Hz, 0.3H), 7.03 (ddd, J = 16.3, 7.4 Hz, J_{HF} = 0.7 Hz, 0.3H), 6.98 (d, J = 2.7 Hz, 1H), 6.55 (ddd, J = 11.5, 8.1, J_{HF} = 1.5 Hz, 1H), 3.97 (s, 0.3H), 3.96 (s, 1H), 3.91 (s, 1H), 3.90 (s, 3H), *cis*:*trans* (3:1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4 (0.3C), 191.6 (d, J_{CF} = 3.1 Hz, 1C), 159.7 (0.3C), 159.6 (1C), 154.37 (d, J_{CF} = 263.3 Hz, 0.3C), 153.1 (d, J_{CF} = 257.1 Hz, 1C), 142.0 (d, J_{CF} = 2.8 Hz, 0.3C), 141.5 (d, J_{CF} = 2.6 Hz, 1C), 139.8 (1C), 138.5 (d, J_{CF} = 29.2 Hz, 0.3C), 138.2 (d, J_{CF} = 28.7 Hz, 1C), 137.3 (d, J_{CF} = 10.4 Hz, 0.3C), 136.4 (1C), 134.6 (1C), 132.2 (0.3C), 131.9 (1C), 128.2 (d, J_{CF} = 1.6 Hz, 1C), 127.4 (d, J_{CF} = 1.6 Hz, 0.3C), 122.3 (d, J_{CF} = 12.5 Hz, 0.3C), 121.8 (0.3C), 121.6 (d, J_{CF} = 2.8 Hz, 1C), 121.2 (d, J_{CF} = 2.8 Hz, 0.3C), 102.2 (d, J_{CF} = 5.3 Hz, 1C), 101.6 (d, J_{CF} = 5.3 Hz, 0.3C), 55.9 (0.3C), 55.8 (1C), *cis*:*trans* (3:1); HRMS (ESI) calcd for $C_{13}H_{11}FNO_2$ $[M + H]^+$ 232.1, found 232.1.

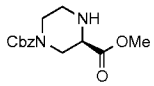
Scheme 4. Synthesis of *N*-protected piperazine building blocks





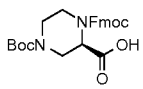
(*R*)-1-Benzyl 2-methyl piperazine-1,2-dicarboxylate (19). (*R*)-Piperazine-2-carboxylic acid dihydrochloride **17a** (4.94 g, 24.3 mmol) was dissolved in 6 M NaOH (aq) (13 mL) and added a suspension of $Cu(OAc)_2$ (2.2 g, 11.4 mmol) in H_2O (9 mL) The mixture was stirred for 10 minutes. Then acetone (36 mL) was added followed by slow addition of CbzCl (4.52 mL, 31.6 mmol) and the mixture was stirred at rt for 2 h and then concentrated *in vacuo*. The residue was taken up in H_2O (20 mL), followed by addition of K_2CO_3 (4.4 g, 31.6 mmol) and EDTA (4.5 g, 11.4 mmol) and then stirred for 10 min. A solution of Boc_2O (3.5 g, 31.6 mmol) in dioxane (20 mL) was then added and the mixture was stirred overnight at rt. HCl (conc. aq) was then added until pH 4-5, the aqueous phase was separated and further extracted with EtOAc (3 x 100 mL). The combined the organic layers were concentrated *in vacuo*. The residue was taken up in 0.78 M HCl in MeOH (premixed by addition of AcCl (6.6 mL) to MeOH (30 mL) at 0 °C) and stirred for 4 h at reflux. The mixture was concentrated *in vacuo* and then added EtOAc (100 mL) followed by addition of saturated $NaHCO_3$ (aq) until neutral pH. The phases were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (1% Et_3N in EtOAc, R_f = 0.2) to give the title compound as a colorless oil (4.86 g, 72%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.18 (m, 5H), 5.17 (s, 2H), 4.77 and 4.66 (2 x d, *J* = 2:5 Hz, 1H), 3.93 (m, 1H), 3.77 and 3.71 (2 x s, 3H), 3.56 and 3.51 (2 x d, *J* = 12.7 Hz, 1H), 3.25 and 3.13 (2 x td, *J* = 12.7, 3.2 Hz, 1H), 3.05 - 2.86 (m, 2H), 2.81 - 2.64 (m, 1H), 2.41 (br s, 1H), *R*otamers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 and 171.2, 156.5 and 156.0, 136.5, 128.6 (2C), 128.2, 128.0 (2C), 67.6 and 67.5, 55.2 and 54.7, 52.6, 47.1 and 46.9, 45.1, 42.3 and 42.0, rotamers; IR (neat) cm^{-1}: 3344,

2952, 2911, 2862, 1739, 1699, 1430, 1357, 1228, 763, 699; HRMS (ESI) calcd for $C_{14}H_{19}N_2O_4$ [M + H]$^+$ 279.1339, found 279.1342; $[\alpha]_D^{23}$ = - 44.7 (*c* 1.0, $CHCl_3$).



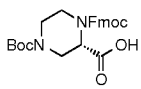
(*R*)-1-Benzyl-3-methyl-piperazine-1,3-dicarboxylate (21). A suspension of $Cu(OAc)_2$ (4.50 g, 24.8 mmol) in water (9.2 mL) was added to a solution of (*R*)-piperazine-2-carboxylic acid dihydrochloride (**17a**) (10.0 g, 49.2 mmol) in aqueous NaOH (6 M, 25.5 mL, 153 mmol) and stirred for 40 min at rt. Acetone (85 mL) was then added and the mixture was cooled to 0 °C, followed by drop-wise addition of CbzCl (9.20 mL, 64.4 mmol). After stirring at rt for another 1 h 40 min, EDTA (18.4 g, 49.2 mmol), K_2CO_3 (6.80 g, 64.0 mmol), and water (40 mL) were added. After 20 min, Boc_2O (14.0 g, 64.1 mmol) in acetone (40 mL) was added and the mixture was stirred for 5 days at rt. Additional K_2CO_3 (3.40 g, 24.6 mmol) and Boc_2O (1.10 g, 4.90 mmol) were added and the reaction mixture was stirred for 2 days. The acetone was removed *in vacuo* and the mixture was acidified to pH 5-6 using conc. HCl (aq) and then extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a yellow oil. AcCl (16.5 mL, 231 mmol) was added drop-wise to MeOH (75 mL) at 0 °C and the solution was added to the yellow oil and the mixture was stirred for 3 h 20 min at reflux and then concentrated *in vacuo*. EtOAc (200 mL) and sat. $NaHCO_3$ (aq) (100 mL) were added, the layers separated, and the aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (100% EtOAc to EtOAc:MeOH (19:1), R_f = 0.2 in 100% EtOAc) to give the title compound as a yellow oil (5.60 g, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.45 - 7.25 (m, 5H), 5.36 - 4.85 (m, 2H), 3.80 (br s, 1H), 3.63 (s, 3H), 3.58 - 3.38 (m, 2H), 3.20 - 3.02 (m, 1H), 2.95 - 2.81 (m, 1H), 2.77 (br s, 1H), 2.57 (t, *J* = 8.9 Hz, 1H), 2.54 - 2.46 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.5, 154.4, 136.9, 128.4, 127.9, 127.5, 66.3, 56.0, 51.7, 45.6, 43.8, 43.2; IR (neat) cm^{-1}: 3340, 2952, 1737, 1693, 1426, 1205, 1153, 1117, 754, 697. HRMS (ESI) calcd for $C_{14}H_{19}N_2O_4$ [M + H]$^+$ 279.1339, found 279.1340; $[\alpha]_D^{23}$ = + 62.4 (*c* 1.0, $CHCl_3$).

General procedure II: Synthesis of bis-protected piperazine-2-carboxylic acid



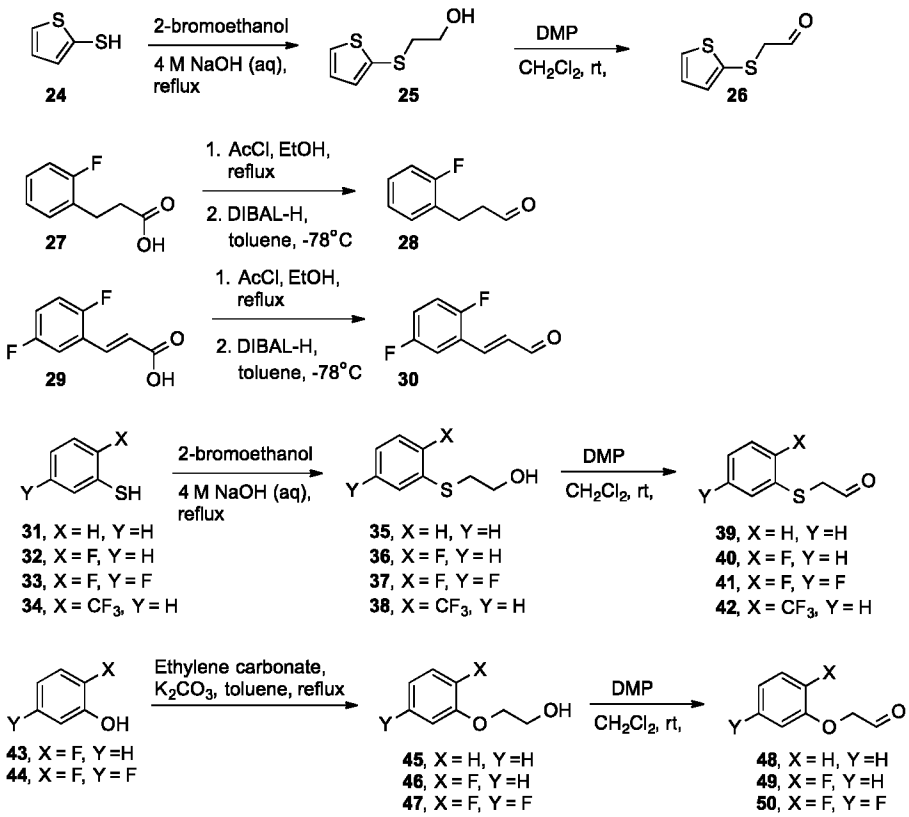
(*R*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (23a). To a solution of (*R*)-piperazine-2-car-

boxylic acid **17a** (2.96 g, 22.7 mmol) in 2 M NaOH (aq) (12 mL) a suspension of $Cu(OAc)_2$ (2.06 g, 11.4 mmol) in H_2O (9 mL) was added and the mixture was stirred for 10 minutes. Then Boc_2O (6.44 g, 29.5 mmol) dissolved in acetone (33 mL) was added followed by stirring at rt for 1.5 h. Then the mixture was filtered and the filter cake was rinsed with cold acetone:H_2O (2:1). The solids were dried *in vacuo* to give the copper complex **22a** as a light-blue solid (5.54 g, 93%). The copper complex **22a** (5.46 g, 10.5 mmol) was suspended in H_2O (50 mL), followed by the addition of EDTA (3.89 g, 10.5 mmol) and K_2CO_3 (3.76 g, 27.2 mmol) and stirred at rt for 10 minutes. Then FmocCl (5.41 g, 20.9 mmol) dissolved in dioxane (50 mL) was added and the reaction mixture was stirred for 30 min at rt. The mixture was then concentrated *in vacuo* to remove dioxane and the aqueous phase was extracted with EtOAc (10 mL). The mixture was acidified (pH < 4) with conc. HCl (aq) and extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a white amorphous solid (8.96 g, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.70 (m, 2H), 7.57 (dd, *J* = 6.9, 4.6 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.43 - 7.35 (m, 2H), 7.35 - 7.26 (m, 2H), 4.88 - 4.35 (m, 4H), 4.34 - 4.16 (m, 1H), 4.15 - 3.78 (m, 2H), 3.41 - 2.97 (m, 2H), 2.82 (s, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.7, 154.5, 143.8, 141.5, 127.9, 127.3, 125.1, 124.9, 120.2, 81.0, 68.2, 54.0, 47.3, 44.4, 41.4, 40.9, 28.4; IR (neat) cm^{-1}: 3012, 2971, 2940, 1697, 1637; $[\alpha]_D^{23}$ = + 8.5 (*c* 1.0, $CHCl_3$).

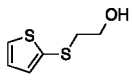


(*S*)-1-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-(*tert*-butoxycarbonyl)piperazine-2-carboxylic acid (23b).[v] Following ***general procedure II***, using (*S*)-piperazine-2-carboxylic acid dihydrochloride **17b** (4.95 g, 24.4 mmol), 2 M NaOH (aq) (49 mL), $Cu(OAc)_2$ (2.22 g, 12.2 mmol), Boc_2O (6.92 g, 31.7 mmol), EDTA (4.53 g, 12.2 mmol), K_2CO_3 (4.38 g, 31.7 mmol) and FmocCl (6.31 g, 24.4 mmol), the title compound was isolated as a white solid via extraction (7.72 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 - 7.63 (m, 2H), 7.50 (dd, *J* = 7.0, 4.8 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.36 - 7.27 (m, 2H), 7.27 - 7.19 (m, 1H), 4.79 - 4.31 (m, 4H), 4.25 - 4.10 (m, 1H), 4.01 - 3.70 (m, 2H), 3.33 - 3.08 (m, 1H), 3.07 - 2.89 (m, 1H), 2.86 - 2.67 (m, 1H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.7, 154.5, 143.8, 141.5, 127.9, 127.3, 125.1, 124.9, 120.2, 81.0, 68.2, 54.0, 47.3, 44.4, 41.4, 40.9, 28.4; m.p.: 179 - 180 °C; IR (neat) cm^{-1}: 3020, 2966, 2915, 1757, 1681, 1662; MS (ESI) calcd for $C_{25}H_{29}N_2O_6$ $[M + H]^+$ 543.20, found 453.37; $[\alpha]_D^{23}$ = – 9.2 (*c* 1.0, $CHCl_3$). All spectroscopic data were consistent with those in the literature.

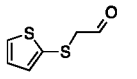
Scheme 5. Synthesis of aldehyde building blocks



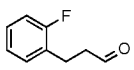
General procedure III: Alkylation of thiols with bromoethanol[vi]



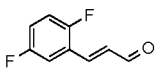
2-(Thiophen-2-ylthio)ethanol (25).[vii] Thiophene-2-thiol (**24**) (5.00 g, 43.3 mmol) and 2-bromoethanol (5.81 g, 46.8 mmol) were dissolved in 4 M NaOH (aq) (10 mL) and stirred at reflux. After 2 h the reaction was allowed to cooled to rt and CH_2Cl_2 (75 mL) was added, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 75 mL). The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc:heptane (1:4), R_f = 0.1) to give the title compound as a red/brown oil (5.89 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 5.4, 1.1 Hz, 1H), 7.16 (dd, J = 3.5, 1.1 Hz, 1H), 6.98 (dd, J = 5.4, 3.5 Hz, 1H), 3.74 (t, J = 5.9 Hz, 2H), 2.96 (t, J = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.7, 132.8, 130.0, 127.8, 60.2, 41.9; IR (neat) cm^{-1}: 3332, 3100, 2922, 1402, 1337, 1283, 1216, 1043, 845, 695, 495, 471; HRMS (ESI) calcd for $C_6H_9OS_2$ $[M + H]^+$ 161.0089, found 161.0090. All spectroscopic data were consistent with those in the literature.



2-(Thiophen-2-ylthio)acetaldehyde (26).[viii] Following ***general procedure I***, using alcohol **25** (5.39 g, 33.6 mmol), DMP (15.7 g, 3.70 mmol), 2 M NaOH (aq) (400 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The title compound was isolated as a red/brown oil (2.82 g, 53%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:9), R_f = 0.2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51 (t, J = 2.8 Hz, 1H), 7.64 (dd, J = 5.3, 1.2 Hz, 1H), 7.22 (dd, J = 3.6, 1.3 Hz, 1H), 7.04 (dd, J = 5.3, 3.6 Hz, 1H), 3.71 (d, J = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.1, 134.7, 131.2, 131.0, 128.2, 47.3. All spectroscopic data were consistent with those in the literature.

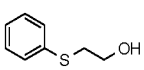


3-(2-Fluorophenyl)propanal (28). AcCl (2.42 mL, 33.9 mmol) was dissolved in ethanol (7.4 mL), whereupon 3-(2-fluorophenyl)propanoic acid (0.500 g, 2.97 mmol) was added and the reaction was stirred at reflux. After 30 min the solvent was removed *in vacuo* and the remaining crude was taken up in sat. Na_2CO_3 (aq) (15 mL) and CH_2Cl_2 (30 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude ester was dissolved in dry toluene (30 mL) and cooled to -78 °C followed by the dropwise addition of 1 M DIBAL-H in toluene (3.57 mL, 3.57 mmol). After stirring for 3 h at -78 °C, 1M HCl (aq) (20 mL, 20 mmol) was added and the reaction mixture was removed from the cooling bath and allowed to heat to room temperature until clear separation of the two phases (1 h). Then the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL), whereupon the organic layers were combined, dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (1:9), R_f = 0.25) to give the title compound as a white amorphous solid (0.375 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.24 - 7.14 (m, 2H), 7.04 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 2.78 (t, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 161.2 (d, J_{CF} = 245.0 Hz), 130.8 (d, J_{CF} = 4.8 Hz), 128.3 (d, J_{CF} = 8.1 Hz), 127.3 (d, J_{CF} = 15.6 Hz), 124.3 (d, J_{CF} = 3.6 Hz), 115.5 (d, J_{CF} = 21.9 Hz), 44.0 (d, J_{CF} = 1.3 Hz), 22.0 (d, J_{CF} = 2.8 Hz).

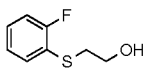


(*E*)-3-(2,5-Difluorophenyl)acrylaldehyde (30). AcCl (10.8 mL, 151 mmol) was dissolved in ethanol (34 mL), whereupon (*E*)-3-(2,5-difluorophenyl)acrylic acid (2.50 g, 13.6 mmol) was added and the reaction was stirred at reflux. After 30 min the solvent was removed *in vacuo* and the remaining crude was taken up in sat. Na2CO_3 (aq) (25 mL) and CH_2Cl_2 (50 mL). The layers were separated

and the aqueous phase was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude ester was dissolved in dry toluene (150 mL) and cooled to -78 °C followed by the dropwise addition of 1M DIBAL-H in toluene (16.3 mL, 16.3 mmol). After stirring for 2 h at -78 °C a mixture of the ester, aldehyde and alcohol was obtained and 1 M DIBAL-H in toluene (8.15 mL, 8.15 mmol) was added to reduce the ester and the aldehyde to the alcohol. After stirring for another 1 h at -78 °C 1M HCl (aq) (40 mL, 40 mmol) was added and the reaction mixture was removed from the cooling bath and allowed to heat to room temperature until clear separation of the two phases (1 h). Then the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 mL), whereupon the organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Following ***general procedure I***, the remaining crude was oxidized by DMP (6.33 g, 14.9 mmol) to give the title compound as a white amorphous solid (1.03 g, 45%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:9), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, J = 7.6 Hz, 1H), 7.60 (dd, J = 16.2, 1.0 Hz, 1H), 7.34 - 7.22 (m, 1H), 7.17 - 7.07 (m, 2H), 6.74 (dd, J = 16.2, 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 158.9 (dd, J_{CF} = 244.1, 2.4 Hz), 157.3 (dd, J_{CF} = 250.8, 2.4 Hz), 143.3 (dd, J_{CF} = 3.2, 2.4 Hz), 131.4 (d, J_{CF} = 5.0 Hz), 123.5 (dd, J_{CF} = 14.1, 8.0 Hz), 119.5 (dd, J_{CF} = 24.4, 9.0 Hz), 117.7 (dd, J_{CF} = 24.9, 8.5 Hz), 114.6 (dd, J_{CF} = 24.6, 2.9 Hz).

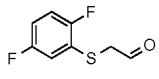


2-(phenylthio)ethanol (35).[ix] Following ***general procedure III***, thiophenol (446 µL, 4.54 mmol) was alkylated using 2-bromoethanol (0.386 µL, 5.45 mmol) and 4 M NaOH (aq) (1.14 mL) to give the title compound as a colorless oil (436 mg, 62%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:4), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.36 (m, 2H), 7.33 - 7.27 (m, 2H), 7.24 - 7.19 (m, 1H), 3.74 (t, J = 6.0 Hz, 2H), 3.11 (t, J = 6.0 Hz, 2H), 2.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 130.3, 129.2, 126.8, 60.4, 37.4. All spectroscopic data were consistent with those in the literature.

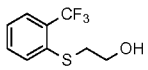


2-((2-Fluorophenyl)thio)ethanol (36). Following ***general procedure III***, 2-fluorobenzenethiol (0.517 g, 4.03 mmol) was alkylated using 2-bromoethanol (0.504 g, 4.03 mmol) and 4 M NaOH (aq) (1 mL) to give the title compound as a colorless oil (0.358 g, 51%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:4), R_f = 0.2).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (td, J = 7.8, 1.7 Hz, 1H), 7.30 - 7.22 (m, 1H), 7.15 - 7.03 (m, 2H), 3.71 (t, J = 5.9 Hz, 2H), 3.08 (t, J

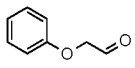
= 5.9 Hz, 2H), 2.02 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (d, J_{CF} = 245.6 Hz), 133.8 (d, J_{CF} = 1.4 Hz), 129.5 (d, J_{CF} = 7.9 Hz), 124.8 (d, J_{CF} = 3.8 Hz), 121.4 (d, J_{CF} = 17.8 Hz), 116.1 (d, J_{CF} = 22.8 Hz), 60.5, 37.4 (d, J_{CF} = 2.2 Hz); IR (neat) cm^{-1}: 3361, 2929, 2879, 1571, 1473, 1446, 1260, 1220, 1071, 821, 752; HRMS (ESI) calcd for $C_8H_8FS^+$ [M - OH]$^+$ 155.0325, found 155.0319.



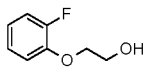
2-((2,6-Difluorophenyl)thio)ethanol (37). Following ***general procedure III***, 2,5-difluorobenzenethiol (95 mg, 0.65 mmol) was alkylated using 2-bromoethanol (81 mg, 0.65 mmol) and 4 M NaOH (aq) (0.16 mL) to give the title compound as a colorless oil (56 mg, 45%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:4), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (ddd, J = 8.6, 5.8, 3.1 Hz, 1H), 7.02 (td, J = 8.9, 4.6 Hz, 1H), 6.95 - 6.86 (m, 1H), 3.75 (t, J = 5.9 Hz, 2H), 3.10 (t, J = 5.9 Hz, 2H), 2.05 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (dd, J_{CF} = 244.9, 2.6 Hz), 157.8 (dd, J_{CF} = 241.0, 2.7 Hz), 123.9 (dd, J_{CF} = 20.4, 8.3 Hz), 118.7 (dd, J_{CF} = 25.1, 2.1 Hz), 116.0 (ddd, J = 147.3, 24.7, 8.5 Hz), 60.5, 36.7 (d, J = 2.3 Hz); IR (neat) cm^{-1}: 3356, 2932, 2881, 1614, 1583, 1480, 1245, 1186, 1059, 757; HRMS (ESI) calcd for $C_8H_7F_2S$ [M - OH]$^+$ 173.0231, found 173.0233.



2-((2-(Trifluoromethyl)phenyl)thio)ethanol (38). Following ***general procedure III***, 2-(trifluoromethyl)benzenethiol (0.500 g, 2.81 mmol) was alkylated using 2-bromoethanol (239 µL, 3.37 mmol) and 4 M NaOH (aq) (0.70 mL) to give the title compound as a colorless oil (450 mg, 72%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:7), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 3.75 (t, J = 5.9 Hz, 2H), 3.17 (t, J = 5.9 Hz, 2H), 2.07 (s, 1H); ^{13}C NMR (1000 MHz, $CDCl_3$) δ 134.8, 132.4, 132.3, 131.0 (q, J_{CF} = 29.9 Hz), 127.1 (q, J_{CF} = 5.6 Hz), 123.9 (q, J_{CF} = 274 Hz), 126.7, 60.4, 38.2; IR (neat) cm^{-1}: 3346, 2932, 2879, 1593, 1440, 1310, 1257, 1169, 1111, 1032, 759; HRMS (ESI) calcd for $C_9H_9F_3S$ [M - OH]$^+$ 205.0293, found 205.0291.

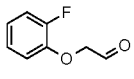


2-Phenoxyacetaldehyde (48). The aldehyde was freshly prepared from 2-phenoxyethanol (**45**) using ***general procedure I***.

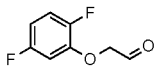


2-(2-Fluorophenoxy)ethan-1-ol (46). 2-Fluorophenol (**43**) (2.00 g, 17.8 mmol), ethylenecarbonate (3.14 g, 35.7 mmol) and K_2CO_3 (3.95 g, 28.6

mmol) were heated to reflux in toluene (90 mL). After stirring for 26 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give the title compound as a colorless oil (1.93 g, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 - 7.02 (m, 2H), 6.98 (td, *J* = 8.4, 1.7 Hz, 1H), 6.95 - 6.88 (m, 1H), 4.18 - 4.08 (m, 2H), 4.15 - 4.11 (m, 2H), 3.97 (d, *J* = 4.1 Hz, 2H), 2.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0 (d, J_{CF} = 245.3 Hz), 146.8 (d, J_{CF} = 10.6 Hz), 124.5 (d, J_{CF} = 3.9 Hz), 121.8 (d, J_{CF} = 6.9 Hz), 116.4 (d, J_{CF} = 18.3 Hz), 115.5 (d, J_{CF} = 1.7 Hz), 71.0, 61.4.

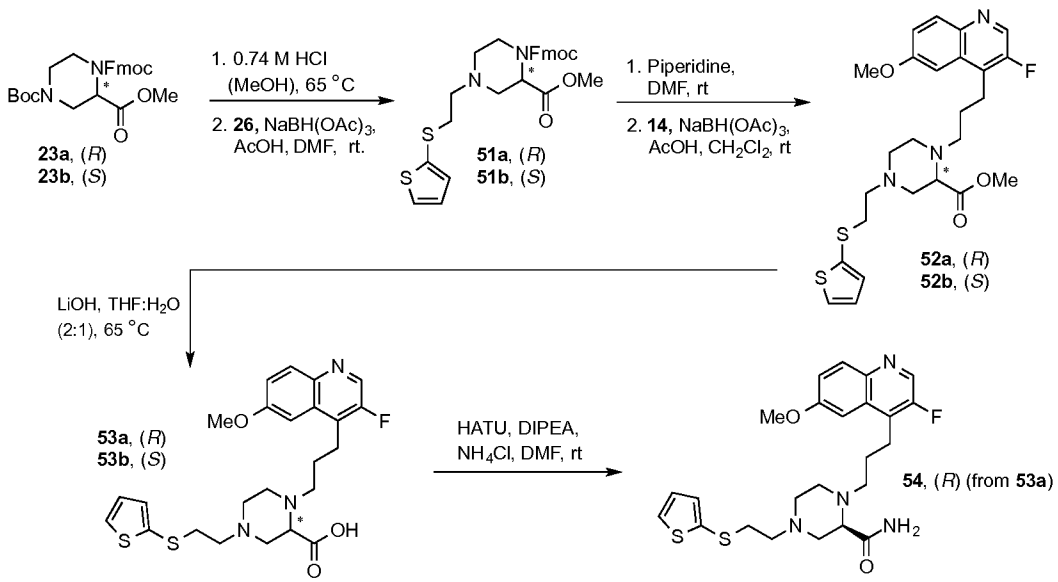


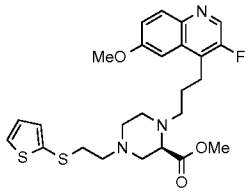
2-(2-Fluorophenoxy)acetaldehyde (49). The aldehyde was freshly prepared from 2-phenoxyethanol (**46**) using ***general procedure I***.



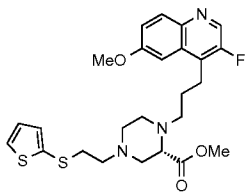
2-(2,5-Difluorophenoxy)acetaldehyde (50). 2,5-Difluorophenol (44) (3.00 g, 23.1 mmol), ethylenecarbonate (4.01 g, 46.1 mmol) and K_2CO_3 (5.1 g, 36.9 mmol) were heated to reflux in toluene (115 mL). After stirring for 26 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0:2) to the intermediate alcohol **47** (2.59 g, 65%). Following ***general procedure I***, the alcohol was oxidized using DMP (6.9 g, 14.9 mmol) to give the title compound as a white amorphous solid (2.30 g, 90%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:7), R_f = 0.2). The compound was not characterized due to rapid decomposition.

Scheme 6. Synthesis of compounds **53a**, **53b** and **54**



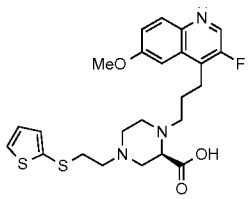


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylate (52a). A 50 mL flask was charged with a magnetic stirring bar and MeOH and cooled to 0 °C. Then AcCl (215 μL) was added and the mixture was stirred for 5 min. The bis-protected piperazine **23a** (500 mg, 1.10 mmol) was added and the mixture was stirred for 2 h at reflux, and then concentrated *in vacuo*. CH_2Cl_2 was added to the mixture and then removed *in vacuo* (repeated 3 times). The HCl salt was then dissolved in DMF (5.5 mL) and added aldehyde **14** (0.210 mg, 1.33 mmol) followed by $NaBH(OAc)_3$ (formed *in situ* by addition of AcOH to $NaBH_4$ (50 mg, 1.33 mmol)) and the mixture was stirred for 1 h at rt. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2) to give the intermediate **51a** (165 mg, 29%). The intermediate product **51a** (157 mg, 0.309 mmol) was dissolved in DMF and added piperidine (61 μL, 0.618 mmol) and the mixture was stirred for 20 min at rt. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography (gradient from 0-10% MeOH in EtOAc, R_f = 0.1 in EtOAc:MeOH (19:1)) to give the free amine (79 mg, 89%). The amine (79 mg, 0.27 mmol) was then dissolved in CH_2Cl_2 (3 mL) and added aldehyde **14** (64 mg, 0.27 mmol) followed by $NaBH(OAc)_3$ (formed *in situ* by addition of AcOH to $NaBH_4$ (13 mg, 0.33 mmol)) and the mixture was stirred for 20 min at rt. The solvent was removed and the residue was purified by flash column chromatography on silica gel (EtOAc:heptane (11:9), R_f = 0.2) to give the title compound as a colorless oil (110 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.33 - 7.28 (m, 2H), 7.17 (d, *J* = 2.6 Hz, 1H), 7.10 (dd, *J* = 3.5, 0.9 Hz, 1H), 6.95 (dd, *J* = 5.3, 3.6 Hz, 1H), 3.94 (s, 3H), 3.66 (s, 3H), 3.34 - 3.26 (m, 1H), 3.13 - 2.95 (m, 3H), 2.91 - 2.76 (m, 3H), 2.75 - 2.65 (m, 1H), 2.65 - 2.36 (m, 7H), 1.85 (q, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 134.4, 133.8, 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.4, 129.3 (d, J_{CF} = 3.9 Hz), 127.6, 120. 2 (d, J_{CF} = 2.5 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 63.4, 57.4, 55.7, 55.4, 55.2, 53.0, 51.7, 48.6, 35.8, 26.6, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2947, 2813, 1739, 1620, 1509, 1466, 1229, 1031, 831; HRMS (ESI) calcd for $C_{25}H_{31}FN_3O_3S_2$ $[M + H]^+$ 504.1785, found 504.1786 $[\alpha]_D^{23}$= + 16.7 (*c* 1.0, $CHCl_3$).



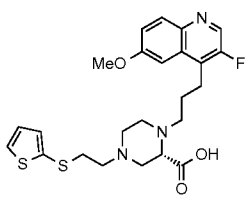
(*S*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylate (52b). The compound was prepared according to **52a** starting from **23b** (500 mg, 1.10 mmol) to give the title compound as a colorless oil (134 mg, 24% over the 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.17 (d, *J* = 2.5 Hz, 1H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.95 (dd, *J* = 5.2, 3.6 Hz, 1H), 3.94 (s, 3H), 3.66 (s, 3H), 3.34 - 3.27 (m, 1H), 3.12 - 2.95 (m, 3H), 2.90 - 2.77 (m, 3H), 2.75 - 2.66 (m, 1H), 2.64 - 2.36 (m, 7H), 1.86 (q, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.3 (d, *J* = 29.4 Hz), 134.4, 133.8, 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.4, 129.3 (d, J_{CF} = 3.9 Hz), 127.6, 120.2 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.4, 57.4, 55.7, 55.4, 55.2, 52.9, 51.7, 48.7, 35.8, 26.6, 22.0 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3072, 2948, 2814, 1740, 1620, 1509, 1468, 1229, 1031, 831, 705; HRMS (ESI) calcd for $C_{25}H_{31}FN_3O_3S_2$ [M + H]$^+$ 504.1785, found 504.1784; $[\alpha]_D^{23}$ = – 11.3 (*c* 1.0, $CHCl_3$).

General procedure IV: Hydrolysis of methyl ester

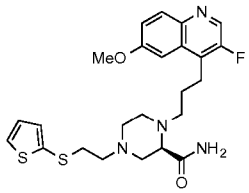


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylic acid (53a). Methyl ester **52a** (0.040 g, 0.080 mmol) was charged in a glass vial. 0.9 M LiOH (aq) (260 µL, 0.234 mmol) and THF (520 µL) were then added. The vial was sealed with a lid, and placed on a heated shaker (65 °C) for 1-2 days, whereupon the reaction was quenched with 0.9 M AcOH (aq) (260 µL, 0.234 mmol). The reaction mixture was then concentrated under a flow of pressurized air, and purified by preparative HPLC to give the title compound as an off-white solid (25 mg, 51%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.60 (d, *J* = 5.3 Hz, 1H), 7.38 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.34 (d, *J* = 2.6 Hz, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 7.04 (dd, *J* = 5.3, 3.6 Hz, 1H), 3.94 (s, 3H), 3.20 - 3.15 (m, 1H), 3.13 - 2.96 (m, 3H), 2.93 - 2.81 (m, 3H), 2.66 - 2.58 (m, 2H), 2.54 - 2.30 (m, 6H), 1.86 - 1.72 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.8, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 134.8, 132.8, 131.8, 130.2, 129.6 (d, J_{CF} = 12.8 Hz), 129.3 (d, J_{CF} = 3.8 Hz), 127.9, 120.4 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.3 Hz), 60.8, 56.1, 55.9, 54.9, 54.4, 51.4, 47.9, 34.9, 25.8, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3477 (br), 2998, 2953, 2828, 1722, 1620, 1509, 1468, 1230, 1028,

831; HRMS (ESI) calcd for $C_{27}H_{31}FN_3O_4$ $[M + H]^+$ 480.2293, found 480.2302; $[\alpha]_D^{23} = -13.5$ (*c* 1.0, $CHCl_3$).

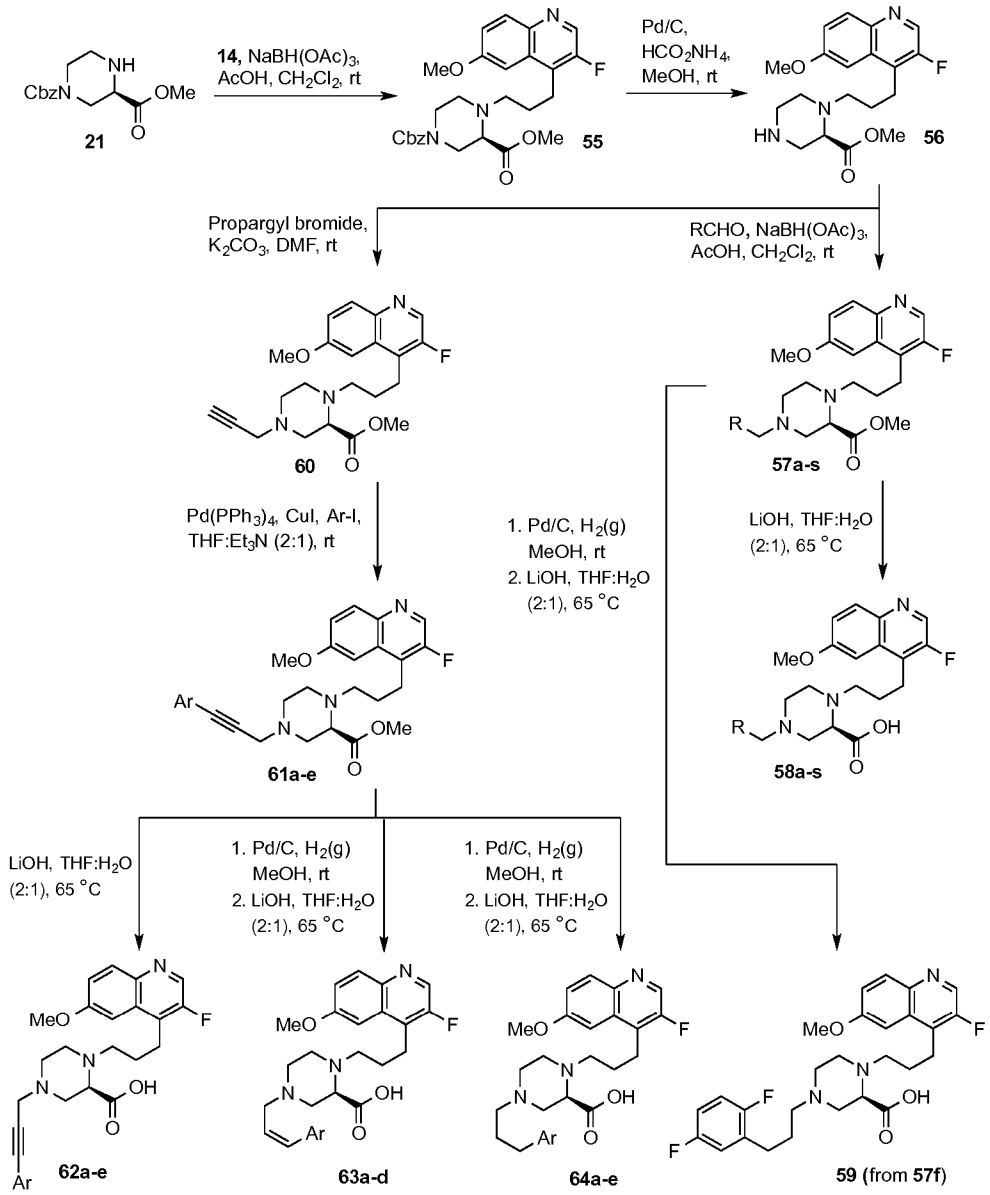


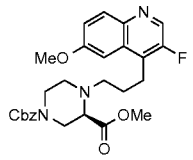
(*S*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(thiophen-2-yl-thio)ethyl)piperazine-2-carboxylic acid (53b). Following ***general procedure IV***, methyl ester **52b** (0.045 g, 0.089 mmol), was hydrolyzed with aqueous LiOH to give the title compound as a colorless oil (28 mg, 57%) after purification by preparative HPLC. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.61 (dd, *J* = 5.3, 1.2 Hz, 1H), 7.42 - 7.32 (m, 2H), 7.18 (dd, *J* = 3.5, 1.3 Hz, 1H), 7.04 (dd, *J* = 5.3, 3.5 Hz, 1H), 3.95 (s, 3H), 3.23 - 2.97 (m, 4H), 2.95 - 2.81 (m, 3H), 2.68 - 2.56 (m, 2H), 2.50 - 2.29 (m, 6H), 1.87 - 1.71 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.8, 155 (d, J_{CF} = 251.5, Hz), 141.5 (d, J_{CF} = 2.2 Hz), 138.1 (d, J_{CF} = 29.4 Hz), 134.6, 133.0, 131.7, 130.0, 129.4 (d, J_{CF} = 12.9 Hz), 129.2 (d, J_{CF} = 3.9 Hz), 127.8, 120.4 (d, J_{CF} = 2.4 Hz), 101.7 (d, J_{CF} = 5.4 Hz), 61.8, 56.2, 55.8, 54.9, 54.4, 51.3, 48.2, 34.0, 25.5, 21.8 (d, J_{CF} = 3.0 Hz).



(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(thiophen-2-ylthio)-ethyl)piperazine-2-carboxamide (54). Carboxylic acid **53a** (10 mg, 0.02 mmol) was dissolved in DMF (200 µL) where after DIPEA (11 µL, 0.06 mmol) and HATU (9 mg, 0.02 mmol) were added and the mixture was stirred for 5 min at rt. Then NH_4Cl (2 mg, 0.03 mmol) was added and the mixture was stirred for 1 h at rt. The mixture was then purified by preparative HPLC to give the title compound as an orange oil (7 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J_{HF} = 2.1 Hz, 1H), 8.23 (d, *J* = 9:3 Hz, 1H), 7.49 (dd, *J* =9.3, 2.5 Hz, 1H), 7.41 (dd, *J* =5.4, 1.2 Hz, 1H), 7.28 (d, *J* = 2:5 Hz, 1H), 7.17 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.00 (dd, *J* = 5.4, 3.6 Hz, 2H), 6.85 (br s, 2H), 4.00 (s, 3H), 3.86 (d, **J** = 6.0 Hz, 1H), 3.48 - 3.29 (s, 1H), 3.32 - 2.97 (m, 11H), 2.97 - 2.87 (m, 1H), 2.84 - 2.75 (m, 1H), 2.11 - 2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 154.8 (d, J_{CF} = 248.6 Hz), 136.1, 135.6, 133.9 (d, J_{CF} = 34.5 Hz), 131.1, 130.8 (d, J_{CF} = 8.8 Hz), 130.1 (d, J_{CF} = 4.1 Hz), 128.3, 127.1, 124.1, 117.4, 114.5, 102.0, 56.2, 55.2 54.1, 53.2, 50.8, 47.8, 41.7, 32.8, 25.0, 22.4.

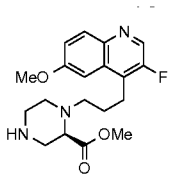
Scheme 7. Synthesis of compounds **58a-s**, **59**, **62a-e**, **63a-f** and **64a-e**





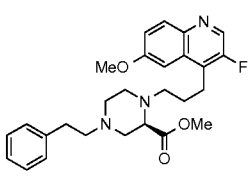
1-Benzyl 3-methyl (*R*)-4-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazin-e-1,3-dicarboxylate (55). A solution of piperazine **21** (4.50 g, 16.2 mmol) in CH_2Cl_2 (100 mL) was added to aldehyde **14** followed by the addition of AcOH (93.0 µL, 1.62 mmol) and $NaBH(OAc)_3$ (5.14 g, 24.3 mmol). The reaction mixture was stirred for 1 h 50 min at rt before quenching with sat. aqueous $NaHCO_3$ (120 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL), the combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography on silica gel (EtOAc:heptane (9:11), R_f = 0.20) to give the title compound as a yellow oil (6.80 g, 85%). ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.43 - 7.23 (m, 7H), 5.06 (s, 2H), 3.94 (s, 3H), 3.90 - 3.76 (m, 1H), 3.76 - 3.57 (m, 1H), 3.54 - 3.45 (m, 3H), 3.41 -

3.37 (m, 1H), 3.28 (dd, *J* = 13.2, 3.9 Hz, 1H), 3.07 (t, *J* = 7.4 Hz, 3H), 2.94 (t, *J* = 9.2 Hz, 1H), 2.73 - 2.65 (m, 1H), 2.62 - 2.52 (m, 1H), 2.48 - 2.38 (m, 1H), 1.88 - 1.68 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.4, 158.4, 154.7 (d, J_{CF} = 250.1 Hz), 154.3, 141.2 (d, J_{CF} = 2.1 Hz), 138.1 (d, J_{CF} = 29.0 Hz), 137.0, 131.5, 130.1 (d, J_{CF} = 12.9 Hz), 129.0 (d, J_{CF} = 3.9 Hz), 128.6, 128.0, 127.7, 120.6 (d, J_{CF} = 2.3 Hz), 102.6 (d, J_{CF} = 5.4 Hz), 66.5, 60.5, 55.8, 54.4, 51.4, 46.4, 45.8, 43.5, 26.5, 21.4 (d, J_{CF} = 2.6 Hz); IR (neat) cm^{-1}: 3032, 3001, 2949, 2860, 1737, 1699, 1620, 1508, 1465, 1427, 1281, 1226, 1118, 1027.



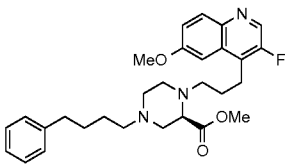
Methyl (*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl) piperazine-2-carbox-ylate (56). Compound **55** (6.80 g, 13.7 mmol) was dissolved in MeOH (80 mL) and placed under an argon atmosphere. Pd/C (1.46 g, 1.37 mmol) and HCO_2NH_4 (3.46 g, 54.9 mmol) were added and the reaction mixture was stirred for 21 h at rt. The reaction mixture was filtered through celite, washed with MeOH (170 mL), and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (100 mL) and sat. $NaHCO_3$ (100 mL) was added. The mixture was transferred to a separatory funnel and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4 and then concentrated *in vacuo* and purified by flash column chromatography on silica gel (MeOH:Et_3N:CH_2Cl_2 (1:3:100), R_f = 0.25) to give the title compound as a yellow oil (3.60 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J_{HF} = 1.0 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.19 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 3H), 3.66 (s, 3H), 3.23 (t, *J* = 4.5 Hz, 1H), 3.14 - 2.99 (m, 4H), 2.99 - 2.90 (m, 2H), 2.91 - 2.82 (m, 1H), 2.76 - 2.64 (m, 1H), 2.58 - 2.46 (m, 1H), 2.41 - 2.31 (m, 1H), 2.10 (br s, 1H), 1.95 - 1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.6, 154.9 (d, J_{CF} = 251.4 Hz), 141.5 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.7, 129.8 (d, J_{CF} = 13.0 Hz), 129.2 (d, J_{CF} = 3.9 Hz), 120.1 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.1, 55.7, 55.6, 51.5, 49.2, 48.5, 45.7, 26.2, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3297, 2948, 2830, 1736, 1619, 1507, 1467, 1428, 1227, 1130.

General procedure V: Reductive alkylation of amines

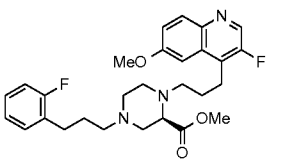


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-phenethylpip-erazine-2-carboxylate (57a). In a small vial, $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 μL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) was added to a

solution of amine **56** (50 mg, 0.14 mmol) and 2-phenylacetaldehyde (31 μL, 0.28 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred for 1.5 h at rt, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give the title compound as a colorless oil (62 mg, >95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.28 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 2H), 7.191 - 7.13 (m, 4H), 3.92 (s, 3H), 3.64 (s, 3H), 3.36 - 3.27 (m, 1H), 3.14 - 2.94 (m, 3H), 2.85 - 2.38 (m, 11H), 1.85 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 140.2, 138.2 (d, J_{CF} = 29.4 Hz), 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 126.1, 120.2 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.7, 60.1, 55.6, 55.2, 53.2, 51.7, 48.9, 33.4, 26.5. 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3064, 3027, 2949, 2811, 1741, 1621, 1509, 1467, 1321, 1230, 1031, 831, 700; HRMS (ESI) calcd for $C_{27}H_{33}FN_3O_3$ [M + H]$^+$ 466.2500, found 466.2500; $[\alpha]_D^{23}$= + 13.6 (*c* 1.0, $CHCl_3$).

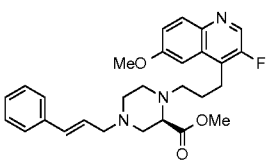


(*R*)- Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(4-phenyl-butyl)piperazine-2-carboxylate (57c). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol) was reductively alkylated using 4-phenylbutanal (23 mg, 0.15 mmol), AcOH (5.9 μL, 0.10 mmol), and $NaBH(OAc)_3$ (43 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) to give the title compound as a colorless oil (26 mg, 51%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3.1), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 1.0 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.34 - 7.24 (m, 4H), 7.21 - 7.13 (m, 4H), 3.95 (s, 3H), 3.65 (s, 3H), 3.33 - 3.28 (m, 1H), 3.14 - 2.96 (m, 3H), 2.88 - 2.76 (m, 1H), 2.67 - 2.24 (m, 10H), 1.87 (p, *J* = 7.6 Hz, 2H), 1.68 - 1.54 (m, 2H), 1.54 - 1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 142.6, 141.7 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.0 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 128.5, 128.4, 125.8, 120.3 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.9, 58.1, 55.7, 55.7, 55.3, 53.3, 51.7, 49.0, 35.9, 29.3, 26.6, 26.4, 22.1 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2940, 2857, 2811, 1742, 1620, 1508, 1468, 1362, 1320, 1230, 1031, 831, 700; HRMS (ESI) calcd for $C_{29}H_{37}FN_3O_3$ [M + H]$^+$ 494.2813 found 494.2814; $[\alpha]_D^{23}$ = + 17.9 (*c* 1.0, $CHCl_3$).

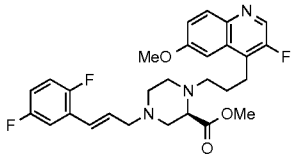


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(2-fluoro-phenyl)propyl)piperazine-2-carboxylate (57d). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol)

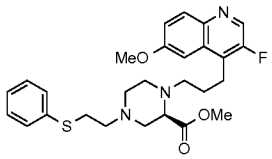
was reductively alkylated using aldehyde **28** (23 mg, 0.15 mmol), AcOH (5.9 μL, 0.10 mmol), and $NaBH(OAc)_3$ (43 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) to give the title compound as a colorless oil (29 mg, 56%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:1), R_f = 0.25). ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 1.0 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.31 (dd, J = 9.2, 2.7 Hz, 1H), 7.21 - 7.11 (m, 3H), 7.07 - 6.94 (m, 2H), 3.95 (s, 3H), 3.67 (s, 3H), 3.36 - 3.27 (m, 1H), 3.16 - 2.95 (m, 3H), 2.88 - 2.77 (m, 1H), 2.76 - 2.26 (m, 10H), 1.87 (p, J = 7.4 Hz, 2H), 1.76 (p, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 161.3 (d, J_{CF} = 244.6 Hz), 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.6, 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.8 (d, J_{CF} = 5.2 Hz), 130.1 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 129.0 (d, J_{CF} = 16.0 Hz), 127.6 (d, J_{CF} = 8.1 Hz), 124.0 (d, J_{CF} = 3.5 Hz), 120.3 (d, J_{CF} = 2.6 Hz), 115.3 (d, J_{CF} = 22.2 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 63.6, 57.4, 55.7, 55.5, 55.3, 53.3, 51.7, 48.9, 27.2, 26.8 (d, J_{CF} = 2.4 Hz), 26.6, 22.1 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 2949, 2813, 1741, 1620, 1508, 1467, 1457, 1229, 1032, 831, 757; HRMS (ESI) calcd for $C_{28}H_{34}F_2N_3O_3$ $[M + H]^+$ 498.2563 found 498.2555; $[\alpha]_D^{23}$ = + 12.8 (*c* 1.0, $CHCl_3$).



(*R*)-Methyl 4-cinnamyl-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-piperazine-2-carboxylate (57e). Following ***general procedure V***, amine **56** (50 mg, 0.14 mmol) was reductively alkylated using cinnamaldehyde (23 μL, 0.18 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 μL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min in CH_2Cl_2 (1.5 mL)) to give the title compound as a colorless oil (66 mg, >95%) after purification by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 0.6 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.35 (d, J = 7.2 Hz, 2H), 7.32 - 7.26 (m, 3H), 7.21 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 2.7 Hz, 1H), 6.49 (d, J = 15.9 Hz, 1H), 6.20 (dt, J = 15.9, 6.6 Hz, 1H), 3.93 (s, 3H), 3.65 (s, 3H), 3.31 (t, J = 5.0 Hz, 1H), 3.17 - 2.96 (m, 5H), 2.85 - 2.76 (m, 1H), 2.72 - 2.64 (m, 2H), 2.59 - 2.48 (m, 3H), 2.47 - 2.39 (m, 1H), 1.87 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 136.9, 133.2, 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.2 (d, J_{CF} = 3.9 Hz), 128.6, 127.6, 126.4, 126.2, 120.2 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.9, 60.8, 55.6, 55.6, 55.2, 53.1, 51.7, 49.1, 26.5, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3026, 2999, 2949, 2810, 2768, 1741, 1621, 1509, 1468, 1362, 1321, 1230, 1032, 831; HRMS (ESI) calcd for $C_{28}H_{33}FN_3O_3$ $[M + H]^+$ 478.2500, found 478.2502; $[\alpha]_D^{23}$= + 8.0 (*c* 1.0, $CHCl_3$).

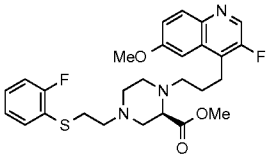


(*R,E*)-methyl 4-(3-(2,5-difluorophenyl)allyl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)propyl)piperazine-2-carboxylate (57f). Following ***general procedure V***, amine **56** (77 mg, 0.21 mmol) was reductively alkylated using aldehyde **30**, AcOH (12 µL, 0.013 mmol), and $NaBH(OAc)_3$ (91mg, 0.43 mmol) in CH_2Cl_2 (2 mL) to give the title compound as a colorless oil (77 mg, 70%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:1), R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 1.0 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.10 (ddd, J = 9.2, 5.8, 3.1 Hz, 1H), 6.96 (td, J = 9.2, 4.6 Hz, 1H), 6.91 - 6.82 (m, 1H), 6.61 (d, J = 16.1 Hz, 1H), 6.26 (dt, J = 16.1, 6.5 Hz, 1H), 3.94 (s, 3H), 3.66 (s, 3H), 3.35 - 3.29 (m, 1H), 3.22 - 2.96 (m, 5H), 2.88 - 2.77 (m, 1H), 2.76 - 2.60 (m, 2H), 2.60 - 2.49 (m, 3H), 2.48 - 2.39 (m, 1H), 1.87 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.9 (dd, J_{CF} = 241.6, 2.2 Hz), 158.6, 156.2 (dd, J_{CF} = 244.8, 2.2 Hz), 155.0 (d, J_{CF} = 251.4 Hz), 141.7 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.3, 129.9 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 126.1 (dd, J_{CF} = 14.8, 8.0 Hz), 124.5, 120.2 (d, J_{CF} = 2.6 Hz), 116.8 (dd, J_{CF} = 25.2, 8.8 Hz), 115.2 (dd, J_{CF} = 24.4, 8.7 Hz), 113.2 (dd, J_{CF} = 24.5, 4.1 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.7, 60.7, 55.7, 55.6, 55.2, 53.2, 51.7, 48.9, 26.6, 22.1 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 2950, 2812, 1740, 1620, 1508, 1490, 1468, 1429, 1264, 1229, 1193, 1147, 1031, 830; HRMS (ESI) calcd for $C_{28}H_{31}F_3N_3O_3$ $[M + H]^+$ 514.2312 found 514.2304; $[\alpha]_D^{23}$ = + 11.3 (*c* 1.0, $CHCl_3$).

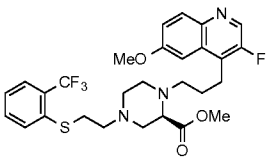


(*R*)-methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(phenyl-thio)ethyl)piperazine-2-carboxylate (57g). Following ***general procedure V***, amine **56** (50 mg, 0.14 mmol) was reductively alkylated using aldehyde **39** (23 mg, 0.15 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 µL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as an orange oil (51 mg, 74%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:2), R_f = 0.3). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.59 (s, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.37 - 7.25 (m, 5H), 7.23 - 7.15 (m, 2H), 3.96 (s, 3H), 3.68 (s, 3H), 3.36 - 3.29 (m, 1H), 3.13 - 3.05 (m, 3H), 3.02 (t, J = 7.5 Hz, 2H), 2.88 - 2.71 (m, 2H), 2.69 - 2.48 (m, 6H), 2.47 - 2.39 (m, 1H), 1.87 (p, J = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.4, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.3 (d, J_{CF} = 29.4

Hz), 136.4, 131.8, 129.9 (d, J = 12.9 Hz), 129.3, 129.2, 129.0, 126.1, 120.2 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.5, 57.3, 55.7, 55.5, 55.2, 53.0, 51.7, 48.7, 30.9, 26.5, 22.0 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 2948, 2814, 1740, 1620, 1509, 1467, 1230, 1029, 831; HRMS (ESI) calcd for $C_{27}H_{33}FN_3O_3S$ $[M + H]^+$ 498.2221, found 498.2218; $[\alpha]_D^{23}$= + 9.3 (*c* 1.0, $CHCl_3$).

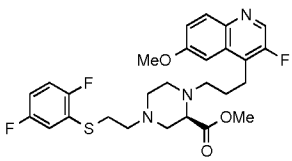


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-((2-fluoro-phenyl)thio)ethyl)piperazine-2-carboxylate (57h). Following ***general procedure V***, amine **56** (50 mg, 0.14 mmol) was reductively alkylated using aldehyde **40** (73 mg, 0.43 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (285 μL, 4.98 mmol) and $NaBH_4$ (24 mg, 0.62 mmol) for 5 min) in CH_2Cl_2 (1.2 mL) to give the title compound as a yellow oil (27 mg, 38%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), *R*f = 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.36 (td, J = 7.5, 1.6 Hz, 1H), 7.30 (dd, J = 9.2, 2.6 Hz, 1H), 7.23 - 7.16 (m, 2H), 7.10 - 7.01 (m, 2H), 3.94 (s, 3H), 3.67 (s, 3H), 3.30 (s, 1H), 3.14 - 2.94 (m, 5H), 2.89 - 2.69 (m, 2H), 2.67 - 2.35 (m, 7H), 1.86 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 161.5 (d, J_{CF} = 245.1 Hz), 158.5, 154.9 (d, J_{CF} = 251.4 Hz), 141.5, 138.1 (d, J_{CF} = 29.4 Hz), 132.2 (d, J_{CF} = 1.8 Hz), 131.7, 129.9, 129.2 (d, J_{CF} = 3.8 Hz), 128. 5 (d, J_{CF} = 7.8 Hz), 124.4 (d, J_{CF} = 3.7 Hz), 123.0 (d, J_{CF} = 17.4 Hz), 120.1, 115.7 (d, J_{CF} = 22.5 Hz), 101.9 (d, J_{CF} = 5.4 Hz), 63.3, 57.2, 55.6, 55.3, 55.1, 52.8, 51.6, 48.5, 30.6, 26.4, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2948, 2814, 1740, 1620, 1509, 14712, 1320, 1263, 1229, 1031, 831, 755; HRMS (ESI) calcd for $C_{27}H_{32}F_2N_3O_3S$ $[M + H]^+$ 516.2127, found 516.2122; $[\alpha]_D^{23}$= + 12.6 (*c* 1.0,$CHCl_3$).

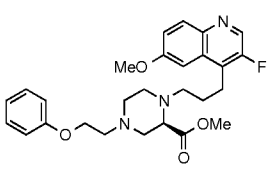


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-((2-(tri-fluoromethyl)phenyl)thio)ethyl)piperazine-2-carboxylate (58i). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol) was reductively alkylated using aldehyde **42** (70 mg, 0.17 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 μL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as a yellow oil (46 mg, 59%) after purification by flash column chromatography on silica gel (EtOAc:heptane (3:2), R_f = 0.3). ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.45 - 7.34 (m, 2H), 7.26 - 7.16 (m,

2H), 7.11 (d, J = 2.5 Hz, 1H), 3.88 (s, 3H), 3.60 (s, 3H), 3.26 - 23.22 (m, 1H), 3.06 - 2.90 (m, 5H), 2.81 - 2.65 (m, 2H), 2.61 - 2.32 (m, 7H), 1.79 (p, J = 7.3, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 136. 3, 132.1, 131.8, 131.0, 129.9 (m), 129.3 (d, J_{CF} = 3.9 Hz), 126.9 (q, J = 5.7 Hz), 126.0, 123.7 (q, J_{CF} = 274 Hz), 120.2 (d, J = 2.6 Hz), 102.1 (d, J = 5.4 Hz), 63.3, 56.9, 55.7, 55.5, 55.1, 52.9, 51.7, 48.6, 31.7, 26.7, 22.0 (d, J = 3.1 Hz); IR (neat) cm^{-1}: 2950, 2817, 1741, 1620, 1509, 1469, 1313, 1230, 1129, 1034, 831, 764; HRMS (ESI) calcd for $C_{28}H_{32}F_4N_3O_3S$ [M + H]$^+$ 566.2095, found 566.2091; $[\alpha]_D^{23}$ = + 7.6 (*c* 1.0, $CHCl_3$).

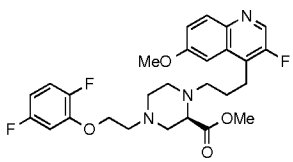


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-((2-(tri-fluoromethyl)phenyl)thio)ethyl)piperazine-2-carboxylate (57j). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol) was reductively alkylated using aldehyde **41** (89 mg, 0.21 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 µL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as a yellow oil (68 mg, 92%) after purification by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.00 (d, J = 9.2 Hz, 1H), 7.32 (dd, J = 9.2, 2.5 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.08 - 6.95 (m, 2H), 6.90 - 6.82 (m, 1H), 3.96 (s, 3H), 3.69 (s, 3H), 3.35 - 3.30 (m, 1H), 3.14 - 2.96 (m, 5H), 2.89 - 2.73 (m, 2H), 2.67 - 2.39 (m, 7H), 1.87 (p, J = 7.3 Hz, 2H); ^{13}NMR (100 MHz, $CDCl_3$) δ 173.2, 158.6, 158.6 (dd, J_{CF} = 244.3, 2.5 Hz) 157.2 (dd, J_{CF} = 241.4 Hz) 155.0 (dd, J_{CF} = 251.4, 2.5 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 125.6 (dd, J_{CF} = 20.4, 8.3 Hz), 120.2 (d, J_{CF} = 2.6 Hz), 117.3 (dd, J_{CF} = 25.4, 2.4 Hz), 116.3 (dd, J_{CF} = 25.2, 8.9 Hz), 114.1 (dd, J_{CF} = 24.0, 8.1 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.3, 56.9, 55.7, 55.4, 55.1, 52.9, 51.7, 48.5, 30.3 (d, J_{CF} = 2.3 Hz), 26.6, 22.0 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 2949, 2815, 1739, 1612, 1509, 1481, 1229, 1186, 1031, 831, 757; HRMS (ESI) calcd for $C_{27}H_{31}F_3N_3O_3S$ [M + H]$^+$ 534.2033, found 534.2031; $[\alpha]_D^{23}$ = + 13.0 (*c* 1.0, $CHCl_3$).

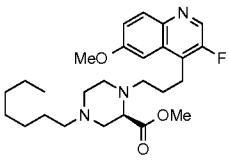


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-phenoxy-ethyl)piperazine-2-carboxylate (57k). Following ***general procedure V***, amine **56** (50 mg, 0.14 mmol) was reductively alkylated using aldehyde **48** (35 mg, 0.28 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (400 µL, 7.00 mmol) and $NaBH_4$ (16

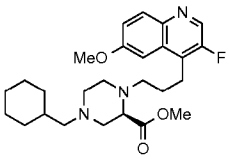
mg, 0.28 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as a colorless oil (46 mg, 69%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.28 (dd, J = 9.2, 2.9 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 2.6 Hz, 1H), 6.91 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 8.0 Hz, 2H), 4.03 (td, J = 5.7, 2.5 Hz, 2H), 3.91 (s, 3H), 3.61 (s, 3H), 3.31 (d, J = 5.7 Hz, 1H), 3.12 - 2.93 (m, 3H), 2.86 - 2.69 (m, 5H), 2.58 (t, J = 4.6 Hz, 2H), 2.56 - 2.47 (m, 1H), 2.42 (dt, J = 10.4, 5.0 Hz, 1H), 1.84 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.7, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.5, 129.2 (d, J_{CF} = 5.4 Hz), 120.9, 120.2 (d, J_{CF} = 2.6 Hz), 114.6, 102.0 (d, J_{CF} = 5.4 Hz), 65.8, 63.6, 56.9, 56.1, 55.6, 55.2, 53.5, 51.6, 48.8, 26.5, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2948, 2829, 1740, 1620, 1508, 1467, 1230, 1034, 831, 755; HRMS (ESI) calcd for $C_{27}H_{33}FN_3O_4$ $[M + H]^+$ 482.2450, found 482.2450; $[\alpha]_D^{23}$ = + 15.8 (*c* 1.0, $CHCl_3$).



(*R*)-Methyl 4-(2-(2,5-difluorophenoxy)ethyl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)propyl)- piperazine-2-carboxylate (57m). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol) was reductively alkylated using aldehyde **50** (26 mg, 0.15 mmol) and $NaBH(OAc)_3$ (43 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) to give the title compound as a colorless oil (36 mg, 68%) after purification by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.98 (d, J = 8.6 Hz, 1H), 7.30 (dd, J = 9.2, 2.6 Hz, 1H), 7.18 (d, J = 2.6 Hz, 1H), 6.99 (ddd, J = 10.6, 9.0, 5.3 Hz, 1H), 6.67 (ddd, J = 9.7, 6.7, 2.9 Hz, 1H), 6.62 - 6.51 (m, 1H), 4.08 (t, J = 5.6 Hz, 2H), 3.94 (s, 3H), 3.64 (s, 3H), 3.33 (dd, J = 6.0, 3.5 Hz, 1H), 3.16 - 2.96 (m, 3H), 2.92 - 2.77 (m, 4H), 2.77 - 2.70 (m, 1H), 2.67 - 2.49 (m, 3H), 2.49 - 2.39 (m, 1H), 1.86 (p, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.8 (dd, J_{CF} = 242.1, 2.5 Hz), 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 149.1 (dd, J_{CF} = 241.4, 3.3 Hz), 147.5 (dd, J_{CF} = 12.6, 10.4 Hz), 141.7 (d, J_{CF} = 2.2 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.0 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 120.2 (d, J_{CF} = 2.6 Hz), 116.3 (dd, J_{CF} = 20.8, 10.2 Hz), 106.9 (dd, J_{CF} = 23.8, 6.9 Hz), 103.1 (dd, J_{CF} = 27.4, 1.8 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 67.9, 63.5, 56.6, 56.2, 55.7, 55.2, 53.5, 51.7, 48.7, 25.7, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2950, 2830, 1740, 1622, 1511, 1468, 1322, 1206, 1156, 1031, 832; $[\alpha]_D^{23}$ = + 7.0 (*c* 0.5, $CHCl_3$).

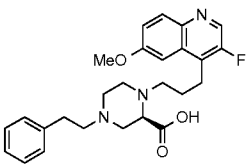


(*R*)-Methyl 1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-heptylpiperazine-2-carboxylate (57o). Following ***general procedure V***, amine **56** (50 mg, 0.14 mmol) was reductively alkylated using heptanal (27 μL , 0.15 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 μL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as a colorless oil (68 mg, 92%) after purification by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2). ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 0.6 Hz, 1H), 7.95 (d, *J* = 9.2 Hz, 1H), 7.27 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.15 (d, *J* = 2.7 Hz, 1H), 3.92 (s, 3H), 3.63 (s, 3H), 3.27 (t, *J* = 5.0 Hz, 1H), 3.11 - 2.94 (m, 3H), 2.84 - 2.73 (m, 2H), 2.63 - 2.34 (m, 6H), 2.34 - 2.19 (m, 2H), 1.84 (p, *J* = 7.4 Hz, 2H), 1.47 - 1.35 (m, 2H), 1.31 - 1.18 (m, 8H), 0.84 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 158.6, 155.0 (d, J_{CF} = 251.5 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.8, 129.9 (d, J_{CF} = 13.0 Hz), 129.2 (d, J_{CF} = 3.9 Hz), 120.2 (d, J_{CF} = 2.6 Hz), 101.9 (d, J_{CF} = 5.4 Hz), 63.9, 58.4, 55.6, 55.6, 55.3, 53.3, 51.6, 49.1, 31.9, 29.3, 27.4, 26.8, 26.5, 22.7, 22.0 (d, J_{CF} = 3.1 Hz), 14.15; IR (neat) cm^{-1}: 2930, 2856, 2811, 1743, 1621, 1509, 1468, 1230, 1032, 831; HRMS (ESI) calcd for $C_{26}H_{39}FN_3O_3$ $[M + H]^+$ 460.2970, found 460.2971; $[\alpha]_D^{23}$= + 18.3 (*c* 1.0, $CHCl_3$).

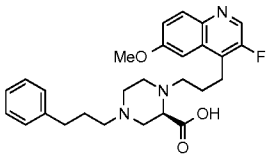


(*R*)-Methyl 4-(cyclohexylmethyl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)-propyl)piperazine-2-carboxylate (57r). Following ***general procedure V***, amine **56** (37 mg, 0.10 mmol) was reductively alkylated using cyclohexanecarbaldehyde (20 μL, 0.17 mmol) and $NaBH(OAc)_3$ (freshly prepared by premixing AcOH (200 μL, 3.50 mmol) and $NaBH_4$ (8 mg, 0.24 mmol) for 5 min) in CH_2Cl_2 (1.5 mL) to give the title compound as a colorless oil (42 mg, 66%) after purification by flash column chromatography on silica gel (EtOAc:heptane (2:3), R_f = 0.2). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (d, *J* = 0.7 Hz, 1H), 7.97 (d, *J*= 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 3.94 (s, 3H), 3.64 (s, 3H), 3.33 - 3.26 (m, 1H), 3.12 - 2.94 (m, 3H), 2.86 - 2.76 (m, 1H), 2.67 - 2.61 (s, 1H), 2.60 - 2.47 (m, 2H) , 2.44 - 2.35 (m, 3H), 2.06 (dd, *J* = 7.1, 1.9 Hz, 2H), 1.85 (p, *J* = 7.4 Hz, 2H), 1.75 - 1.59 (m, 5H), 1.48 - 1.36 (m, 1H), 1.26 - 1.09 (m, 3H), 0.88 - 0.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 158.6, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.0 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3,9 Hz), 120.3 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 65.1, 63.7, 56.1, 55.7, 55.3, 53.8, 51.5, 48.9, 35.1, 31.8, 31.7, 26.9, 26.6, 26.2, 26.2, 22.1 (d, J_{CF} = 3.9 Hz); IR (neat) cm^{-1}: 2922, 2849, 2807, 1743, 1621, 1509, 1467, 1230, 1033, 831;

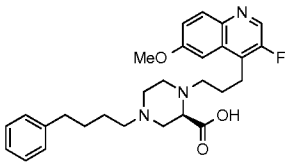
HRMS (ESI) calcd for $C_{26}H_{37}FN_3O_3$ [M + H]$^+$ 458.2813, found 458.2811; $[\alpha]_D^{23}$= + 11.2 (*c* 1.0, $CHCl_3$).



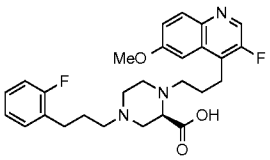
(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-phenethylpiperazine- 2-carboxylic acid (58a). Following ***general procedure IV***, methyl ester **57a** (55mg, 0.12 mmol) was hydrolyzed to give the title compound as an amorphous solid after preparative HPLC (39 mg, 73%).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (d, *J* = 0.5 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.29 - 7.14 (m, 5H), 3.95 (s, 3H), 3.20 (dd, *J* = 5.6, 3.6 Hz, 1H), 3.16 - 2.95 (m, 4H), 2.91 - 2.80 (m, 1H), 2.77 - 2.52 (m, 7H), 2.47 - 2.34 (m, 2H), 1.88 - 1.71 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.6, 158.2, 154.5 (d, J_{CF} = 250.2 Hz), 141.0 (d, J_{CF} = 2.1 Hz), 140.1, 137.9 (d, J_{CF} = 28.9 Hz), 131.3, 129.7 (d, J_{CF} = 13.2 Hz), 128.8 (d, J_{CF} = 4.0 Hz), 128.7, 128.2, 125.9, 120.5, 102.3 (d, J_{CF} = 5.3 Hz), 62.8, 59.1, 55.7, 55.0, 54.2, 51.9, 47.9, 32.4, 25.9, 21.3 (d, J_{CF} = 2.4 Hz); IR (neat) cm^{-1}: 3054, 3029, 2960, 2943, 2924, 2820, 2773, 1620, 1513, 1451, 1375, 1339, 1262, 1237, 1178, 1102, 1064, 1031, 980, 864, 828, 792, 745, 698, 546, 510; HRMS (ESI) calcd for $C_{26}H_{31}FN_3O_3$ [M + H]$^+$ 452.2344 found 452.2343; $[\alpha]_D^{22}$ = + 6.9 (*c* 0.5, in CH_3OH).



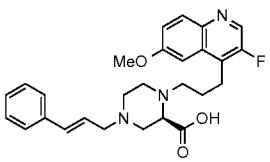
(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-phenylpropyl)piperazine-2-carboxylic acid (58b). Following ***general procedure IV***, methyl ester **57b** (58 mg, 0.12 mmol) was hydrolyzed to give the title compound as an amorphous solid after preparative HPLC (28 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J_{HF} = 0.8 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.26 – 7.19 (m, 3H), 7.15 – 7.11 (m, 2H), 7.11 – 7.06 (m, 2H), 3.88 (s, 3H), 3.34 (t, *J* = 3.2 Hz, 1H), 3.12 (d, *J* = 10.6 Hz, 1H), 3.05 – 2.87 (m, 4H), 2.82 – 2.70 (m, 2H), 2.70 – 2.62 (m, 1H), 2.61 – 2.46 (m, 5H), 2.40 – 2.30 (m, 1H), 1.88 – 1.78 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.8, 155.0 (d, J_{CF} = 251.4 Hz), 141.5 (d, J_{CF} = 2.2 Hz), 140.7, 138.2 (d, J_{CF} = 29.5 Hz), 131.7, 129.9 (d, J_{CF} = 12.8 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 128.7, 128.4, 126.4, 120.3 (d, J_{CF} = 2.5 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 60.5, 56.6, 55.8, 54.6, 54.4, 51.6, 46.9, 33.2, 26.9, 26.0, 22.0 (d, J_{CF} = 3.0 Hz);MS (ESI) calcd for $C_{27}H_{33}FN_3O_3$ [M + H]$^+$ 466.3 found 466.3.



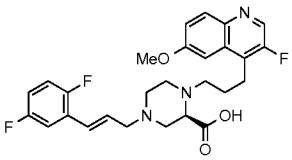
(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(4-phenylbutyl)-piperazine-2-carboxylic acid (58c). Following ***general procedure IV***, methyl ester **57c** (25 mg, 0.051 mmol) was hydrolyzed to give the title compound as an amorphous solid after preparative HPLC (16 mg, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.0 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.28 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.25 - 7.21 (m, 2H), 7.19 - 7.16 (m, 2H), 7.16 - 7.10 (m, 2H), 3.93 (s, 3H), 3.36 (t, *J* = 2.8 Hz, 1H), 3.17 (d, *J* = 10.4 Hz, 1H), 3.08 - 2.92 (m, 4H), 2.85 - 2.65 (m, 3H), 2.65 - 2.44 (m, 5H), 2.42 - 2.29 (m, 1H), 2.06 - 1.80 (m, 2H), 1.73 - 1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.7, 141.6, 138.2 (d, J_{CF} = 29.5 Hz), 131.8, 129.9 (d, J_{CF} = 12.7 Hz), 129.4 (d, J_{CF} = 3.9 Hz), 128.6, 128.5, 126.1, 120.3, 102.1 (d, J_{CF} = 5.4 Hz), 60.2, 57.1, 55.8, 54.8, 54.4, 51.6, 46.8, 35.5, 28.8, 26.2, 24.7, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3024, 2939, 2860, 2831, 1716, 1509, 1468, 1454, 1362, 1322, 1231, 1029, 750; HRMS (ESI) calcd for $C_{28}H_{35}FN_3O_3$ [M + H]$^+$ 480.2657 found 480.2658; $[\alpha]_D^{23}$= + 3.6 (*c* 1.0, $CHCl_3$).



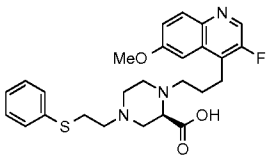
(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(2-fluorophenyl)-propyl)piperazine-2-carboxylic acid (58d). Following ***general procedure IV***, methyl ester **57d** (28 mg, 0.056 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (14 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br. s, 1H), 8.59 (d, *J* = 0.9 Hz, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.24 - 7.14 (m, 3H), 7.11 - 6.98 (m, 2H), 3.97 (s, 3H), 3.45 (t, *J* = 3.2 Hz, 1H), 3.21 (d, *J* = 9.6 Hz, 1H), 3.16 - 3.00 (m, 4H), 2.87 (t, *J* = 7.0 Hz, 2H), 2.80 - 2.72 (m, 1H), 2.73 - 2.60 (m, 5H), 2.55 - 2.44 (m, 1H), 2.07 - 1.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 161.2 (d, J_{CF} = 244.8 Hz), 158.8, 155.0 (d, J_{CF} = 251.4 Hz), 141.5 (d, J_{CF} = 2.1 Hz), 138.1 (d, J_{CF} = 29.5 Hz), 131.7, 130.7 (d, J_{CF} = 4.9 Hz), 129.8 (d, J_{CF} = 12.9 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 128.2 (d, J_{CF} = 8.1 Hz), 127.6 (d, J_{CF} = 15.9 Hz), 124.3 (d, J_{CF} = 3.5 Hz), 120.4, 115.5 (d, J_{CF} = 22.1 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 60.7, 56.6, 55.8, 54.7, 54.3, 51.6, 47.0, 26.7 (d, J_{CF} = 2.2 Hz), 25.9, 25.7, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2947, 2868, 2829, 1717, 1620, 1509, 1468, 1362, 1322, 1229, 1029, 831, 757; HRMS (ESI) calcd for $C_{27}H_{32}F_2N_3O_3$ [M + H]$^+$ 484.2406 found 484.2400; $[\alpha]_D^{23}$= + 5.0 (*c* 1.0, $CHCl_3$).



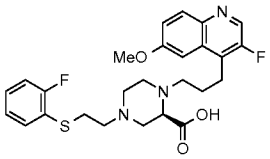
(*R*)-4-Cinnamyl-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazin-e-2-carboxylic acid (58e). Following ***general procedure IV***, methyl ester **57e** (49 mg, 0.10 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (34 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (br s, 1H), 8.56 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.39 - 7.21 (m, 6H), 7.19 (d, *J* = 2.6 Hz, 1H), 6.58 (d, *J* = 15.7 Hz, 1H), 6.18 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.93 (s, 3H), 3.47 (t, *J* = 3.8 Hz, 1H), 3.37 (d, *J* = 6.9 Hz, 2H), 3.27 - 3.14 (m, 2H), 3.10 - 2.82 (m, 5H), 2.82 - 2.67 (m, 2H), 2.59 (td, *J* = 9.1, 2.7 Hz, 1H), 2.07 - 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.8, 155.0 (d, J_{CF} = 251.4 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.1 (d, J_{CF} = 29.5 Hz), 137.0, 135.9, 131.7, 129.6 (d, J_{CF} = 12.9 Hz), 129.3 (d, J_{CF} = 3.7 Hz), 128.8, 128.5, 126.8, 121.1, 120.4 (d, J_{CF} = 2.4 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 61.4, 59.6, 55.8, 54.7, 53.9, 51.0, 47.1, 25.7, 21.9 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3396, 2955, 2829, 1620, 1509, 1468, 1362, 1230, 1029, 750; HRMS (ESI) calcd for $C_{27}H_{31}FN_3O_3$ [M + H]$^+$ 464.2344 found 464.2342; $[\alpha]_D^{23}$ = + 14.9 (*c* 1.0, $CHCl_3$).



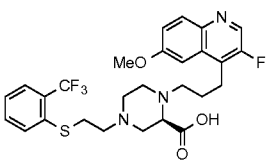
(*R,E*)-4-(3-(2,5-Difluorophenyl)allyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (58f). Following ***general procedure IV***, methyl ester **57f** (42 mg, 0.082 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (23 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (br s, 1H), 8.57 (d, *J* = 0.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.12 (ddd, *J* = 8.9, 5.7, 3.0 Hz, 1H), 6.98 (td, *J* = 9.3, 4.5 Hz, 1H), 6.90 (tt, *J* = 9.0, 3.7 Hz, 1H), 6.68 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0, 6.9 Hz, 1H), 3.94 (s, 3H), 3.48 (t, *J* = 3.7 Hz, 1H), 3.36 (d, *J* = 6.8 Hz, 2H), 3.20 - 3.10 (m, 2H), 3.06 (t, *J* = 7.4 Hz, 2H), 3.02 - 2.82 (m, 3H), 2.74 (d, *J* = 12.2 Hz, 2H), 2.56 (t, *J* = 9.0 Hz, 1H), 2.07 - 1.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 158.7 (dd, J_{CF} = 242.4, 2.1 Hz), 158.7, 156.2 (dd, J_{CF} = 245.8, 2.1 Hz), 154.9 (d, *J* = 251.5 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, *J* = 29.5 Hz), 131.6, 129.5 (d, J_{CF} = 12.8 Hz), 129.2 (d, J_{CF} = 3.8 Hz), 127.6, 125.9, 125.0 (dd, J_{CF} = 14.5, 7.8 Hz), 120.3 (d, J_{CF} = 2.4 Hz), 116.9 (dd, J_{CF} = 25.1, 8.7 Hz), 116.0 (dd, J_{CF} = 24.4, 8.8 Hz), 113.5 (dd, J_{CF} = 24.6, 3.8 Hz), 101.9 (d, J_{CF} = 5.3 Hz); IR (neat) cm^{-1}: 2946, 2830, 1718, 1621, 1509, 1490, 1362, 1231, 1030, 973, 830, 756; HRMS (ESI) calcd for $C_{27}H_{29}F_3N_3O_3$ [M + H]$^+$ 500.2156 found 500.2155; $[\alpha]_D^{23}$= + 12.8 (*c* 1.0, $CHCl_3$).



(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(phenylthio)-ethyl)piperazine-2-carboxylic acid (58g). Following ***general procedure IV***, methyl ester **57g** (38 mg, 0.076 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (27 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 8.57 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.37 - 7.23 (m, 5H), 7.23 - 7.15 (m, 2H), 3.95 (s, 3H), 3.42 (t, *J* = 3.8 Hz, 1H), 3.11 - 3.00 (m, 6H), 2.86 - 2.78 (m, 3H), 2.76 - 2.65 (m, 4H), 2.49 - 2.42 (m, 1H), 2.09 - 1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.9, 155.0 (d, J_{CF} = 251.4 Hz), 141.5 (d, J_{CF} = 2.3 Hz), 138.1 (d, J_{CF} = 29.5 Hz), 135.0, 131.7, 130.2, 129.5 (d, J_{CF} = 12.8 Hz), 129.3, 126.9, 120.4 (d, J_{CF} = 2.5 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 61.4, 56.2, 55.8, 54.9, 54.3, 51.3, 47.9, 30.4, 25.5, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3402, 2946, 1620, 1509, 1468, 1362, 1230, 742; HRMS (ESI) calcd for $C_{26}H_{31}FN_3O_3S$ $[M + H]^+$ 484.2065 found 484.2061; $[\alpha]_D^{23}$ = - 6.0 (*c* 1.0, $CHCl_3$).

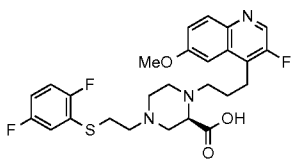


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-((2-fluorophen-yl)thio)ethyl)piperazine-2-carboxylic acid (58h). Following ***general procedure IV***, methyl ester **57h** (30 mg, 0.057 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (17 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 0.8 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.40 (td, *J* = 7.5, 1.6 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.28 - 7.21 (m, 2H), 7.18 (d, *J* = 2.6 Hz, 1H), 7.10 - 7.03 (m, 2H), 3.95 (s, 3H), 3.44 (t, *J* = 3.7 Hz, 1H), 3.14 - 2.91 (m, 6H), 2.91 - 2.79 (m, 3H), 2.77 - 2.68 (m, 4H), 2.48 (dd, *J* = 14.6, 6.2 Hz, 1H), 2.09 - 1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.1 (d, J_{CF} = 245.9 Hz), 158.9, 155.0 (d, J_{CF} = 251.4 Hz), 141.4 (d, J_{CF} = 2.3 Hz), 138.0 (d, *J* = 29.6 Hz), 133.6, 131.6, 129.6 (d, J_{CF} = 8.0 Hz), 129.6 (d, J_{CF} = 8.4 Hz), 129.3 (d, J_{CF} = 3.7 Hz), 124.8 (d, J_{CF} = 3.7 Hz), 121.6, 120.5, 116.1 (d, J_{CF} = 22.6 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 61.4, 56.3, 55.9, 54.9, 54.2, 51.2, 47.9, 30.1 (d, J_{CF} = 3.0 Hz), 25.5, 21.9 (d, J_{CF} = 3.2 Hz); IR (neat) cm^{-1}: 3395, 2945, 2825, 1620, 1509, 1472, 1362, 1230, 756; HRMS (ESI) calcd for $C_{26}H_{30}F_2N_3O_3S$ $[M + H]^+$ 502.1970 found 502.1968; $[\alpha]_D^{23}$ = - 5.4 (*c* 0.50, $CHCl_3$).

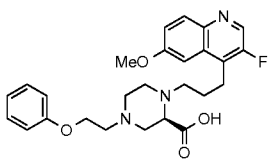


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-((2-(trifluorome-thyl)phenyl)thio)ethyl)piperazine-2-carboxylic acid (58i). Following ***general procedure IV***, methyl ester **57i** (40 mg, 0.071 mmol) was hydrolyzed to give the title compound

as an off-white solid after preparative HPLC (27 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (br s, 1H), 8.57 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.55 - 7.41 (m, 2H), 7.37 - 7.27 (m, 2H), 7.17 (d, *J* = 2.7 Hz, 1H), 3.94 (s, 3H), 3.44 (dd, *J* = 4.8, 3.5 Hz, 1H), 3.15 - 2.99 (m, 5H), 2.99 - 2.88 (m, 2H), 2.88 - 2.78 (m, 2H), 2.78 - 2.67 (m, 4H), 2.52 (t, *J* = 8.6 Hz, 1H), 2.09 - 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 158.9, 155.0 (d, J_{CF} = 251.5 Hz), 141.5 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.5 Hz), 134.9, 132.4, 132.0, 131.7, 130.8 (q, J_{CF} = 30.1 Hz), 129.4, 129.2 (d, J_{CF} = 3.7 Hz), 127.1 (q, J_{CF} = 5.6 Hz), 126.8, 123.8 (q, J_{CF} = 273.8 Hz), 120.5 (d, J_{CF} = 2.4 Hz), 102.0 (d, J_{CF} = 5.3 Hz), 62.1, 56.1, 55.8, 54.9, 54.1, 51.3, 48.1, 31.2, 25.3, 21.8 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3379, 2954, 2828, 1621, 1509, 1469, 1313, 1231, 1129, 1034; HRMS (ESI) calcd for $C_{27}H_{30}F_4N_3O_3S$ [M + H]$^+$ 552.1939 found 552.1937; $[\alpha]_D^{23}$ = + 2.4 (*c* 1.0, $CHCl_3$).

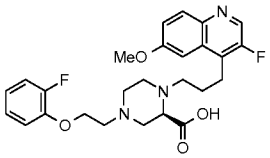


(*R*)-4-(2-((2,5-Difluorophenyl)thio)ethyl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)propyl)piperazine-2-carboxylic acid (58j). Following ***general procedure IV***, methyl ester **57j** (46 mg, 0.086 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (34 mg, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.51 (br s, 1H), 8.56 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.17 (d, *J* = 2.6 Hz, 1H), 7.06 (ddd, *J* = 8.5, 5.7, 3.1 Hz, 1H), 7.00 (ddd, *J* = 8.9, 4.6, 4.6 Hz, 1H), 6.92 - 6.82 (m, 1H), 3.95 (s, 3H), 3.44 (dd, *J* = 4.6, 3.5 Hz, 1H), 3.14 - 2.98 (m, 6H), 2.93 (dd, *J* = 9.0, 3.9 Hz, 2H), 2.83 (td, *J* = 13.0, 6.9 Hz, 2H), 2.78 - 2.65 (m, 4H), 2.50 (t, *J* = 8.6 Hz, 1H), 2.10 - 1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.3 (dd, J_{CF} = 97.6, 2.6 Hz), 158.9, 156.9 (d, J_{CF} = 96.5 Hz), 155.0 (d, J_{CF} = 251.5 Hz), 141.46 (d, J_{CF} = 2.2 Hz), 138.1 (d, J_{CF} = 29.4 Hz), 131.7, 129.4 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.8 Hz), 124.0 (dd, J_{CF} = 20.3, 8.1 Hz), 120.4 (d, J_{CF} = 2.5 Hz), 118.4 (d, J_{CF} = 25.2 Hz), 116.7 (dd, J_{CF} = 25.3, 8.9 Hz), 115.2 (dd, J_{CF} = 24.0, 8.1 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 61.9, 56.2, 55.8, 54.9, 54.2, 51.2, 48.1, 29.8, 25.4, 21.8 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3395, 2946, 2830, 1620, 1509, 1481, 1230, 1186, 757; HRMS (ESI) calcd for $C_{26}H_{29}F_3N_3O_3S$ [M + H]$^+$ 520.1876 found 520.1869. $[\alpha]_D^{23}$ = - 4.3 (*c* 1.0, $CHCl_3$).

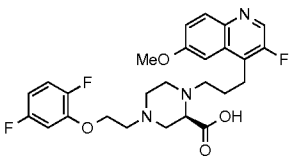


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-phenoxyethyl)-piperazine-2-carboxylic acid (58k). Following ***general procedure IV***, methyl ester **57k** (53 mg, 0.11 mmol) was hydrolyzed to give the title compound as an off-white solid after

preparative HPLC (38 mg, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (s, 1H), 8.57 (d, *J* = 0.8 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.35 - 7.23 (m, 3H), 7.19 (d, *J* = 2.6 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 2H), 4.12 (t, *J* = 5.0 Hz, 2H), 3.95 (s, 3H), 3.47 (dd, *J* = 3.8, 3.8 Hz, 1H), 3.22 - 2.62 (m, 12H), 2.11 - 1.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 158.9, 158.1, 155.0 (d, J_{CF} = 251.4 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.6 Hz), 131.6, 129.7, 129.5, 129.3 (d, J_{CF} = 3.8 Hz), 121.5, 120.5 (d, J_{CF} = 2.5 Hz), 114.6, 102.0 (d, J_{CF} = 5.4 Hz), 64.1, 61.5, 56.1, 55.8, 54.8, 54.5, 51.7, 47.7, 25.5, 21.8 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3395, 2948, 2831, 1620, 1509, 1467, 1231, 1031, 755; HRMS (ESI) calcd for $C_{26}H_{31}FN_3O_4$ $[M + H]^+$ 468.2293 found 468.2291; $[\alpha]_D^{23}$ = + 9.9 (*c* 1.0, $CHCl_3$).

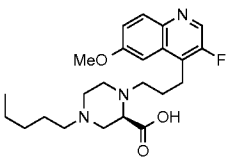


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(2-(2-fluorophen-oxy)ethyl)piperazine-2-carboxylic acid (58l). Following ***general procedure V,*** amine **56** (32 mg, 0.089 mmol) was reductively alkylated using fluorophenyl aldehyde **49** (41 mg, 0.27 mmol), and $NaBH(OAc)_3$ (94 mg, 0.44 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as an off-white amorphous solid after preparative HPLC (2 mg, 4%). HRMS (ESI) calcd for $C_{26}H_{30}F_2N_3O_4$ $[M + H]^+$ 486.2199, found 486.2202.

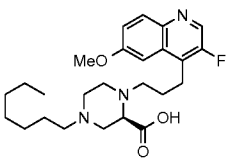


(*R*)-4-(2-(2,5-Difluorophenoxy)ethyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (58m). Following ***general procedure IV***, methyl ester **57m** (35 mg, 0.068 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (20 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (br. s, 1H), 8.57 (d, *J* = 0.9 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.00 (ddd, *J* = 10.6, 9.0, 5.3 Hz, 1H), 6.67 (ddd, *J* = 9.6, 6.7, 3.0 Hz, 1H), 6.60 (ddt, *J* = 9.0, 7.8, 3.1 Hz, 1H), 4.15 (t, *J* = 4.9 Hz, 3H), 3.95 (s, 3H), 3.46 (t, *J* = 3.6 Hz, 1H), 3.21 - 3.10 (m, 1H), 3.10 - 2.93 (m, 6H), 2.91 - 2.74 (m, 4H), 2.72 - 2.60 (m, 1H), 2.11 - 1.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 158.8, 158.6 (dd, J_{CF} = 242.8, 2.5 Hz), 154.9 (d, J_{CF} = 251.5 Hz), 149.0 (dd, J_{CF} = 241.9, 3.3 Hz), 146.7 (dd, J_{CF} = 12.6, 10.5 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.5 Hz), 131.6, 129.4 (d, J_{CF} = 12.6 Hz), 129.2 (d, J_{CF} = 3.8 Hz), 120.3 (d, *J* = 2.4 Hz), 116.5 (dd, J_{CF} = 20.7, 10.1 Hz), 107.6 (dd, J_{CF} = 23.7, 6.9 Hz), 103.2 (dd, J_{CF} = 27.4, 1.6 Hz), 101.9 (d, J_{CF} = 5.4 Hz), 66.4, 61.3, 55.8, 55.7, 54.7, 54.5, 51.9, 47.8, 25.5,

21.7 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2947, 2927, 2843, 1621, 1511, 1469, 1431, 1362, 1324, 1264, 1230, 1206, 1156, 1029, 833; $[\alpha]_D^{23}$= + 7.0 (*c* 1.0, $CHCl_3$).

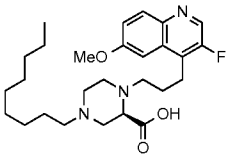


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-pentylpiperazine-2-carboxylic acid (58n). Following ***general procedure V,*** amine **56** (60.0 mg, 0.166 mmol) was reductively alkylated using pentanal (41 mg, 0.27 mmol), and $NaBH(OAc)_3$ (53 mg, 0.25 mmol) in CH_2Cl_2 (1.7 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as an off-white amorphous solid after preparative HPLC (37 mg, 54%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J_{HF} = 0.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.21 (d, *J* = 2.6 Hz, 1H), 3.96 (s, 3H), 3.43 - 3.36 (m, 1H), 3.23 (d, *J* = 10.6 Hz, 1H), 3.11 - 2.94 (m, 4H), 2.89 - 2.68 (m, 3H), 2.67 - 2.45 (m, 3H), 2.45 - 2.30 (m, 1H), 2.06 - 1.81 (m, 2H), 1.64 - 1.49 (m, 2H), 1.38 - 1.20 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.6, 154.9 (d, J_{CF} = 251.3 Hz), 141.5 (d, J_{CF} = 2.2 Hz), 138.1 (d, J_{CF} = 29.4 Hz), 131.7, 129.8 (d, J_{CF} = 15.7 Hz), 129.3 (d, J_{CF} = 3.8 Hz), 120.1, 102.0 (d, J_{CF} = 5.4 Hz), 60.0, 57.2, 55.7, 54.7, 54.4, 51.5, 46.7, 29.2, 26.1, 24.8, 22.3, 21.9 (d, J_{CF} = 3.0 Hz), 13.9; IR (neat) cm^{-1}: 3405, 2955, 2932, 2862, 1618, 1508, 1468, 1361, 1228; HRMS (ESI) calcd for $C_{23}H_{33}FN_3O_3$ $[M + H]^+$ 418.2501, found 418.2490; $[\alpha]_D^{20}$ = +5.1 (*c* 1.0, in $CHCl_3$).

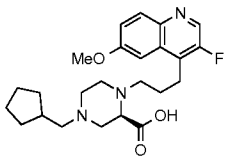


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-heptylpiperazine-2-carboxylic acid (58o). Following ***general procedure IV***, methyl ester **57o** (53 mg, 0.12 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (27 mg, 53%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 0.9 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.20 (d, *J* = 2.7 Hz, 1H), 3.95 (s, 3H), 3.40 - 3.35 (m, 1H), 3.30 - 3.26 (m, 1H), 3.11 - 3.03 (m, 4H), 2.91 - 2.76 (m, 2H), 2.72 - 2.68 (m, 1H), 2.65 - 2.49 (m, 3H), 2.43 - 2.37 (m, 1H), 2.03 - 1.81 (m, 2H), 1.60 - 1.53 (m, 2H), 1.36 - 1.15 (m, 9H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.2 (d, J_{CF} = 29.5 Hz), 131.8, 130.0 (d, J_{CF} = 12.8 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 120.2 (d, J_{CF} = 2.4 Hz), 102.2 (d, J_{CF} = 5.3 Hz), 60.3, 57.4, 55.8, 54.8, 54.5, 51.5, 46.6, 31.7, 29.0, 27.1, 26.3, 25.0, 22.6, 22.0 (d, J_{CF} = 3.0 Hz), 14.2; IR (neat) cm^{-1}: 3397, 2929, 2856, 1620, 1509, 1468, 1231;

HRMS (ESI) calcd for $C_{25}H_{37}FN_3O_3$ [M + H]$^+$ 446.2813 found 446.2816; $[\alpha]_D^{23}$ = + 3.9 (*c* 1.0, $CHCl_3$).

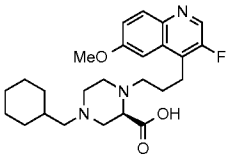


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-nonylpiperazine-2-carboxylic acid (58p). Following ***general procedure V,*** amine **56** (60.0 mg, 0.17 mmol) was reductively alkylated using nonal (43.0 µL, 0.25 mmol), and $NaBH(OAc)_3$ (53 mg, 0.25 mmol) in CH_2Cl_2 (1.7 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as an off-white amorphous solid after preparative HPLC (37.1 mg, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.21 (d, *J* = 2.6 Hz, 2H), 2.88 - 2.77 (m, 1H), 2.77 - 2.66 (m, 2H), 2.65 - 2.43 (m, 3H), 2.42 - 2.30 (m, 1H), 2.09 - 1.79 (m, 2H), 1.65 - 1.47 (m, 2H), 1.41 - 1.15 (m, 12H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 158.7, 155.0 (d, J_{CF} = 251.3 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.5 Hz), 131.8, 130.0 (d, J_{CF} = 12.8 Hz), 129.4 (d, J_{CF} = 4.0 Hz), 120.3 (d, J_{CF} = 2.5 Hz), 102.1 (d, J_{CF} = 5.5 Hz), 60.0, 57.3, 55.8, 54.8, 54.6, 51.7, 46.9, 32.0, 29.5, 29.4, 29.3, 27.2, 26.3, 25.3, 22.8, 22.0 (d, J_{CF} = 3.0 Hz), 14.2; IR (neat) cm^{-1}: 3418, 2923, 2852, 2815, 1619, 1509, 1468, 1321, 1209; HRMS (ESI) calcd for $C_{27}H_{41}FN_3O_3$ [M + H]$^+$ 474.3127, found 474.3128; $[\alpha]_D^{23}$ = + 4.1 (*c* 1.0, $CHCl_3$).

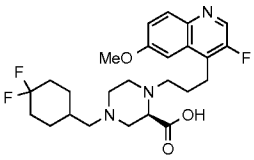


(*R*)-4-(Cyclopentylmethyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-piperazine-2-carboxylic acid (58q). Following ***general procedure V***, amine **56** (60 mg, 0.17 mmol) was reductively alkylated using cyclopentanecarbaldehyde (27 µL, 0.25 mmol), AcOH (1.0 µL, 0.017 mmol), and $NaBH(OAc)_3$ (53 mg, 0.25 mmol) in CH_2Cl_2 (1.7 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as an off-white amorphous solid after preparative HPLC (42 mg, 58%, over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J_{HF} = 1.0 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 3.97 (s, 3H), 3.40 (t, *J* = 2.6 Hz, 1H), 3.15 - 3.02 (m, 3H), 2.96 (d, *J* = 11.1 Hz, 1H), 2.86 - 2.71 (m, 3H), 2.69 - 2.56 (m, 1H), 2.52 - 2.40 (m, 3H), 2.41 - 2.28 (m, 1H), 2.16 - 2.05 (m, 1H), 2.05 - 1.87 (m, 2H), 1.86 - 1.73 (m, 2H), 1.68 - 1.48 (m, 4H), 1.22 - 1.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 158.8, 155.1 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.8, 129.9 (d, J_{CF} = 12.7 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 120.4 (d, J_{CF} = 2.5 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 63.1, 59.8, 55.8, 54.9, 54.8, 52.3, 47.5, 36.3, 31.4, 31.3, 26.1, 25.3, 25.3, 22.0 (d, J_{CF} = 3.2 Hz); IR

(neat) cm^{-1}: 3406, 2948, 2866, 2828, 1619, 1508, 1454, 1322, 1229; HRMS (ESI) calcd for $C_{24}H_{33}FN_3O_3$ $[M + H]^+$ 430.2501, found 430.2503; $[\alpha]_D^{20}$ = + 4.6 (*c* 1.0, in $CHCl_3$).

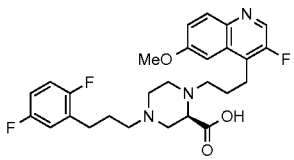


(R)*-4-(cyclohexylmethyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)pip-erazine-2-carboxylic acid (58r).** Following ***general procedure V, amine **56** (60 mg, 0.17 mmol) was reductively alkylated using cyclopentanecarbaldehyde (27 µL, 0.25 mmol), AcOH (1.0 µL, 0.017 mmol), and $NaBH(OAc)_3$ (53 mg, 0.25 mmol) in CH_2Cl_2 (1.7 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as an off-white amorphous solid after preparative HPLC (42 mg, 58%). Following ***general procedure IV***, methyl ester **57r** (32 mg, 0.069 mmol) was hydrolyzed to give the title compound as an off-white solid after preparative HPLC (24 mg, 77%, over two steps) ^1H NMR (400 MHz, $CDCl_3$) δ 9.58 (br s, 1H), 8.57 (d, *J* = 1.0 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.20 (d, *J* = 2.6 Hz, 1H), 3.96 (s, 3H), 3.43 (dd, *J* = 3.2, 3.2 Hz, 1H), 3.17 - 2.70 (m, 8H), 2.60 - 2.57 (m, 1H), 2.47 - 2.40 (m, 2H), 2.34 (dd, *J* = 12.5, 7.2 Hz, 1H), 2.10 - 1.85 (m, 2H), 1.81 - 1.63 (m, 5H), 1.61 - 1.52 (m, 1H), 1.30 - 1.05 (m, 3H), 1.00 - 0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 158.9, 155.0 (d, J_{CF} = 251.3 Hz), 141.4 (d, J_{CF} = 2.3 Hz), 138.0 (d, J_{CF} = 29.6 Hz), 131.6, 129.9 (d, J_{CF} = 12.5 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 120.5 (d, J_{CF} = 2.5 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 64.0, 60.4, 55.9, 54.9, 54.8, 52.2, 47.3, 34.0, 31.3, 26.3, 25.8, 25.7, 22.0 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3385, 2924, 2850, 1621, 1509, 1468, 1231; HRMS (ESI) calcd for $C_{25}H_{35}FN_3O_3$ $[M + H]^+$ 444.2657 found 444.2668; $[\alpha]_D^{23}$ = + 2.4 (*c* 1.0, $CHCl_3$).

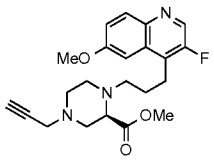


(*R*)-4-((4,4-Difluorocyclohexyl)methyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (58s). Following ***general procedure V***, amine **56** (60.0 mg, 0.17 mmol) was reductively alkylated using 4,4-difluorocyclo-hexanecarbaldehyde (freshly prepared using ***general procedure I*** from (4,4-difluorocyclohexyl)methanol (35 µL, 0.33 mmol)), AcOH (1.0 µL, 0.017 mmol), and $NaBH(OAc)_3$ (88 mg, 0.41 mmol) in CH_2Cl_2 (1.7 mL). The reaction mixture was concentrated *in vacuo* and the crude ester was hydrolyzed following ***general procedure IV*** to give the title compound as a light brown solid after preparative HPLC (6 mg, 7%, over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J_{HF} = 0.7 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.20 (d, *J* = 2.6 Hz, 1H), 3.97 (s, 3H), 3.40 (t, *J* = 2.6 Hz, 1H), 3.07 (t, *J* = 7.5

Hz, 2H), 3.00 - 2.82 (m, 2H), 2.82 - 2.55 (m, 4H), 2.45 (m, 1H), 2.39 - 2.23 (m, 3H), 2.10 - 1.59 (m, 9H), 1.33 - 1.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 158.8, 155.1 (d, J_{CF} = 251.3 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.9, 129.7 (d, J_{CF} = 12.2 Hz), 129.4 (d, J_{CF} = 3.7 Hz), 123.4 (dd, J_{CF} = 242.7, 239.6 Hz), 120.4 (d, J_{CF} = 2.5 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 63.1 (d, J_{CF} = 2.2 Hz), 60.0, 55.8, 55.0, 54.9, 52.4, 47.8, 33.3 (dd, J_{CF} = 23.0, 3.6 Hz), 33.1 (dd, J_{CF} = 22.6, 3.2 Hz), 32.7, 27.50 (d, J_{CF} = 9.7 Hz), 27.4 (d, J_{CF} = 9.7 Hz), 26.0, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3397, 3071, 2937, 2864, 2829, 1722, 1621, 1509, 1468, 1372, 1231, 1114, 832, 756; HRMS (ESI) calcd for $C_{25}H_{33}F_3N_3O_3$ [M + H]$^+$ 480.2469, found 480.2461; $[\alpha]_D^{20}$ = + 24.8 (*c* 0.5, in $CHCl_3$).

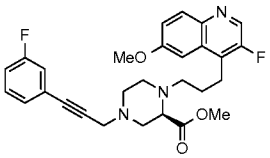


(*R*)-4-(3-(2,5-Difluorophenyl)propyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (59). Methyl ester **57f** (35 mg, 0.068 mmol) and 10% Pd/C (87 mg, 0.82 mmol) was dissolved in methanol under a hydrogen atmosphere and stirred at rt for 1 h. The reaction mixture was then filtered through a pad of celite, concentrated *in vacuo* and redissolved in 0.3 M LiOH (aq) (THF:water (2:1)) to a concentration of 0.1 M of the ester. After shaking in a closed reaction vial for 16 h at 65 °C, AcOH (3 equiv) was added, THF was removed under a flow of pressurized air, and the mixture was purified by preparative HPLC to give the title compound as an off-white amorphous solid (7.6 mg, 22% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 0.9 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.00 - 6.91 (m, 1H), 6.90 - 6.82 (m, 2H), 3.94 (s, 3H), 3.53 - 3.46 (m, 1H), 3.35 - 3.19 (m, 2H), 3.13 - 2.87 (m, 5H), 2.83 - 2.49 (m, 7H), 1.98 (q, *J* = 7.3 Hz, 2H), 1.88 (q, *J* J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 158.9, 158.7 (dd, J_{CF} = 242.3, 2.2 Hz), 157.1 (dd, J_{CF} = 240.4, 2.4 Hz), 155.0 (d, J_{CF} = 251.3 Hz), 141.4, 138.0 (d, J_{CF} = 29.5 Hz), 131.6, 130.0 (d, J_{CF} = 11.5 Hz), 129.4 (d, J_{CF} = 3.9 Hz), 129.1 (d, J_{CF} = 7.1 Hz), 120.5, 116.9 (dd, J_{CF} = 23.8, 5.2 Hz), 116.5 (dd, J_{CF} = 25.2, 8.7 Hz), 114.5 (dd, J_{CF} = 23.9, 8.5 Hz), 102.1 (d, J_{CF} = 5.3 Hz), 56.5, 55.8, 54.7, 54.0, 51.2, 46.7, 26.6, 25.6, 25.2, 21.8 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 2946, 2831, 1673, 1621, 1508, 1469, 1231, 1207, 1140, 1029, 831, 753; HRMS (ESI) calcd for $C_{27}H_{31}F_3N_3O_3$ [M + H]$^+$ 502.2312, found 502.2306; $[\alpha]_D^{23}$ = + 15.0 (*c* 0.5, $CHCl_3$).



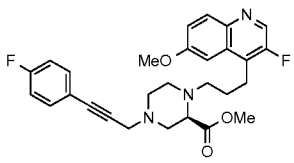
Methyl (*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(prop-2-yn-1-yl)-piperazine-2-carboxylate (60). Amine **56** (1.98 g, 5.48 mmol) was dissolved in DMF (32 mL), whereupon K_2CO_3 (1.14 g, 822 mmol) and propargyl bromide (0.650 mL, 5.48 mmol) were added and the reaction mixture was stirred for 21 h. Water (200 mL) and CH_2Cl_2 (200 mL) were added and the layers were separated. The aqueous phase was extracted with EtOAc (2 x 200 mL) and the combined organic layers were dried over Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography (EtOAc:heptane (2:1), R_f = 0.35) to give the title compound as an orange/brown amorphous solid (1.31 g, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J_{HF} = 1.0 Hz, 1H), 7.99 (d, J = 9.2 Hz, 1H), 7.31 (dd, J = 9.2, 2.7 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 3.96 (s, 3H), 3.67 (s, 3H), 3.35 (t, J = 4.8 Hz, 1H), 3.31 (d, J = 2.4 Hz, 2H), 3.18 - 2.96 (m, 3H), 2.88 - 2.72 (m, 3H), 2.59 (t, J = 5.0 Hz, 2H), 2.57 - 2.50 (m, 1H), 2.50 - 2.42 (m, 1H), 2.25 (t, J = 2.4 Hz, 1H), 1.87 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 158.7, 155.1 (d, J_{CF} = 251.4 Hz), 141.7 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.9, 130.0 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 120.3 (d, J_{CF} = 2.6 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 78.2, 73.8, 63.4, 55.8, 55.2, 54.4, 51.8, 51.5, 48.6, 46.9, 26.7, 22.1 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3296, 2949, 2829, 1737, 1620, 1508, 1467, 1320, 1227, 1133; HRMS (ESI) calcd for $C_{22}H_{27}F_2N_3O_3$ $[M + H]^+$.2031, found 400.2029; $[\alpha]_D^{20}$ = + 17.1 (*c* 1.0, in $CHCl_3$).

General procedure VI: Sonogashira cross-coupling on alkyne 60

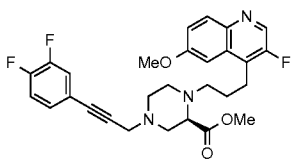


Methyl (*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(3-fluoro-phenyl)prop-2-yn-1-yl)piperazine-2-carboxylate (61a). Alkyne **60** (190 mg, 0.497 mmol) was dissolved in THF (3 mL) and Et_3N (2 mL), whereupon 1-fluoro-3-iodobenzene (158 mg, 0.713 mmol) was added, and the mixture was degassed with argon for 40 min. Then CuI (5 mg, 0.02 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.014 mmol) were added and the reaction mixture was degassed with argon for 30 min and stirred at rt under an argon atmosphere for 25 h. Water (10 mL) and CH_2Cl_2 (15 mL) were added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried using Na_2SO_4, concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give the title compound as a yellow oil (209 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.40 - 7.25 (m, 4H), 7.19 (d, J = 9.5 Hz, 1H), 7.12 - 7.03 (m, 1H), 4.01 (s, 3H), 3.76 (s, 3H), 3.60 (s, 2H), 3.49 - 3.43 (m, 1H), 3.30 - 3.04 (m,

3H), 3.00 - 2.84 (m, 3H), 2.74 (t, J = 4.8 Hz, 2H), 2.69 - 2.50 (m, 2H), 1.96 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 162.4 (d, J_{CF} = 246.4 Hz), 158.6, 155.0 (d, J_{CF} = 251.5 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.2 (d, J_{CF} =29.4 Hz), 131.8, 129.9 (d, J_{CF} = 8.7 Hz), 129.9 (d, J_{CF} =13.0 Hz), 129.2 (d, J_{CF} =3.8 Hz), 127.7 (d, J_{CF} =3.0 Hz), 124.9 (d, J_{CF} =9.5 Hz), 120.2 (d, J_{CF} =2.6 Hz), 118.6 (d, J_{CF} =22.7 Hz), 115.6 (d, J_{CF} =21.1 Hz), 102.0 (d, J_{CF} =5.4 Hz), 85.0, 84.6 (d, J_{CF} =3.3 Hz), 63.4, 55.6, 55.1, 54.6, 51.8 (d, J_{CF} =7.6 Hz), 48.7, 47.6, 26.6, 22.0 (d, J_{CF} =3.1 Hz).

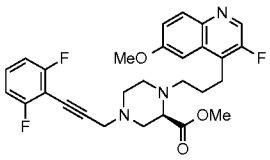


Methyl (*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl) propyl)-4-(3-(*p*-tolyl)prop-2-yn-1-yl)piperazine-2-carboxylate (61b). Following ***general procedure VI***, alkyne **60** (300 mg, 0.75 mmol) and 4-fluoro-iodobenzene (130 µL, 1.1 mmol) were coupled using CuI (21 mg, 0.11 mmol) and $Pd(PPh_3)_4$ (87 mg, 0.075 mmol) in THF:Et_3N (3:2) (8 mL) to give the title compound as a yellow oil (286 mg, 76%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J_{HF} = 0.8 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.43 - 7.36 (m, 2H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.01 - 6.95 (m, 2H), 3.93 (s, 3H), 3.67 (s, 3H), 3.51 (s, 2H), 3.37 (t, J = 4.8 Hz, 1H), 3.20 - 2.95 (m, 3H), 2.89 - 2.76 (m, 3H), 2.70 - 2.61 (m, 2H), 2.61 - 2.43 (m, 2H), 1.94 - 1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 162.5 (d, J_{CF} = 249.2 Hz), 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.7 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 133.7 (d, J_{CF} = 8.3 Hz), 131.9, 129.9 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.8 Hz), 120.3 (d, J_{CF} = 2.6 Hz), 119.2 (d, J_{CF} = 3.6 Hz), 115.7 (d, J_{CF} = 22.0 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 84.8, 83.6, 63.6, 55.7, 55.2, 54.7, 51.8, 51.8, 48.8, 47.7, 26.6, 22.1 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 3072, 2950, 2830, 1740, 1679, 1621, 1507, 1468, 1229, 1155, 834; HRMS (ESI) calcd for $C_{28}H_{30}F_2N_3O_3$ $[M + H]^+$ 494.2250, found 494.2250; $[\alpha]_D^{20}$ = + 7.4 (*c* 1.0, in $CHCl_3$).

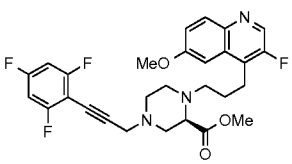


Methyl (*R*)-4-(3-(3,4-difluorophenyl)prop-2-yn-1-yl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylate (61c). Following ***general procedure VI***, alkyne **60** (190 mg, 0.497 mmol) and 1,2-difluoro-4-iodobenzene (171 mg, 0.713 mmol) were coupled using CuI (5 mg, 0.02 mmol) and $Pd(PPh_3)_4$ (17 mg, 0.014 mmol in THF:Et_3N (3:2) (5 mL) to give the title compound as a yellow oil (214 mg, 88%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (s, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H), 7.25 - 7.17 (m, 2H), 7.16 - 7.12 (m, 1H), 7.11 - 7.03 (m, 1H), 3.93 (s,

3H), 3.67 (s, 3H), 3.49 (s, 2H), 3.40 - 3.31 (m, 1H), 3.19 - 2.96 (m, 3H), 2.91 - 2.74 (m, 3H), 2.64 (t, J = 4.9 Hz, 2H), 2.59 - 2.43 (m, 2H), 1.88 (p, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 151.5 (dd, J_{CF} = 59.4, 12.8 Hz), 149.1 (dd, J_{CF} = 57.0, 12.8 Hz), 141.7 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.9, 129.9 (d, J_{CF} =13.0 Hz), 129.3 (d, J_{CF} =3.9 Hz), 128.4 (dd, J_{CF} = 6.4, 3.6 Hz), 120.8 (d, J_{CF} = 18.3 Hz), 120.2 (d, J_{CF} = 2.6 Hz), 119.9 (dd, J_{CF} = 7.7, 4.2 Hz), 117.5 (d, J_{CF} = 18.5 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 84.7 (d, J_{CF} = 1.7 Hz), 83.80 (dd, J_{CF} = 2.4, 1.8 Hz), 63.5, 55.7, 55.2, 54.7, 51.8, 51.8, 48.8, 47.6, 26.6, 22.1 (d, J_{CF} = 3.1 Hz).

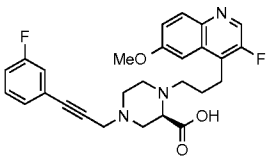


Methyl (*R*)-4-(3-(2,6-difluorophenyl)prop-2-yn-1-yl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylate (61d). Following ***general procedure VI***, alkyne **60** (190 mg, 0.497 mmol) and 1,3-difluoro-2-iodobenzene (171 mg, 0.713 mmol) were coupled using CuI (5 mg, 0.02 mmol) and $Pd(PPh_3)_4$ (28 mg, 0.024 mmol) in THF:Et_3N (3:2) (5 mL) to give the title compound as a yellow oil (99 mg, 41%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.28 (dd, J = 9.2, 2.7 Hz, 1H), 7.24 - 7.19 (m, 1H), 7.17 (d, J = 2.7 Hz, 1H), 6.87 (dd, J = 8.3, 7.1 Hz, 2H), 3.92 (s, 3H), 3.67 (s, 3H), 3.60 (d, J = 3.3 Hz, 2H), 3.42 - 3.37 (m, 1H), 3.22 - 3.14 (m, 1H), 3.12 - 2.99 (m, 2H), 2.98 - 2.89 (m, 1H), 2.89 - 2.80 (m, 2H), 2.68 (t, J = 5.0 Hz, 2H), 2.63 - 2.47 (m, 2H), 1.92 - 1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.3 (dd, J_{CF} = 253.3, 5.3 Hz), 158.7, 155.0 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.2 Hz), 138.2 (d, J_{CF} = 29.4 Hz), 131.7, 130.0 (d, J_{CF} = 13.0 Hz), 129.7 (t, J_{CF} = 9.9 Hz), 129.3 (d, J_{CF} = 3.8 Hz), 120.4 (d, J_{CF} = 2.6 Hz), 111.3 (d, J_{CF} = 5.6 Hz), 111.1 (d, J_{CF} = 5.7 Hz), 102.1 (d, J_{CF} =1 9.8 Hz), 101.9 (d, J_{CF} = 5.5 Hz), 94.4 (t, J_{CF} = 3.1 Hz), 72.8, 63.1, 55.6, 55.0, 54.4, 51.7 (d, J_{CF} = 7.0 Hz), 48.5, 47.8, 26.7, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2951, 2831, 1738, 1620, 1508, 1468, 1321, 1229, 1031, 1003, 910, 830, 784, 732.

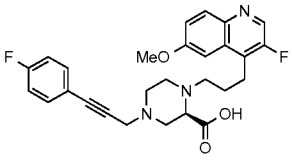


Methyl (*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(2,4,6-trifluorophenyl)prop-2-yn-1-yl)piperazine-2-carboxylate (61e). Following ***general procedure VI***, alkyne **60** (190 mg, 0.497 mmol) and 1,3,6-trifluoro-2-iodobenzene (245 mg, 0.951 mmol) were coupled using CuI (9 mg, 0.05 mmol) and $Pd(PPh_3)_4$ (44 mg, 0.038 mmol in THF:Et_3N (3:2) (5 mL) to give the title compound as a yellow oil (160

mg, 63%) after purification by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.30 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.18 (d, *J* = 2.7 Hz, 1H), 6.67 (dd, *J* = 8.6, 7.1 Hz, 2H), 3.94 (s, 3H), 3.68 (s, 3H), 3.59 (d, *J* = 3.1 Hz, 2H), 3.43 - 3.37 (m, 1H), 3.22 - 3.13 (m, 1H), 3.12 - 2.98 (m, 2H), 2.97 - 2.78 (m, 3H), 2.68 (t, *J* = 4.9 Hz, 2H), 2.63 - 2.48 (m, 2H), 1.93 - 1.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.6 (ddd, J_{CF} = 254.2, 14.7, 8.0 Hz), 162.2 (dd, J_{CF} = 252.5, 14.8 Hz), 158.7, 155.1 (d, J_{CF} = 251.4 Hz), 141.6 (d, J_{CF} = 2.3 Hz), 138.3 (d, J_{CF} = 29.4 Hz), 131.8, 130.0 (d, J_{CF} = 13.0 Hz), 129.3 (d, J_{CF} = 3.9 Hz), 120.3 (d, J_{CF} = 2.6 Hz), 101.9 (d, J_{CF} = 5.4 Hz), 100.95 - 100.10 (m), 98.8 (td, J_{CF} = 20.2, 4.8 Hz), 94.2 (dd, J_{CF} = 5.4, 3.1 Hz), 71.8, 63.2, 55.7, 55.1, 54.4, 51.7, 51.7, 48.5, 47.8, 26.7, 22.0 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2951, 2832, 1739, 1620, 1501, 1443, 1322, 1229, 1124, 1039, 999, 831, 732.

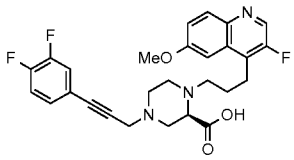


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(3-fluorophen-yl)prop-2-yn-1-yl)piperazine-2-carboxylic acid (62a). Following ***general procedure IV***, methyl ester **61a** (36 mg, 0.072 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (24 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 0.8 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.34 - 7.23 (m, 2H), 7.23 - 7.15 (m, 2H), 7.15 - 7.09 (m, 1H), 7.06 - 6.99 (m, 1H), 3.95 (s, 3H), 3.65 - 3.41 (m, 3H), 3.14 - 2.95 (m, 4H), 2.93 - 2.76 (m, 5H), 2.76 - 2.66 (m, 1H), 2.25 - 1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 162.4 (d, J_{CF} = 246.9 Hz), 158.9, 155.0 (d, J_{CF} = 251.5 Hz), 141.5 (d, J_{CF} = 2.3 Hz), 138.1 (d, J_{CF} = 29.4 Hz), 131.8, 130.2 (d, J_{CF} = 8.6 Hz), 129.4, 129.2, 127.9 (d, J_{CF} = 3.1 Hz), 124.2 (d, J_{CF} = 9.4 Hz), 120.4 (d, J_{CF} = 2.5 Hz), 118.8 (d, J_{CF} = 22.8 Hz), 116.2 (d, J_{CF} = 21.1 Hz), 101.9 (d, J_{CF} = 5.4 Hz), 85.9 (d, J_{CF} = 3.2 Hz), 82.8, 61.7, 55.8, 54.9, 53.1, 50.5, 48.3, 46.9, 25.6, 21.8 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2943, 2833, 1620, 1580, 1509, 1469, 1361, 1231, 1150, 1028, 910, 787, 731; HRMS (ESI) calcd for $C_{27}H_{28}F_2N_3O_3$ [M + H]$^+$ 480.2093 found 480.2089.

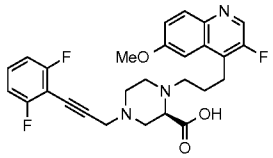


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(4-fluoro-phenyl)prop-2-yn-1-yl)piperazine-2-carboxylic acid (62b). Following ***general procedure IV***, methyl ester **61b** (63 mg, 0.13 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (32 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (br s, 1H), 8.57 (d, J_{HF} = 0.7 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.46 - 7.36 (m, 2H), 7.30 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 7.07 - 6.93 (m, 2H),

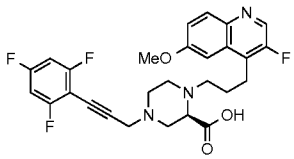
3.93 (s, 3H), 3.67 - 3.35 (m, 3H), 3.25 - 3.15 (m, 1H), 3.13 - 2.71 (m, 9H), 2.13 - 1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 162.7 (d, J_{CF} = 250.2 Hz), 158.9, 154.9 (d, J_{CF} = 251.6 Hz), 141.3 (d, JC J_{CF} F = 2.3 Hz), 137.9 (d, J_{CF} = 29.5 Hz), 133.8 (d, J_{CF} = 8.4 Hz), 131.6, 129.0 (d, JC J_{CF} F = 3.6 Hz), 128.9 (d, J_{CF} = 12.3 Hz), 120.4 (d, J_{CF} = 2.5 Hz), 118.3 (d, J_{CF} = 3.5 Hz), 115.7 (d, J_{CF} = 22.1 Hz), 101.7 (d, J_{CF} = 5.4 Hz), 86.1, 81.2, 62.8, 55.7, 54.9, 52.8, 49.7, 48.6, 46.8, 24.9, 21.6 (d, J_{CF} = 3.0 Hz); IR (neat) cm^{-1}: 3411, 2946, 2831, 1720, 1620, 1506, 1468, 1362, 1229, 1155, 834, 754; HRMS (ESI) calcd for $C_{27}H_{28}F_2N_3O_3$ $[M + H]^+$ 480.2093, found 480.2090; $[\alpha]_D^{20}$ = + 6.0 (*c* 1.0, $CHCl_3$).



(*R*)-4-(3-(3,4-Difluorophenyl)prop-2-yn-1-yl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)propyl)piperazine-2-carboxylic acid (62c). Following ***general procedure IV***, methyl ester **61c** (30 mg, 0.059 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (27 mg, 92%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 - 8.53 (m, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.25 - 7.15 (m, 3H), 7.14 - 7.06 (m, 1H), 3.96 (s, 3H), 3.62 - 3.52 (m, 2H), 3.52 - 3.42 (m, 1H), 3.14 - 2.97 (m, 3H), 2.96 - 2.59 (m, 7H), 2.13 - 1.87 (m, 2H); IR (neat) cm^{-1}: 2944, 2834, 1672, 1620, 1513, 1469, 1231, 732; HRMS (ESI) calcd for $C_{27}H_{27}F_3N_3O_3$ $[M + H]^+$ 498.1999 found 498.1988.



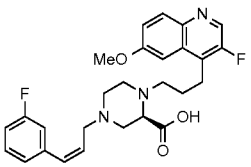
(*R*)-4-(3-(2,6-Difluorophenyl)prop-2-yn-1-yl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)propyl)piperazine-2-carboxylic acid (62d). Following ***general procedure IV***, methyl ester **61d** (25 mg, 0.049 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (12 mg, 50%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 0.9 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.33 - 7.27 (m, 2H), 7.20 (d, *J* = 2.7 Hz, 1H), 6.96 - 6.87 (m, 2H), 3.96 (s, 3H), 3.71 (d, *J* = 1.9 Hz, 2H), 3.50 (t, *J* = 2.9 Hz, 1H), 3.07 (t, *J* = 7.7 Hz, 3H), 2.95 - 2.73 (m, 6H), 2.72 - 2.61 (m, 1H), 2.11 - 1.81 (m, 2H); IR (neat) (neat) cm^{-1}: 2952, 1674, 1621, 1509, 1468, 1232, 1004; HRMS (ESI) calcd for $C_{27}H_{27}F_3N_3O_3$ $[M + H]^+$ 498.1999 found 498.1989.



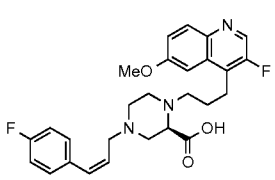
(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(2,4,6-trifluoro-phenyl)prop-2-yn-1-yl)piperazine-2-carboxylic acid (62e). Following ***general procedure IV***, methyl ester

61e (40 mg, 0.076 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (13 mg, 34%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 0.9 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.20 (d, *J* = 2.7 Hz, 1H), 6.70 (dd, *J* = 8.6, 7.1 Hz, 2H), 3.96 (s, 3H), 3.68 (d, *J* = 2.6 Hz, 2H), 3.49 (t, *J* = 2.9 Hz, 1H), 3.11 - 3.02 (m, 3H), 2.92 - 2.84 (m, 1H), 2.84 - 2.70 (m, 5H), 2.70 - 2.59 (m, 1H), 2.10 - 1.97 (m, 1H), 1.96 - 1.83 (m, 1H); IR (neat) (neat) cm^{-1}: 3072, 2928, 2857, 1674, 1638, 1505, 1444, 1232, 1126, 1040; HRMS (ESI) calcd for $C_{27}H_{26}F_4N_3O_3$ $[M + H]^+$ 516.1905 found 516.1902.

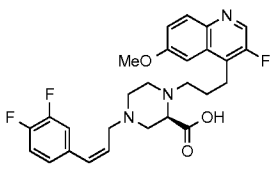
General procedure VII: Hydrogenation of alkynes and subsequent hydrolysis of methyl ester



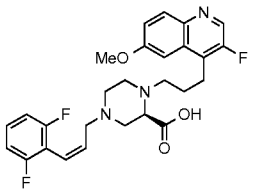
(*R*,*Z*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(3-fluorophen-yl)allyl)piperazine-2-carboxylic acid (63a). Alkyne **61a** (37 mg, 0.068 mmol) and 10% Pd/C (1 mg, 0.001 mmol) was dissolved in methanol under a hydrogen atmosphere and stirred at rt for 1 h. The reaction mixture was then filtered through a pad of celite, concentrated *in vacuo* and redissolved in 0.3 M LiOH (THF:water (2:1)) to a concentration of 0.1 M of the ester. After shaking in a closed reaction vial for 16 h at 65 °C, AcOH (3 equiv) was added, THF was removed under a flow of pressurized air, and the mixture was purified by preparative HPLC to give the title compound as an off-white amorphous solid (14 mg, 39% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 0.9 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.36 - 7.28 (m, 2H), 7.20 (d, *J* = 2.7 Hz, 1H), 7.03 - 6.91 (m, 2H), 6.87 (dd, *J* = 9.8, 1.7 Hz, 1H), 6.68 (d, *J* = 11.7 Hz, 1H), 5.76 (dt, *J* = 12.0, 6.6 Hz, 1H), 3.95 (s, 3H), 3.45 - 3.37 (m, 3H), 3.14 - 3.01 (m, 3H), 2.98 - 2.89 (m, 1H), 2.86 - 2.72 (m, 3H), 2.72 - 2.62 (m, 1H), 2.45 (dd, *J* = 11.5, 2.2 Hz, 1H), 2.35 (td, *J* = 11.0, 4.2 Hz, 1H), 2.07 - 1.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 162.7 (d, J_{CF} = 246.4 Hz), 158.6, 154.9 (d, J_{CF} = 251.4 Hz), 141.4, 138.2, 138.1 (d, J_{CF} = 29.4 Hz), 132.9, 131.7, 130.0 (d, J_{CF} = 8.5 Hz), 129.7 (d, J_{CF} = 12.8 Hz), 129.3 (d, J_{CF} = 3.7 Hz), 126.5, 124.5 (d, J_{CF} = 2.9 Hz), 120.2, 115.5 (d, J_{CF} = 21.6 Hz), 114.5 (d, J_{CF} = 21.1 Hz), 102.0 (d, J_{CF} = 5.5 Hz), 60.1, 55.7, 54.6, 54.6, 53.8, 51.8, 47.4, 25.9, 21.8; IR (neat) cm^{-1}: 3382, 3012, 2944, 2832, 1674, 1620, 1580, 1509, 1469, 1231, 732; HRMS (ESI) calcd for $C_{27}H_{30}F_2N_3O_3$ $[M + H]^+$ 482.2250 found 482.2244.



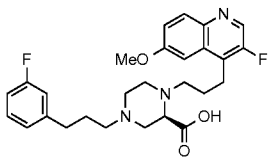
(*R*,*Z*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(4-fluo-rophen-yl)allyl)piperazine-2-carboxylic acid (63b). Following ***general procedure VII***, alkyne **61b** (109 mg, 0.220 mmol) was hydrogenated using 10% Pd/C (2 mg, 0.002 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (13 mg, 12%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.41 - 7.28 (m, 4H), 7.21-7.16 (m, 2H), 6.55 (d, J = 11.9 Hz, 1H), 5.68 (dt, J = 11.8, 6.2 Hz, 1H), 3.93 (s, 3H), 3.22 - 3.16 (m, 1H), 3.13 (d, J = 5.9 Hz, 2H), 3.10 - 2.96 (m, 3H), 2.95 - 2.80 (m, 1H), 2.70 - 2.56 (m, 2H), 2.48 - 2.42 (m, 2H), 2.32 (m, 1H), 1.85 - 1.69 (m, 2H), 1.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.0, 161.1 (d, J_{CF} = 244.3 Hz), 158.2, 154.5 (d, J_{CF} = 250.1 Hz), 141.0 (d, J_{CF} = 2.1 Hz), 137.9 (d, J_{CF} = 29.0 Hz), 133.0 (d, J_{CF} = 3.2 Hz), 131.3, 130.8 (d, J_{CF} = 8.1 Hz), 130.1, 129.8 (d, J_{CF} = 13.1 Hz), 129.2, 128.8 (d, J_{CF} = 4.0 Hz), 120.5 (d, J_{CF} = 2.3 Hz), 115.1 (d, J_{CF} = 21.3 Hz), 102.4 (d, J_{CF} = 5.3 Hz), 62.9, 55.6, 55.2, 55.1, 54.2, 52.1, 47.9, 26.0, 21.3 (d, J_{CF} = 2.5 Hz); IR (neat) cm^{-1}: 3380, 3012, 2928, 2830, 1721, 1620, 1603, 1508, 1468, 1229, 1157, 831, 754; HRMS (ESI) calcd for $C_{27}H_{30}F_2N_3O_3$ [M + H]$^+$ 482.2250, found 482.2252; $[\alpha]_D^{20}$ = -16.2 (*c* 0.5, in $CHCl_3$).



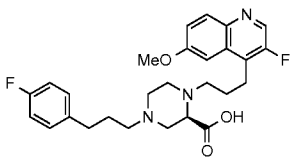
(*R*,*Z*)-4-(3-(3,4-difluorophenyl)allyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (63c). Following ***general procedure VII***, alkyne **61c** (43 mg, 0.83 mmol) was hydrogenated using 10% Pd/C (1 mg, 0.001 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (21 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 1.0 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 9.2, 2.7 Hz, 1H), 7.19 (d, J = 2.6 Hz, 1H), 7.17 - 7.11 (m, 1H), 7.03 - 6.96 (m, 1H), 6.92 - 6.82 (m, 1H), 6.61 (d, J = 11.7 Hz, 1H), 5.82 - 5.68 (m, 1H), 3.94 (s, 3H), 3.46 - 3.35 (m, 3H), 3.15 - 3.02 (m, 3H), 3.00 - 2.86 (m, 2H), 2.85 - 2.70 (m, 3H), 2.58 - 2.49 (m, 1H), 2.45 - 2.35 (m, 1H), 2.06 - 1.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 158.7, 154.9 (d, J_{CF} = 251.4 Hz), 150.1 (dd, J_{CF} = 248.7, 12.7 Hz), 149.7 (dd, J_{CF} = 249.8, 12.5 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.5 Hz), 133.0 (d, J_{CF} = 5.8 Hz), 132.9 (d, J_{CF} = 5.9 Hz), 132.1, 131.6, 129.6 (d, J_{CF} = 12.8 Hz), 129.2 (d, J_{CF} = 3.8 Hz), 126.3, 125.0 (dd, J_{CF} = 6.1, 3.6 Hz), 120.2 (d, J_{CF} = 2.5 Hz), 117.5 (t, J_{CF} = 16.7 Hz), 102.0 (d, J_{CF} = 5.4 Hz), 60.7, 55.7, 54.6, 54.5, 53.8, 51.5, 47.4, 25.7, 21.8 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2943, 2833, 1673, 1620, 1513, 1429, 1276, 1231, 732; HRMS (ESI) calcd for $C_{27}H_{29}F_3N_3O_3$ [M + H]$^+$ 500.2156 found 500.2143.



(*R*,*Z*)-4-(3-(2,6-Difluorophenyl)allyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (63d). Following ***general procedure VII***, alkyne **61d** (25 mg, 0.049 mmol) was hydrogenated using 10% Pd/C (1 mg, 0.001 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (8 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.0 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.32 - 7.27 (m, 2H), 7.20 (d, *J* = 2.7 Hz, 1H), 6.95 - 6.88 (m, 1H), 6.45 (d, *J* = 11.5 Hz, 1H), 5.97 (dt, *J* = 11.5, 6.7 Hz, 1H), 3.95 (s, 3H), 3.40 (t, *J* = 2.8 Hz, 1H), 3.17 - 3.12 (m, 2H), 3.09 - 3.00 (m, 3H), 2.92 - 2.86 (m, 1H), 2.77 (td, *J* = 12.6, 5.9 Hz, 3H), 2.67 - 2.58 (m, 1H), 2.41 (dd, *J* = 11.6, 2.4 Hz, 1H), 2.32 (td, *J* = 10.9, 5.1 Hz, 1H), 2.07 - 1.80 (m, 2H); IR (neat) cm^{-1}: 2943, 1674, 1621, 1509, 1465, 1232, 995, 906, 730; HRMS (ESI) calcd for $C_{27}H_{29}F_3N_3O_3$ [M + H]$^+$ 500.2156 found 500.2157.

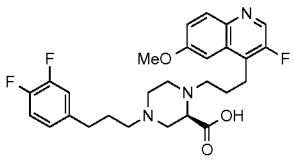


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(3-fluorophenyl)-propyl)piperazine-2-carboxylic acid (64a). Following ***general procedure VII***, alkyne **61a** (32 mg, 0.066 mmol) was hydrogenated using 10% Pd/C (7 mg, 0.007 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (14 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.0 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.26 - 7.22 (m, 1H), 7.22 - 7.19 (m, 1H), 6.96 - 6.83 (m, 3H), 3.96 (s, 3H), 3.43 (t, *J* = 3.1 Hz, 1H), 3.16 (d, *J* = 11.3 Hz, 1H), 3.07 (t, *J* = 7.2 Hz, 2H), 3.02 - 2.92 (m, 2H), 2.90 - 2.72 (m, 3H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.61 - 2.53 (m, 3H), 2.48 - 2.36 (m, 1H), 2.08 - 1.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 163.1 (d, J_{CF} = 245.8 Hz), 158.8, 155.1 (d, J_{CF} = 251.3 Hz), 143.2 (d, J_{CF} = 7.2 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.1 (d, J_{CF} = 29.6 Hz), 131.6, 130.2 (d, J_{CF} = 8.4 Hz), 130.0 (d, J_{CF} = 12.9 Hz), 129.4 (d, J_{CF} = 3.9 Hz), 124.1 (d, J_{CF} = 2.8 Hz), 120.5, 115.3 (d, J_{CF} = 20.9 Hz), 113.4 (d, J_{CF} = 21.0 Hz), 102.1 (d, J_{CF} = 5.3 Hz), 60.3, 56.5, 55.9, 54.8, 54.3, 51.7, 47.1, 32.9, 26.8, 25.9, 22.0; IR (neat) cm^{-1}: 2942, 2866, 1672, 1620, 1509, 1470, 1363, 1232; HRMS (ESI) calcd for $C_{27}H_{32}F_2N_3O_3$ [M + H]$^+$ 484.2406 found 484.2401.

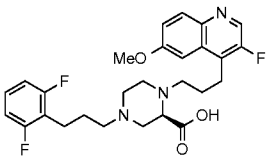


(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(4-fluorophen-yl)propyl)piperazine-2-carboxylic acid (64b). Following ***general procedure VII***, alkyne **61b** (60 mg, 0.12 mmol) was hydrogenated using 10% Pd/C (7 mg, 0.006 mmol)

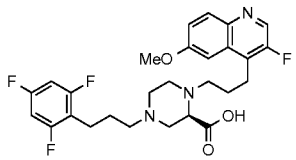
and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (31 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (br s, 1H), 8.55 (s, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.29 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.18 (d, *J* = 2.6 Hz, 1H), 7.12 - 7.05 (m, 2H), 6.99 - 6.90 (m, 2H), 3.93 (s, 3H), 3.43 (t, *J* = 3.5 Hz, 1H), 3.20 (m, 2H), 3.09 - 2.98 (m, 3H), 2.98 - 2.79 (m, 2H), 2.76 - 2.54 (m, 6H), 2.55 - 2.45 (m, 1H), 2.04 - 1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 161.5 (d, J_{CF} = 244.1 Hz), 158.8, 155.0 (d, J_{CF} = 251.3 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.5 Hz), 136.2 (d, J_{CF} = 3.2 Hz), 131.6, 129.8 (d, J_{CF} = 7.8 Hz), 129.7, 129.3 (d, J_{CF} = 3.8 Hz), 120.3 (d, J_{CF} = 2.4 Hz), 115.4 (d, J_{CF} = 21.1 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 61.0, 56.6, 55.8, 54.6, 54.2, 51.3, 46.6, 32.3, 26.7, 25.7, 21.9 (d, J_{CF} = 2.9 Hz); IR (neat) cm^{-1}: 3410, 3035, 2946, 2830, 1722, 1620, 1509, 1468, 1362, 1220, 1156, 1029, 831, 754; HRMS (ESI) calcd for $C_{27}H_{32}F_2N_3O_3$ $[M + H]^+$ 484.2406, found 484.2400; $[\alpha]_D^{20}$ = +11.0 (*c* 1.0, in $CHCl_3$).



(*R*)-4-(3-(3,4-difluorophenyl)propyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (64c). Following ***general procedure VII***, alkyne **61c** (43 mg, 0.085 mmol) was hydrogenated using 10% Pd/C (9 mg, 0.008 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (17 mg, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 1.0 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.31 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.20 (d, *J* = 2.7 Hz, 1H), 7.06 (dt, *J* = 10.2, 8.3 Hz, 1H), 6.96 (ddd, *J* = 11.1, 7.6, 2.1 Hz, 1H), 6.89 - 6.83 (m, 1H), 3.95 (s, 3H), 3.45 (t, *J* = 3.3 Hz, 1H), 3.18 (d, *J* = 11.0 Hz, 1H), 3.11 - 2.95 (m, 4H), 2.87 (dd, *J* = 12.2, 5.1 Hz, 2H), 2.79 - 2.71 (m, 1H), 2.66 - 2.54 (m, 5H), 2.51 - 2.41 (m, 1H), 2.07 - 1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 158.9, 155.1 (d, J_{CF} = 251.2 Hz), 150.4 (dd, J_{CF} = 248.1, 12.7 Hz), 149.1 (dd, J_{CF} = 246.4, 12.5 Hz), 141.4 (d, J_{CF} = 2.2 Hz), 138.0 (d, J_{CF} = 29.7 Hz), 137.6 (d, J_{CF} = 4.1 Hz), 137.6 (d, J_{CF} = 4.1 Hz), 131.6, 129.9 (d, J_{CF} = 12.9 Hz), 129.4 (d, J_{CF} = 3.8 Hz), 124.3 (dd, J_{CF} = 6.0, 3.5 Hz), 120.5 (d, J_{CF} = 2.5 Hz), 117.3 (dd, J_{CF} = 24.2, 16.9 Hz), 102.1 (d, J_{CF} = 5.4 Hz), 60.6, 56.4, 55.9, 54.7, 54.2, 51.6, 46.9, 32.3, 26.8, 25.8, 21.9 (d, J_{CF} = 3.1 Hz); IR (neat) cm^{-1}: 2944, 2868, 2834, 1672, 1620, 1516, 1432, 1283, 1231; HRMS (ESI) calcd for $C_{27}H_{31}F_3N_3O_3$ $[M + H]^+$ 502.2312 found 502.2295.

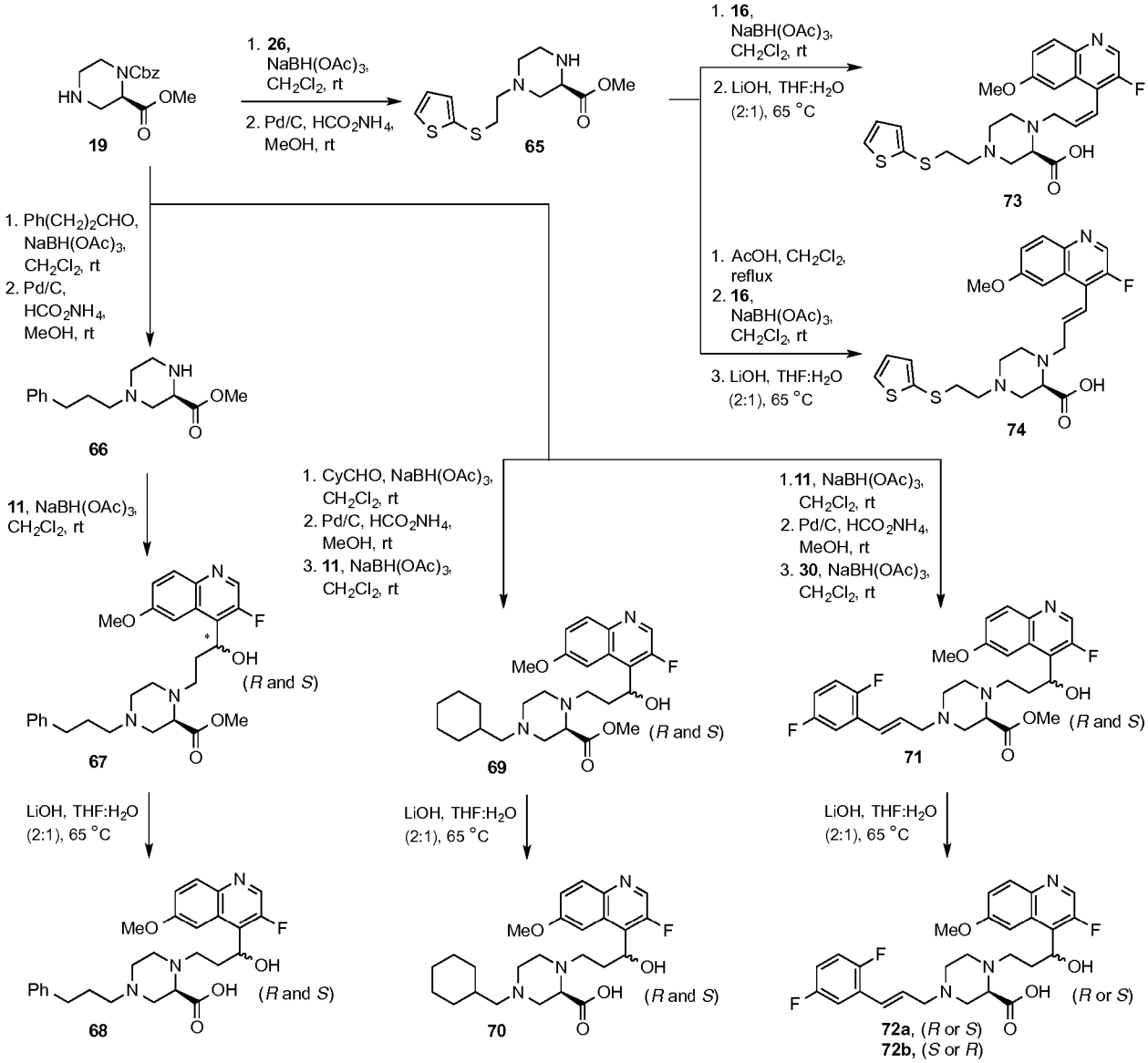


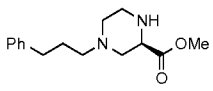
(*R*)-4-(3-(2,6-Difluorophenyl)propyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)propyl)piperazine-2-carboxylic acid (64d). Following ***general procedure VII***, alkyne **61d** (43 mg, 0.085 mmol) was hydrogenated using 10% Pd/C (5 mg, 0.005 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (4 mg, 15%). HRMS (ESI) calcd for $C_{27}H_{31}F_3N_3O_3$ calcd for $[M + H]^+$ 502.2312 found 502.2304.



(*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-4-(3-(2,4,6-trifluor-ophenyl)propyl)piperazine-2-carboxylic acid (64e). Following ***general procedure VII***, alkyne **61e** (40 mg, 0.076 mmol) was hydrogenated using 10% Pd/C (16 mg, 0.015 mmol) and hydrolyzed to give the title compound as an off-white amorphous solid after preparative HPLC (6 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 1.0 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.32 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.21 (d, *J* = 2.7 Hz, 1H), 6.71 - 6.59 (m, 2H), 3.97 (s, 3H), 3.40 (t, *J* = 2.5 Hz, 1H), 3.11 - 3.01 (m, 3H), 2.91 (d, *J* = 9.2 Hz, 1H), 2.76 (ddd, *J* = 16.9, 13.2, 5.0 Hz, 3H), 2.62 (dt, *J* = 13.0, 7.6 Hz, 3H), 2.55 - 2.49 (m, 2H), 2.45 (dd, *J* = 11.4, 2.3 Hz, 1H), 2.34 (td, *J* = 11.3, 4.2 Hz, 1H), 2.09 - 1.96 (m, 1H), 1.89 (ddd, *J* = 19.3, 13.0, 6.7 Hz, 1H), 1.80 (dt, *J* = 15.1, 7.6 Hz, 2H); IR (neat) cm^{-1}: 2943, 1672, 1621, 1509, 1440, 1362, 1231, 1115, 998, 833; HRMS (ESI) calcd for $C_{27}H_{30}F_4N_3O_3$ $[M + H]^+$ 520.2218 found 520.2219.

Scheme 8. Synthesis of final compounds **68**, **70**, **72a-b**, **73** and **74**

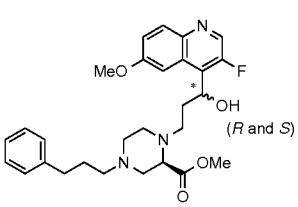




Methyl (*R*)-4-(3-phenylpropyl)piperazine-2-carboxylate (66). Piperazine **19** (2.83 g, 10.2 mmol) was dissolved in CH_2Cl_2 (50 mL) under stirring at rt, followed by addition of hydrocinnamaldehyde (1.61 mL, 12.2 mmol). After 15 min of stirring, conc. AcOH (58 µL, 1.0 mmol) was added, and the solution was stirred for another 15 min. Then $NaBH(OAc)_3$ (4.32 g, 20.4 mmol) was added, and the reaction subsequently ran to completion after 1.5 h. The organic phase was washed with 10% $NaHCO_3$ (aq) (25 mL), followed by separation, and extraction of the aqueous phase with CH_2Cl_2 (50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:heptane (1:3), R_f = 0.2), to give the intermediate amine as a colorless oil (2.46 g, 61%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.24 (m,

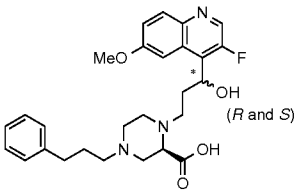
7H), 7.22 - 7.14 (m, 3H), 5.18 (s, 2H), 4.84 - 4.80 and 4.73 - 4.67 (2 x m, 1H), 4.01 - 3.86 (m, 1H), 3.77 and 3.72 (2 x s, 3H), 3.50 - 3.22 (m, 2H), 2.85 - 2.70 (m, 1H), 2.69 - 2.53 (m, 2H), 2.43 - 2.26 (m, 2H), 2.23 - 2.01 (m, 2H), 1.84 - 1.73 (m, 2H), rotamers; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 and 171.0 (1C), 156.5 and 156.0 (1C), 142.1, 136.6, 128.6 (4C), 128.5 (2C), 128.2, 128.00, 127.97, 125.9, 67.6 and 67.5 (1C), 57.0, 55.3 and 55.0 (1C), 53.4, 52.7, 52.5, 41.9 and 41.7 (1C), 33.2, 28.4, rotamers; IR (neat) cm^{-1}: 3027, 2948, 2813, 1747, 1701, 1414, 1292, 1204, 1110, 1040, 746, 697; HRMS (ESI) calcd for $C_{23}H_{29}N_2O_4$ $[M + H]^+$ 397.2127, found 397.2126; $[\alpha]_D^{20}$ = + 26.9 (*c* 1.0, $CHCl_3$).

The intermediate amine (2.31 g, 5.83 mmol) was dissolved in MeOH (25 mL) under stirring at rt, whereupon NH_4COOH (0.735 g, 11.7 mmol) was added. After 25 min of stirring, 10% Pd/C (0.062 g, 0.058 mmol) suspended in MeOH (5 mL) was added to the solution. The reaction mixture was following stirred at rt under argon overnight. Additional 10% Pd/C (0.620 g, 0.583 mmol) and NH_4COOH (0.735 g, 11.7 mmol) were then added, whereupon the reaction ran to completion after 2 days. The reaction mixture was filtered through a pad of celite, followed by removal of MeOH *in vacuo*. The residue was suspended in water and extracted with EtOAc (2x50 mL). The combined organic phases were concentrated *in vacuo* and subjected to flash column chromatography on silica gel (CH_2Cl_2:MeOH (95:5), R_f = 0.2), to give the title compound **66** as a yellow oil (1.05 g, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.33 (m, 2H), 7.30 - 7.23 (m, 3H), 3.82 (s, 3H), 3.67 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.18 - 3.11 (m, 1H), 3.02 - 2.89 (m, 2H), 2.75 - 2.64 (m, 3H), 2.50 - 2.40 (m, 3H), 2.33 - 2.24 (m, 1H), 2.18 (br s, 1H), 1.95 - 1.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 142.2, 128.5 (2C), 128.4 (2C), 125.8, 58.0, 57.3, 55.2, 53.7, 52.1, 44.4, 33.6, 28.4; IR (neat) cm^{-1}: 3352, 3025, 2946, 2808, 1737, 1657, 1452, 1434, 1201, 1143, 746, 699; HRMS (ESI) calcd for $C_{15}H_{23}N_2O_2$ $[M + H]^+$ 263.1760, found 263.1755; $[\alpha]_D^{20}$ = - 6.8 (*c* 1.0, $CHCl_3$).

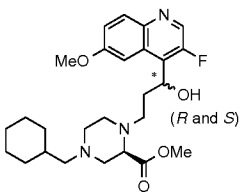


Methyl (2*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropyl)-4-(3-phenylpropyl) piperazine-2-carboxylate (67). Freshly prepared aldehyde **11** (0.048 g, 0.16 mmol) and amine **66** (0.043 g, 0.16 mmol) were mixed and dissolved in CH_2Cl_2 (1.6 mL). Then $NaBH(OAc)_3$ (0.052 g, 0.24 mmol) was added, and the reaction mixture was stirred for 1 h at rt. Sat. $NaHCO_3$ (aq) (5 mL) was subsequently added, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and

concentrated *in vacuo*. The residue was subjected to flash column chromatography on silica gel (EtOAc:heptane (3:2), R_f = 0.2) to afford the title compound **67** as a colorless oil (diastereoisomeric mixture, 0.057 g, 71% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98 - 7.91 (m, 2H), 7.30 - 7.23 (m, 3H), 7.19 - 7.13 (m, 3H), 5.79 (dd, *J* = 10.4, 2.6 Hz, 0.5H), 5.72 (dd, *J* = 10.0, 2.6 Hz, 0.5H), 3.90 (s, 3H), 3.75 (s, 1.5H), 3.72 (s, 1.5H), 3.50 - 3.33 (m, 1.5H), 3.24 - 3.13 (m, 1H), 3.06 - 2.96 (m, 0.5H), 2.88 - 2.23 (m, 12H), 1.83 - 1.66 (m, 3H), diastereoisomers (1:1); MS (ESI) calcd for $C_{28}H_{35}FN_3O_4$ $[M + H]^+$ 496.3, found 496.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.98 - 7.91 (m, 2H), 7.30 - 7.23 (m, 3H), 7.19 - 7.13 (m, 3H), 5.79 (dd, *J* = 10.4, 2.6 Hz, 0.5H), 5.72 (dd, *J* = 10.0, 2.6 Hz, 0.5H), 3.90 (s, 3H), 3.75 (s, 1.5H), 3.72 (s, 1.5H), 3.50 - 3.33 (m, 1.5H), 3.24 - 3.13 (m, 1H), 3.06 - 2.96 (m, 0.5H), 2.88 - 2.23 (m, 12H), 1.83 - 1.66 (m, 3H), diastereoisomers (1:1); MS (ESI) calcd for $C_{28}H_{35}FN_3O_4$ $[M + H^+]$ 496.3, found 496.4.

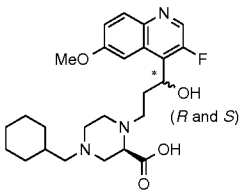


(2*R*)-1-(3-(3-Fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropyl)-4-(3-phenylpropyl)piperazine-2-carboxylic acid (68). Following ***general procedure IV***, methyl ester **67** (56 mg, 0.11 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid (1:1 diastereomeric mixture) after preparative HPLC (43 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 0.5H), 8.49 (s, 0.5H), 7.94 (d, *J* = 9.2 Hz, 1H), 7.91 - 7.85 (m, 0.5H), 7.82 - 7.77 (m, 0.5H), 7.29 - 7.21 (m, 3H), 7.20 - 7.09 (m, 3H), 5.83 (d, *J* = 8.2 Hz, 0.5H), 5.72 (d, *J* = 5.3 Hz, 0.5H), 3.85 (s, 1.5H), 3.81 (s, 1.5H), 3.63 - 3.49 (m, 1.5H), 3.47 - 2.41 (m, 13H), 2.33 - 2.13 (m, 0.5H), 2.06 - 1.79 (m, 3H), acid proton has exchanged, diastereoisomers (1:1); HRMS (ESI) calcd for $C_{27}H_{33}FN_3O_4$ $[M + H^+]$ 482.2455, found 482.2457.

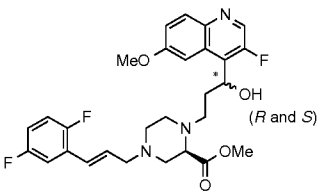


(2*R*)-Methyl 4-(cyclohexylmethyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropyl)piperazine-2-carboxylate (69). A solution of amine **19** (100 mg, 0.36 mmol), cyclohexanecarbaldehyde (52 mg, 0.47 mmol) and $NaBH(OAc)_3$ (114 mg, 0.54 mmol) in CH_2Cl_2 (1.8 mL) was stirred for 30 minutes at rt. The reaction mixture was then concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (7:3), R_f = 0.7) to give the Cbz-protected amine intermediate (96 mg, 71%). The intermediate (59 mg, 0.16 mmol) was dissolved in MeOH followed by the addition of $HCOONH_4$ (60 mg, 0.94 mmol) and Pd/C (9 mg, 0.009 mmol) and stirred for 10 min at rt. The mixture was then filtered through celite which was washed with MeOH and the

filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (40 mL) and washed with H_2O (40 mL) and the phases were separated. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (1 mL) and stirred with aldehyde **11** (freshly prepared, 47 mg, 0.16 mmol) and $NaBH(OAc)_3$ (50 mg, 0.24 mmol) for 15 min at rt. CH_2Cl_2 (40 mL) and water (40 mL) was then added and the mixture transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2), to give the title compound as a colorless oil (40 mg, 38% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 - 8.49 (m, 1H), 8.01 - 7.93 (m, 2H), 7.28 (dd, *J* = 9.2, 2.7 Hz, 1H), 5.81 (dd, *J* = 10.7, 2.7 Hz, 0.5H), 5.75 (dd, *J* = 10.2, 2.6 Hz, 0.5H), 3.92 (s, 1.5H), 3.92 (s, 1.5H), 3.77 (s, 1.5H), 3.72 (s, 1.5H), 3.54 - 3.46 (m, 0.5H), 3.46 - 3.33 (m, 1H), 3.33 - 3.21 (m, 0.5H), 3.22 - 3.13 (m, 1H), 3.02 (td, *J* = 12.9, 3.3 Hz, 0,5H), 2.90 - 2.28 (m, 7H), 2.12 (d, *J* = 7.2 Hz, 2H), 1.79 - 1.59 (m, 6H), 1.52 - 1.37 (m, 1H), 1.29 - 1.08 (m, 3H), 0.92 - 0.76 (m, 2H), mixture of two diastereomers.

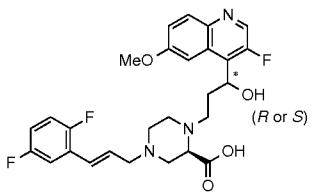


(2*R*)-4-(Cyclohexylmethyl)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropyl)piperazine-2-carboxylic acid (70). Following ***general procedure IV***, methyl ester **69** (31 mg, 0.065 mmol) was hydrolyzed to give the title compound as an off-white amorphous solid (1:1 diastereomeric mixture) after preparative HPLC (17 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.93 (d, *J* = 9.0 Hz, 1H), 7.85 - 7.66 (m, 1H), 7.24 (m, 1H), 5.93 - 5.61 (m, 1H), 3.87 (s, 1.5H), 3.86 (s, 1.5H), 3.60 - 3.48 (m, 1H), 3.36 - 2.09 (m, 11H), 2.07 - 1.89 (m, 1H), 1.80 - 1.41 (m, 6H), 1.32 - 1.05 (m, 3H), 1.02 - 0.73 (m, 2H), mixture of two diastereomers.

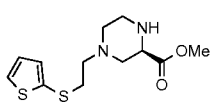


Methyl (2*R*)-4-((*E*)-3-(2,5-difluorophenyl)allyl)-1-(3-(3-fluoro-6-meth-oxyquinolin-4-yl)-3-hydroxypropyl)piperazine-2-carboxylate (71). A solution of amine **19** (100 mg, 0.36 mmol), aldehyde **30** (52 mg, 0.47 mmol) and $NaBH(OAc)_3$ (113 mg, 0.54 mmol) in CH_2Cl_2 (1.8 mL) was stirred for 30 minutes at rt. The reaction mixture was then concentrated *in vacuo*, and purified by flash column chromatography on silica gel (EtOAc:heptane (7:3), R_f = 0.2) to give the Cbz-protected

amine intermediate (123 mg, 80%). The intermediate (68 mg, 0.14 mmol) was dissolved in MeOH followed by the addition of $HCOONH_4$ (20 mg, 0.31 mmol) and Pd/C (8 mg, 0.007 mmol) and stirred for 10 min at rt. The mixture was then filtered through celite which was washed with MeOH and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (40 mL) and washed with H_2O (40 mL) and the phases were separated. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (1 mL) and stirred with aldehyde **11** (freshly prepared, 41 mg, 0.14 mmol) and $NaBH(OAc)_3$ (44 mg, 0.21 mmol) for 15 min at rt. CH_2Cl_2 (40 mL) and water (40 mL) was then added and the mixture transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (EtOAc:heptane (3:1), R_f = 0.2), to give the title compound as a colorless oil (62 mg, 38% over three steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H), 7.95 (d, *J* = 9.4 Hz, 1H), 7.28 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.16 - 7.09 (m,1H), 7.00 (dd, *J* = 9.2, 4.6 Hz, 0.5H) 0.5H), 6.97 (dd, *J* = 9.4, 4.6 Hz, 0.5H), 6.92 - 6.85 (m, 1H), 6.64 (d, *J* = 16.1 Hz, 1H), 6.30 (t, *J* = 6.5 Hz, 0.5H), 6.26 (d, *J* = 6.6 Hz, 0.5H), 5.82 (dd, *J* = 10.6, 2.5 Hz, 0.5H), 5.75 (dd, *J* = 10.0, 2.4 Hz, 0.5H), 3.92 (s, 3H), 3.78 (s, 1.5H), 3.75 (s, 1.5H), 3.52 - 3.45 (m, 0.5H), 3.47. - 3.35 (m, 1H), 3.26–3.13 (m, 3H), 3.10 - 2.96 (m, 0.5H), 2.9 - 2.25 (m, 7H), 1.85 - 1.66 (m, 1H), mixture of two diastereomers.



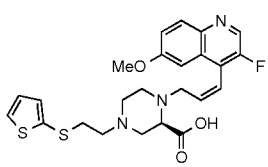
(2*R*)-4-((*E*)-3-(2,5-Difluorophenyl)allyl)-1-(3-(3-fluoro-6-methoxy-quinolin-4-yl)-3-hydroxypropyl)piperazine-2-carboxylic acid (72a and 72b). Following ***general procedure IV***, methyl ester **71** (44 mg, 0.083 mmol) was hydrolyzed to give two fractions of diastereomers **72a** (dr 2:1, 11 mg, 27%) and **72b** (dr 1:9, 9 mg, 21%) after preparative HPLC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.65 (s, 1H), 7.21 - 7.14 (m, 1H), 7.09 - 6.99 (m, 1H), 6.95 - 6.74 (m, 2H), 6.55 (d, *J* = 15.6 Hz, 1H), 6.23 - 6.03 (m, 1H), 5.71 (d, *J* = 7.6 Hz, 1H), 3.75 (s, 3H), 3.62 - 3.52 (m, 1H), 3.48–3.33 (m, 2H), 3.25 - 3.11 (m, 2H), 3.03 - 2.84 (m, 3H), 2.81 - 2.65 (m, 2H), 2.62 - 2.42 (m, 2H), 2.01 - 1.85 (m, 1H), mixture of two diastereomers.



Methyl (*R*)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylate (65). Piperazine **19** (2.12 g, 7.62 mmol) and aldehyde **26** (1.45 g, 9.14 mmol) were dissolved in CH_2Cl_2 (35 mL) together with acetic

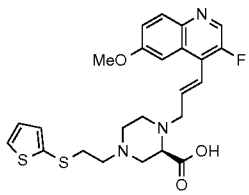
acid (43.5 µL, 0.762 mmol) and $NaBH(OAc)_3$ (3.23 g, 15.2 mmol). The mixture was stirred at rt for 1 h. The reaction was quenched with $NaHCO_3$ (25 mL) and water (50 mL). The aqueous phase was washed with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The compound was purified by flash chromatography on silica gel (1:3 EtOAc:heptane, R_f = 0.2) to give the intermediate Cbz-protected amine as a brown oil (2.35 g, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.28 (m, 6H), 7.14 - 7.07 (m, 1H), 7.00 - 6.91 (m, 1H), 5.22 - 5.06 (m, 2H), 4.89 - 4.59 (m, 1H), 3.98 - 3.82 (m, 1H), 3.74 (m, 3H), 3.47 - 3.11 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.80 - 2.66 (m, 1H), 2.66 - 2.49 (m, 2H), 2.32 - 2.19 (m, 1H), 2.18 - 2.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 156.4, 155.9, 136.6, 133.9, 129.5, 128.6, 128.2, 128.0, 128.0, 127.7, 67.6, 57.2, 55.3, 54.9, 53.6, 52.5, 52.4, 41.8, 35.8 (major rotamer).

The intermediate Cbz-protected amine (2.28 g, 5.42 mmol) was dissolved in diethyl ether (35 mL) and HBr (33% in acetic acid, 35 mL). After 2 h, water (100 mL) was added and the aqueous phase was washed with diethyl ether (3x 50 mL) to remove impurities. The aqueous phase was the basified with $NaHCO_3$ and extracted with diethyl ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the title product as a brown oil (0.679 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.4, 1.2 Hz, 1H), 7.12 (dd, *J* = 3.5, 1.2 Hz, 1H), 6.97 (dd, *J* = 5.3, 3.5 Hz, 1H), 3.76 (s, 3H), 3.73 (dd, *J* = 7.9, 3.4 Hz, 1H), 3.18 - 3.08 (m, 1H), 2.99 - 2.86 (m, 4H), 2.70 - 2.61 (m, 3H), 2.59 - 2.50 (m, 1H), 2.41 - 2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 171.3, 134.1, 134.0, 129.6, 127.7, 57.7, 56.1, 53.9, 52.6, 52.2, 43.1, 35.4.



(*R,Z*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)allyl)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylic acid (73). Amine **65** (0.081 g, 0.28 mmol) was suspended in CH_2Cl_2 (710 µL) under stirring at rt. To this, $NaBH(OAc)_3$ (0.090 g, 0.43 mmol) was added, followed by addition of a suspension of aldehyde **16** (freshly prepared from alcohol **15** (0.121 g, 0.517 mmol)) in CH_2Cl_2 (710 µL). The reaction mixture was left stirring overnight, whereupon water (5 mL) was added to the mixture, and the organic phase was washed with 10% $NaHCO_3$ (aq) (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (2 x 10 mL), followed by washing of the combined organic layers with brine (15 mL) and drying over Na_2SO_4. The concentrated residue was subjected to

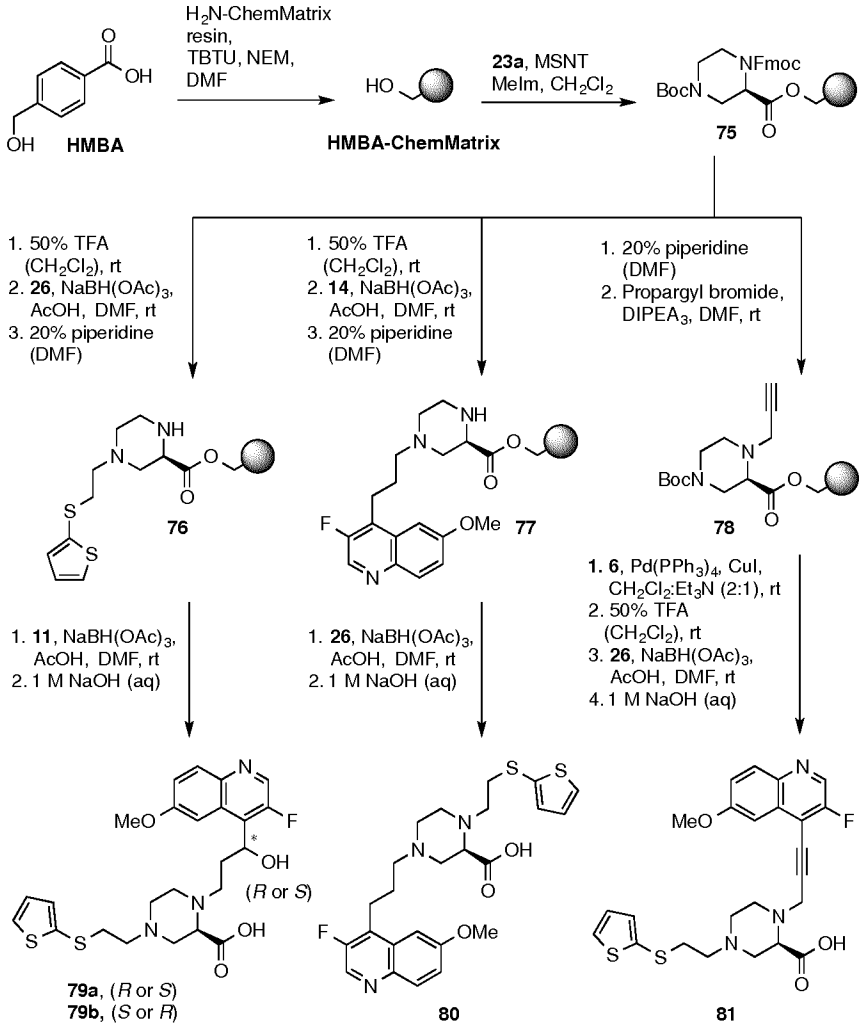
flash chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2) to give the intermediate ester, which was hydrolyzed using ***general procedure IV*** to give the title compound **73** as a white amorphous solid (0.019 g, 17% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.09 (d, *J* = 3.5 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.69 (d, *J* = 11.6 Hz, 1H), 6.33 (dt, *J* = 11.6, 6.3 Hz, 1H), 3.90 (s, 3H), 3.64 - 3.44 (m, 1H), 3.39 - 3.24 (m, 2H), 3.09 - 2.90 (m, 1H), 2.89 - 2.53 (m, 8H), 2.38 (m, 1H), acid proton has exchanged; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 159.0, 152.9 (d, J_{CF} = 254.1 Hz), 141.3 (d, J_{CF} = 2.1 Hz), 138.3 (d, J_{CF} = 29.3 Hz), 134.5, 133.1, 131.5, 123.0, 128.7 (d, J_{CF} = 2.6 Hz), 127.9, 127.8, 124.9, 122.6, 121.1, 102.6 (d, J_{CF} = 5.0 Hz), 62.7, 56.3, 55.8, 54.3, 54.2, 50.9, 48.1, 34.8; IR (neat) cm^{-1}: 3600-3100, 3071, 2944, 2828, 1718, 1620, 1506, 1358, 1227, 831, 752; HRMS (ESI) calcd for $C_{24}H_{27}FN_3O_3S_2$ [M + H]$^+$ 488.1478, found 488.1479; $[\alpha]_D^{20}$ = + 16.0 (*c* 1.0, $CHCl_3$).



(*R,E*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)allyl)-4-(2-(thiophen-2-ylthio)-ethyl)piperazine-2-carboxylic acid (74). Amine **65** (0.081 g, 0.28 mmol) was suspended in CH_2Cl_2 (710 µL), followed by addition of aldehyde **16** (freshly prepared from alcohol **15** (0.121 g, 0.517 mmol)) in CH_2Cl_2 (710 µL). To this mixture, conc. AcOH (10 µL, 0.17 mmol) was added, and the reaction was left for stirring overnight at rt. The reaction was followed on HPLC-UV by taking out fractions of 10 µL and reducing it with $NaBH(OAc)_3$. As only one peak was seen on the HPLC, the reaction mixture was heated to reflux (40 °C) for 3 h. Then $NaBH(OAc)_3$ (0.090 g, 0.43 mmol) was added. Water (5.0 mL) was added to the mixture, and the organic phase was washed with 10% $NaHCO_3$ (aq) (10 mL). The aqueous phase was then extracted with CH_2Cl_2 (2 x 10 mL), followed by washing of the combined organic layers with brine (15 mL) and drying over Na_2SO_4. The concentrated residue was subjected to flash chromatography on silica gel (EtOAc:heptane (1:1), R_f = 0.2), to give the intermediate ester, which was hydrolyzed using ***general procedure IV*** to give the title compound **74** as a beige amorphous solid (0.017 g, 9% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J_{HF} = 1.6 Hz, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 7.37 - 7.33 (m, 2H), 7.30 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.15 (d, *J* = 3.5 Hz, 1H), 7.00 - 6.93 (m, 2H), 6.48 (dt, *J* = 16.1, 6.7 Hz, 1H), 3.95 (s, 3H), 3.69 - 3.52 (m, 2H), 3.10 - 2.88 (m, 6H), 2.84 - 2.68 (m, 3H), 2.63 - 2.49 (m, 1H), acid proton has exchanged; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.0, 154.1 (d, *J* = 256.1 Hz), 141.6 (d, *J* = 2.4 Hz), 138.5 (d, *J* = 29.8 Hz), 135.9, 134.8, 132.8, 131.3, 130.2, 128.4 (d, *J* = 2.6 Hz), 127.9, 125.0 (d, *J* = 9.8 Hz), 123.8 (s), 121.1 (d, *J* = 2.1

Hz), 102.2 (d, J = 5.4 Hz), 60.2, 58.3, 56.2, 55.9, 54.7, 51.7, 48.0, 34.8; IR (neat) cm^{-1}: 3600-3200, 2941, 2826, 1719, 1619, 1507, 1363, 1228, 1150, 1028, 831, 704; HRMS (ESI) calcd for $C_{24}H_{27}FN_3O_3S_2$ $[M + H]^+$ 488.1478, found 488.1477; $[\alpha]_D^{20}$ = - 25.5 (*c* 1.0, $CHCl_3$).

Scheme 9. Solid-phase synthesis of final compounds **79a-b**, **80** and **81**



General protocols for solid-phase synthesis

All solid-phase synthesis reactions were performed in polyethylene syringes with a polypropylene filter. The syringes were attached to Teflon valves, which were connected with Teflon tubes allowing vacuum to be applied to the syringes. Before use, the amino-functionalized ChemMatrix resin (0.3 mmol/g) was washed with DMF (x 6), MeOH (x 6) and CH_2Cl_2 (x 6) followed by lyophilization.

Attachment of the 4-hydroxymethylbenzoic acid (HMBA) linker to the ChemMatrix resin was carried out by dissolving the acid (3 equiv) in DMF followed by addition of *N*-ethylmorpholine (NEM) (4 equiv) and TBTU (2.9 equiv). After 5 min the mixture was added to the resin and the mixture was occasionally stirred over 1 h. The resin was washed with DMF (x 6) and CH_2Cl_2 (x 6) and lyophilized.

Attachment of the piperazine core to the HMBA linker was performed by mixing carboxylic acid **23a** (3 equiv), MSNT (3 equiv) and *N*-methylimidazole (MeIm) (6 equiv) in dry CH_2Cl_2. After 5 min, the mixture was added to the HMBA-functionalized resin and the mixture was occasionally stirred over 1 h. The resin was washed with dry DMF (x 1) and the procedure was repeated once, followed by washes with DMF (x 6) and CH_2Cl_2 (x 6).

Boc-deprotection was performed by adding 50% TFA (CH_2Cl_2) to the resin and the mixture was occasionally stirred over 1 h, followed by washes with CH_2Cl_2 (x 6), 5% Et_3N (DMF) (x 2), DMF (x 6).

Fmoc-deprotection was performed by swelling the resin in 20% piperidine (DMF) for 2 min and then 5 min, followed by wash with DMF (x 6) and CH_2Cl_2 (x 6).

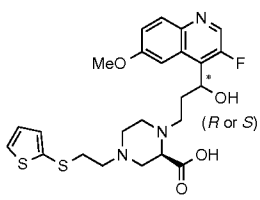
Reductive alkylations were performed by swelling the resin in CH_2Cl_2 or DMF followed by addition of aldehyde (3 - 5 equiv) and $NaBH(OAc)_3$ (5 equiv, either as powder or formed *in situ* by addition of AcOH to $NaBH_4$ in a separate flask). After 2 - 16 h the resin was washed with DMF (x 6) and CH_2Cl_2 (x 6).

Sonogashira cross-couplings were performed by swelling the resin in CH_2Cl_2:Et_3N (2:1) followed by addition of aromatic halide (5 equiv), $Pd(PPh_3)_4$ (10 mol%), CuI (15 mol%) and the syringed was sealed. After shaking for 1 - 3 days the resin was washed with DMF (x 6), MeOH (x 6) and CH_2Cl_2 (x 6).

Cleavage from the HMBA linker for UPLC-MS analysis was performed by treatment of 5 - 10 mg of resin with 0.1 M NaOH (aq) for 30 min, followed by neutralization with 0.1 M HCl (aq).

Cleavage to release NBTI analogs was performed by treatment of 200-300 mg resin with 0.1 M NaOH (aq) for 2-16 h followed by neutralization with 0.1 M HCl (aq). The

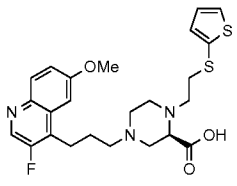
resin was rinsed with MeCN (x 2). The filtrates were concentrated *in vacuo* and the residue was purified by preparative HPLC.



(2*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)-3-hydroxypropyl)-4-(2-(thio-phen-2-ylthio)ethyl)piperazine-2-carboxylic acid (79a and 79b). ***General solid-phase synthesis protocols*** were followed to give the title compound as a mixture of diastereomers (1:1). Crude purity according to UPLC-MS: 71%. The two diastereomers were then separated to give **79a** and **79b**.

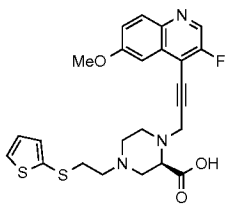
79a: 9:1 dr.; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 1.2 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H), 7.77 (s, 1H), 7.32 (dd, *J* = 5.2, 0.7 Hz, 1H), 7.24 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.11 (d, *J* = 2.8 Hz, 1H), 6.94 (dd, *J* = 5.3, 3.6 Hz, 1H), 5.78 (d, *J* = 9.1 Hz, 1H), 4.78 (br. s, 2H), 3.81 (s, 3H), 3.57 - 3.16 (m, 3H), 3.05 - 2.60 (m, 9H), 2.33 (s, 1H), 1.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 158.2, 153.8 (d, J_{CF} = 253.9 Hz), 142.0, 138.4 (d, *J* = 30.1 Hz), 134.4, 133.2, 131.5, 130.4 (d, *J* = 7.7 Hz), 130.0, 128.1, 127.9, 120.4, 104.1, 65.2, 64.4, 56.5, 55.7, 54.5, 52.5, 50.9, 48.5, 34.9, 31.6; IR (neat) cm^{-1}; 3272 (br), 2953, 2829, 1621, 1509, 1466, 1354, 1230, 1145; HRMS (ESI) calcd for $C_{24}H_{29}FN_3O_4S_2$ [M + H]$^+$ 506.1578, found 506.1574; $[\alpha]_D^{23}$= – 1.4 (*c* 1.0, $CHCl_3$).

79b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 2.3 Hz, 1H), 7.31 (d, *J* = 5.3 Hz, 1H), 7.22 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.09 (d, *J* = 3.4 Hz, 1H), 6.94 (dd, *J* = 5.3, 3.6 Hz, 1H), 5.77 (d, *J* = 7.2 Hz, 1H), 5.35 (br s, 2H), 3.78 (s, 3H), 3.67 - 3.38 (m, 3H), 3.05 - 2.89 (m, 2H), 2.86 - 2.51 (m, 9H), 2.07 - 1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 158.4, 154.05 (d, J_{CF} = 254.2 Hz), 142.0 (d, J_{CF} = 2.1 Hz), 138.5 (d, J_{CF} = 30.2 Hz), 134.3, 133.5, 131.6, 129.9, 129.8, 128.0 (d, J_{CF} = 3.0 Hz), 127.8, 120.4, 103.8 (d, J_{CF} = 4.6 Hz), 66.1, 65.6, 56.6, 55.7, 53.8, 53.8, 49.9, 48.9, 35.3, 30.9; IR (neat) cm^{-1}; 3203 (br), 2953, 2830, 1621, 1509, 1465, 1354, 1231, 1200, 1148; HRMS (ESI) calcd for $C_{24}H_{29}FN_3O_4S_2$ [M + H]$^+$ 506.1578, found 506.1573;$[\alpha]_D^{23}$= – 5.0 (*c* 1.0, $CHCl_3$).



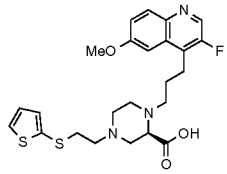
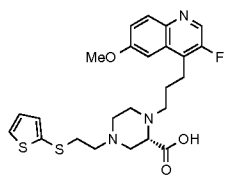
(*R*)-4-(3-(3-Fluoro-6-methoxyquinolin-4-yl)propyl)-1-(2-(thio-phen-2-ylthio)-ethyl)piperazine-2-carboxylic acid (80). ***General solid-phase synthesis protocols*** were followed to give the title compound. Crude purity according to UPLC-MS: >95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.34 - 7.27 (m, 2H), 7.14 (d, *J* = 2.6 Hz, 1H), 7.08 (dd, *J* = 3.5, 1.1 Hz, 1H), 6.93 (dd, *J* = 5.3, 3.6 Hz, 1H), 3.95 (s, 3H), 3.41 - 3.37 (m, 1H), 3.30 (d, *J* = 11.3 Hz, 1H), 3.13 - 2.62 (m, 12H), 2.51 (td, *J* =

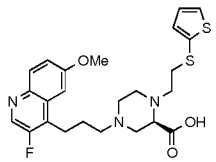
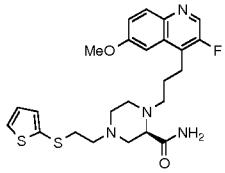
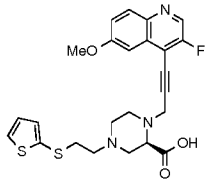
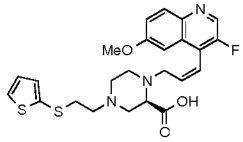
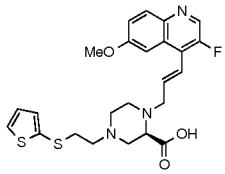
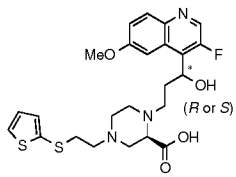
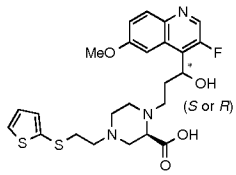
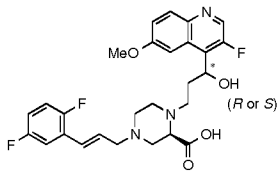
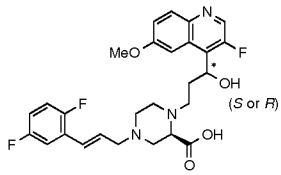
11.3, 3.6 Hz, 1H), 2.06 - 1.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 158.9, 154.9 (d, J_{CF} = 251.8, Hz), 141.5 (d, J_{CF} = 2.3 Hz), 138.0 (d, J_{CF} = 29.2 Hz), 134.3, 133.5, 131.8, 129.2, 128.9 (d, J_{CF} = 3.6 Hz), 128.4 (d, J_{CF} = 12.8 Hz), 127.5, 120.4 (d, J_{CF} = 2.5 Hz), 101.6 (d, J = 5.3 Hz), 70.6, 60.1, 56.8, 55.8, 54.4, 54.0, 51.8, 46.5, 36.5, 24.7, 21.8 (d, J = 3.1 Hz); IR (neat) cm^{-1}: 3402 (br), 3065, 2948, 2830, 1716, 1620, 1509, 1468, 1362, 1323, 1231, 1142; HRMS (ESI) calcd for $C_{24}H_{29}FN_3O_3S_2$ [M + H]$^+$ 490.1629, found 490.1527; $[\alpha]_D^{23}$= + 11.7 (*c* 1.0, $CHCl_3$).

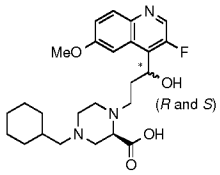
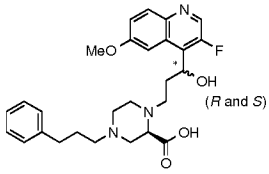


(*R*)-1-(3-(3-fluoro-6-methoxyquinolin-4-yl)prop-2-yn-1-yl)-4-(2-(thiophen-2-ylthio)ethyl)piperazine-2-carboxylic acid (81). ***General solid-phase synthesis protocols*** were followed to give the title compound. Crude purity according to UPLC-MS: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.96 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 2.7 Hz, 1H), 7.36 (dd, J = 5.4, 0.9 Hz, 1H), 7.32 (dd, J = 9.2, 2.8 Hz, 1H), 7.16 (dd, J = 3.5, 0.9 Hz, 1H), 6.97 (dd, J = 5.3, 3.6 Hz, 1H), 4.05 - 3.94 (m, 1H), 3.99 (s, 3H), 3.88 - 3.81 (m, 1H), 3.72 (t, J = 3.2 Hz, 1H), 3.16 - 2.90 (m, 6H), 2.84 - 2.70 (m, 3H), 2.65 - 2.55 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 159.7, 157.4 (d, J_{CF} = 260.5 Hz), 141.2 (d, J = 2.7 Hz), 137.7 (d, J_{CF} = 27.0 Hz), 134.8, 132.8, 131.3, 130.2, 130.1, 127.9, 122.0 (d, J_{CF} = 2.6 Hz), 113.0 (d, J_{CF} = 12.8 Hz), 103.6 (d, J_{CF} = 5.3 Hz), 99.1, 75.5, 60.3, 56.2, 56.1, 54.7, 51.8, 47.5, 45.7, 34.8; IR (neat) cm^{-1}; 3072, 2997, 2930, 2831, 2359, 1720, 1672, 1619, 1504, 1226; HRMS (ESI) calcd for $C_{24}H_{29}FN_3O_3S_2$ [M + H]$^+$ 486.1316, found 486.1309; $[\alpha]_D^{23}$= – 3.4 (*c* 0.5, $CHCl_3$).

Table 1. Biological evaluation of piperazine-based antibiotic agents

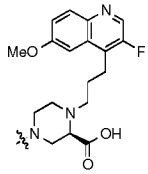
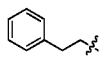
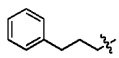
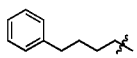
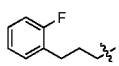
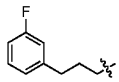
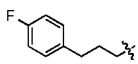
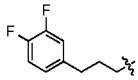
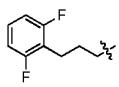
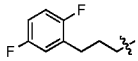
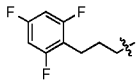
Entry	Compound	Structure	MSSA[a] MIC (μg/mL)	MRSA[b] MIC (μg/mL)	hERG affinity[c] (% inhibition)
1	**53a**		0.4	0.2	ND
2	**53b**		3.1	1.6	ND (25.9)

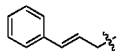
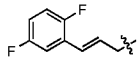
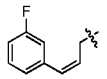
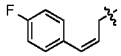
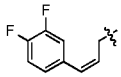
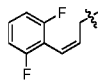
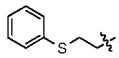
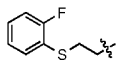
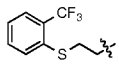
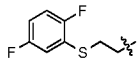
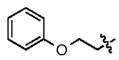
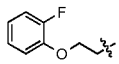
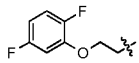
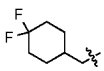
3	**80**		3.1	0.8	100
4	**54**		0.7	0.4	ND
5	**81**		25	12.5	80
6	**73**		12.5	3.1	85
7	**74**		1.5	0.8	92
8	**79a**[d]		12.5	6.2	ND
9	**79b**[d]		12.5	0.8	78
10	**72a**[d]		1.6	0.8	79
11	**72b**[d]		1.6	0.4	65

12	**70**[e]		1.6	0.4	82
13	**68**[e]		3.1	0.8	66

[a] Methicillin-susceptible *S. aureus* RV37. [b] Methicillin-resistant *S. aureus* CC398. [c] Determined as % inhibition of the hERG channel at 30 μM; number in parentheses indicates the established EC_{50} for the hERG channel when available; ND = Not determined. [d] Single diastereomer; stereochemical configuration of the hydroxyl group not determined. [e] Diastereomeric mixture.

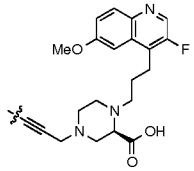
Table 2. Biological evaluation of piperazine-based antibiotic agents

Entry	Compound		MSSA[a] MIC (μg/mL)	MRSA[b] MIC (μg/mL)	hERG affinity[c] (% inhibition)
1	**58a**		6.2	3.1	ND (86.8)
2	**58b**		0.8	0.4	>50[d]
3	**58c**		6.2	3.1	ND
4	**58d**		0.4	0.2	>50[d]
5	**64a**		0.2	0.4	76
6	**64b**		3.1	6.2	98
7	**64c**		1.6	6.2	82
8	**64d**		6.2	0.8	100
9	**59**		0.4	0.4	>50[d]
10	**64e**		6.2	6.2	ND

11	**58e**		0.8	0.2	<50[e] (37.5)
12	**58f**		0.2	0.1	>50[d] (25.1)
13	**63a**		50	12.5	56
14	**63b**		25	50	97
15	**63c**		6.2	12.5	77
16	**63d**		3.1	12.5	100
17	**58g**		0.4	0.2[f]	ND
18	**58h**		0.8	0.4	ND
19	**58i**		12.5	6.3	ND (31)
20	**58j**		0.4	0.2	ND (27.4)
21	**58k**		1.6	0.4	ND (59.1)
22	**58l**		1.6	6.2	>50[d]
23	**58m**		1.6	0.8	ND (86.6)
24	**58n**		0.8	1.6	73
25	**58o**		0.4	0.1	>50[d]
26	**58p**		6.2	25	ND
27	**58q**		3.1	6.2	66
28	**58r**		0.8	0.2	<50[e] (47.4)
29	**58s**		6.2	25	69

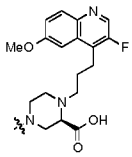
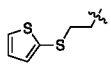
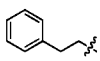
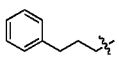
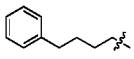
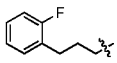
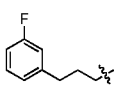
[a] Methicillin-susceptible *S. aureus* RV37. [b] Methicillin-resistant *S. aureus* CC398. [c] Determined as % inhibition of the hERG channel at 30 μM; number in parentheses indicates the established EC_{50} for the hERG channel when available; ND = Not determined. [d] EC_{50} for the hERG channel found to be >30 μM corresponding to <50% inhibition at 30 μM. [e] EC_{50} for the hERG channel found to be <30 μM corresponding to >50% inhibition at 30 μM. [f] Determined against MRSA M2.

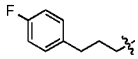
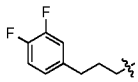
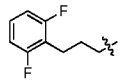
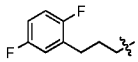
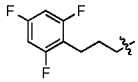
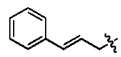
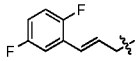
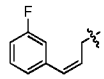
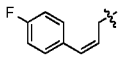
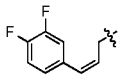
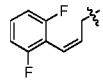
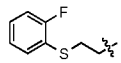
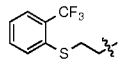
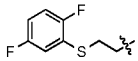
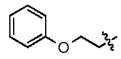
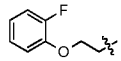
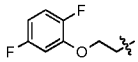
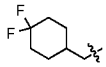
Table 3. Biological evaluation of piperazine-based antibiotic agents

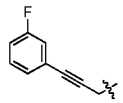
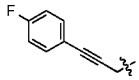
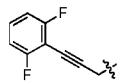
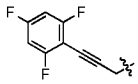
Entry	Compound		MSSA[a] MIC (μg/mL)	MRSA[b] MIC (μg/mL)	hERG affinity[c] (% inhibition)
1	**62a**		12.5	1.6	46
2	**62b**		6.2	25	88
3	**62c**		>50	25	48
4	**62d**		25	3.1	23
5	**62e**		1.6	25	14

[a] Methicillin-susceptible *S. aureus* RV37. [b] Methicillin-resistant *S. aureus* CC398. [c] Determined as % inhibition of the hERG channel at 30 μM.

Table 4. Biological evaluation of piperazine-based antibiotic agents in enzymatic assays against *S. aureus* gyrase and *S. aureus* topoisomerase IV.

Entry	Compound		*S. aureus* gyrase[a] IC_{50} (μM)	*S. aureus* topoisomerase IV[b] IC_{50} (μM)
1	**NXL 101**	-	0.34	8.80
2	**Ciprofloxacin**	-	3.84	9.16
3	**53a**		0.37	7.64
4	**58a**		0.46	10.16
5	**58b**		0.19	3.36
6	**58c**		0.54	12.55
7	**58d**		0.03	8.79
8	**64a**		0.58	0.79

9	**64b**		0.66	12.72
10	**64c**		0.32	2.24
11	**64d**		0.15	1.78
12	**59**		0.02	1.04
13	**64e**		0.46	4.37
14	**58e**		0.37	3.82
15	**58f**		0.28	2.41
16	**63a**		2.40	2.82
17	**63b**		4.15	19.61
18	**63c**		1.08	6.94
19	**63d**		0.90	6.52
20	**58h**		0.23	2.55
21	**58i**		0.13	2.67
22	**58j**		0.70	4.33
23	**58k**		1.41	22.45
24	**58l**		0.90	1.00
25	**58m**		1.59	4.74
26	**58n**		0.24	0.26
27	**58o**		0.47	6.15
28	**58p**		1.73	7.66
29	**58q**		0.83	3.35
30	**58r**		0.13	2.67
31	**58s**		1.07	12.81

32	**62a**		0.35	0.87
33	**62b**		2.03	16.87
34	**62d**		0.33	2.35
35	**62e**		0.82	2.06

[a] IC_{50} for binding to *S. aureus* gyrase. [b] IC_{50} for binding to *S. aureus* topoisomerase IV.

Table 5. Biological evaluation of piperazine-based antibiotic agents in enzymatic assays against *S. aureus* gyrase and *S. aureus* topoisomerase IV.

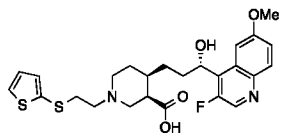
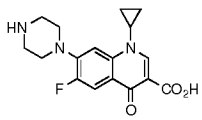
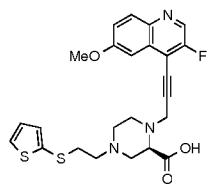
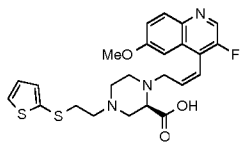
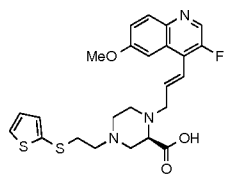
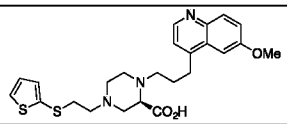
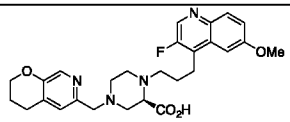
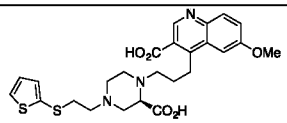
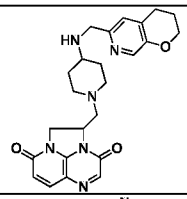
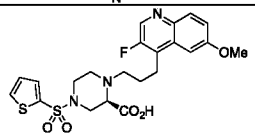
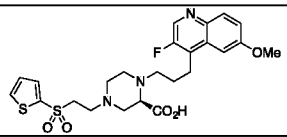
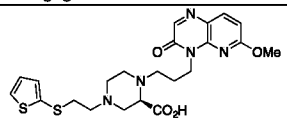
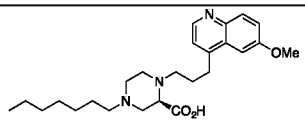
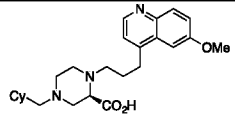
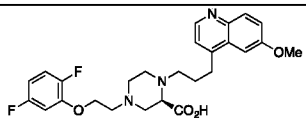
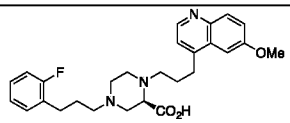
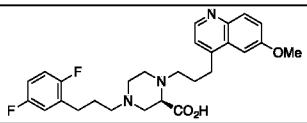
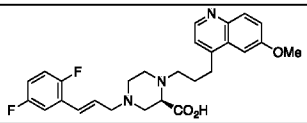
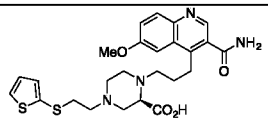
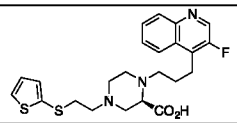
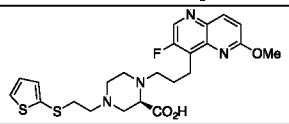
Entry	Compound	Structure	*S. aureus* gyrase[a] IC_{50} (μM)	*S. aureus* topoisomerase IV[b] IC_{50} (μM)
1	**NXL 101**		0.34	8.80
2	**Ciprofloxacin**		3.84	9.16
3	**81**		0.48	2.47
4	**73**		0.28	9.92
5	**74**		0.68	1.81

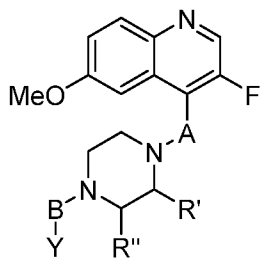
Table 6. Comparative data – compounds are prepared in accordance with the methods specified herein

Compound No.	Structure	MIC (ug/mL)		hERG (ug/mL)	
		MSSA	MRSA	Max effect (%)	Comment
CH-NXL-1-39 MW: 471.63		3.2 (6.8 uM)	3.2 (6.8 uM)	98	80% hERG interaction at 4.7 (10uM)
CH-NXL-1-45 MW: 494.57		6.25 (13 uM)	3.2 (6.5 uM)	34.1	non-significant hERG interaction at 4.9 (10uM)
CH-NXL-1-54 MW: 515.64		>50 (>97 uM)	>50 (>97 uM)	31.7	non-significant hERG interaction at 5.2 (10uM)
CH-NXL-1-62 (GSK) MW: 448,53		0.4 (0.9 uM)	0.8 (1.8 uM)	30.5	non-significant hERG interaction at 4.5 (10uM)
CH-NXL-2-29 MW: 493.57		>50 (>101 uM)	>50 (>101 uM)	56.3	<25% hERG interaction at 4.9 (10uM)
CH-NXL-2-31 MW: 521.62		>50 (>96 uM)	>50 (>96 uM)	66.8	40% hERG interaction at 5.2 (10uM)
CH-NXL-3-9 MW: 489.61		25 (51 uM)	12.5 (26 uM)	53.1	<25% hERG interaction at 4.9 (10uM)
CH-NXL-3-10 MW: 427.59		1.6 (3.7 uM)	1.6 (3.7 uM)	51.5	<25% hERG interaction at 4.3 (10uM)
CH-NXL-3-16 MW: 425.57		3.2 (7.5 uM)	1.6 (3.8 uM)	32.5	non-significant hERG interaction at 4.3 (10uM)
CH-NXL-3-17 MW: 485.53		12.5 (26 uM)	12.5 (26 uM)	47.9	<25% hERG interaction at 4.9 (10uM)
CH-NXL-3-18 MW: 465.57		6.25 (13 uM)	3.1 (6.7 uM)	55.3	30% hERG interaction at 4.7 (10uM)

CH-NXL-3-19 MW: 483.56		6.25 (13 uM)	3.1 (6.5 uM)	74.2	40% hERG interaction at 4.8 (10uM)
CH-NXL-3-21 MW: 481.54		1.6 (3.3 uM)	3.1 (6.6 uM)	66.3	40% hERG interaction at 4.8 (10uM)
CH-NXL-3-81 MW: 514.66		>50 (>97 uM)	>50 (>97 uM)	80.4	50% hERG interaction at 5.1 (10uM)
CH-NXL-4-33 MW: 459.60		3.1 (6.7 uM)	1.6 (3.4 uM)	45.5	<25% hERG interaction at 4.6 (10uM)
CH-NXL-4-46 MW: 490.61		1.6 (3.3 uM)	0.4 (0.8 uM)	50.3	<25% hERG interaction at 4.9 (10uM)

Claims

1. A piperazine derivative having the formula (I)

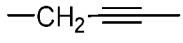


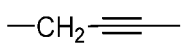
Formula (I)

wherein

R' is selected from –H, -COOH and $–CONH_2$;

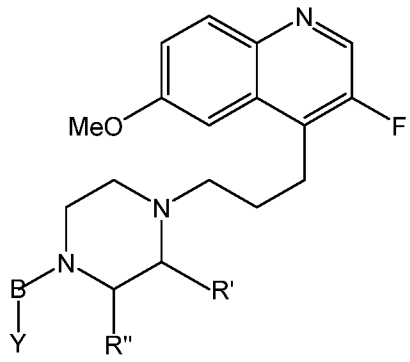
R'' is selected from –H, -COOH and $–CONH_2$ with the proviso that when R' is –COOH or $–CONH_2$ then R'' is not –COOH or $–CONH_2$, and when R'' is –COOH or $–CONH_2$ then R' is not –COOH or $–CONH_2$;

A is selected from $–(CH_2)_3$-, $-(CH_2)_2CH(OH)$-, $-CH_2-CH=CH-$ (cis and trans),  ;

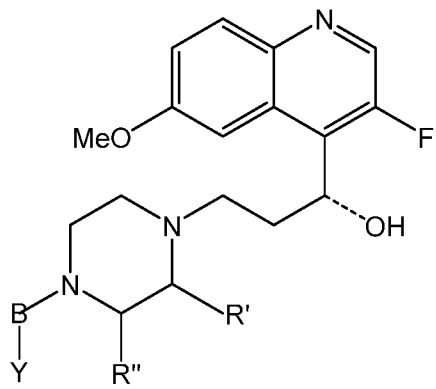
B is selected from $–(CH_2)_n$-, $–(CH_2)_nO$-, $–(CH_2)_nS$- and $–(CH_2)_n-CH=CH-$ (cis and trans),  and wherein n = 1-4; and

Y is selected from C_1-C_7 alkyl (straight or branched), C_5-C_6 cycloalkyl optionally substituted with one or more halogens, thiophene or phenyl optionally substituted with one or more halogens or $–C(hal)_3$ wherein "hal" denotes a halogen,
or a pharmaceutically acceptable salt thereof.

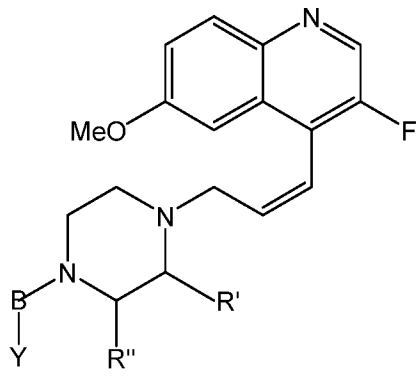
2. A piperazine derivative according to claim 1 having one of the following formulas



Formula (II)

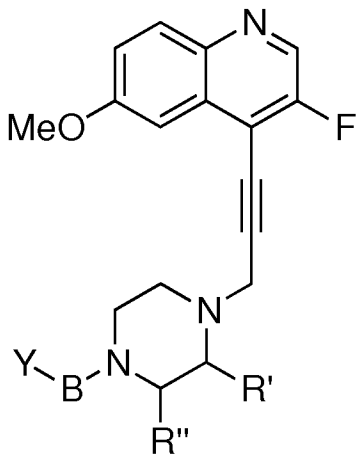


Formula (III)



Formula (IV)

wherein both cis and trans form are included, or

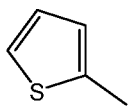


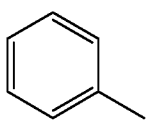
Formula (V),

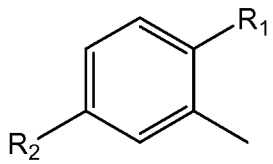
wherein R', R'', B and Y are as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein Y-B- is selected from
Y-S-CH_2-CH_2-,
Y-CH_2-,
Y-CH_2-CH_2-,
Y-CH_2-CH_2-CH_2-,
Y-CH=CH-CH_2-, and
Y-O-CH_2-CH_2-
wherein Y is as defined in claim 1,
or a pharmaceutically acceptable salt thereof.

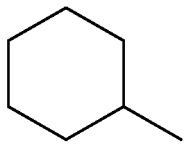
4. A compound according to any of the preceding claims, wherein Y- is selected from





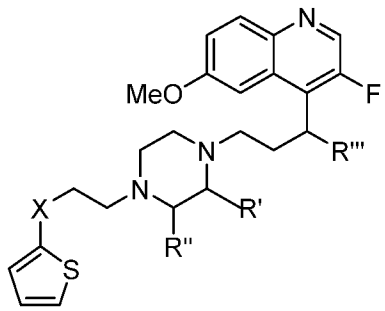


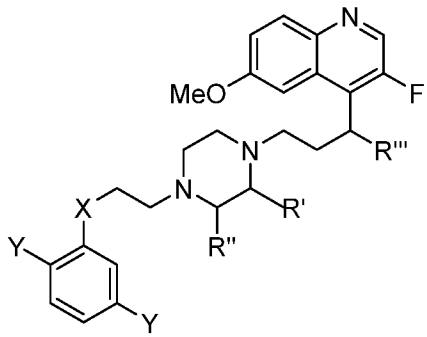
wherein R_1 and/or R_2 is H or halogen selected from F, Br and I


optionally substituted with one or two halogens selected from F, Br and I

or Y-B- is a straight or branched alkyl group having from 4 to 9 carbon atoms,
or a pharmaceutically acceptable salt thereof.

5. A compound according to any of the preceding claims having one of the following structures:





wherein R', R'' are as defined above, R''' is H or OH, X is C, O or S, and Y is H or halogen selected from F, Br, I, preferably F, or a pharmaceutically acceptable salt thereof.

6. A compound according to any of the preceding claims selected from the compounds described in any of Tables 1-5,

or a pharmaceutically acceptable salt thereof.

7. A compound according to any of the preceding claims, wherein R' is –COOH and R'' is H.

8. A compound according to any of the preceding claims for use in medicine.

9. A compound according to any of the preceding claims for use in the treatment of an infectious disease.

10. A compound for use according to claim 6, wherein the infectious disease is caused by a bacterium.

11. A method for preparing a compound defined in any of claims 1-5 essentially as described herein.

Fig. 1

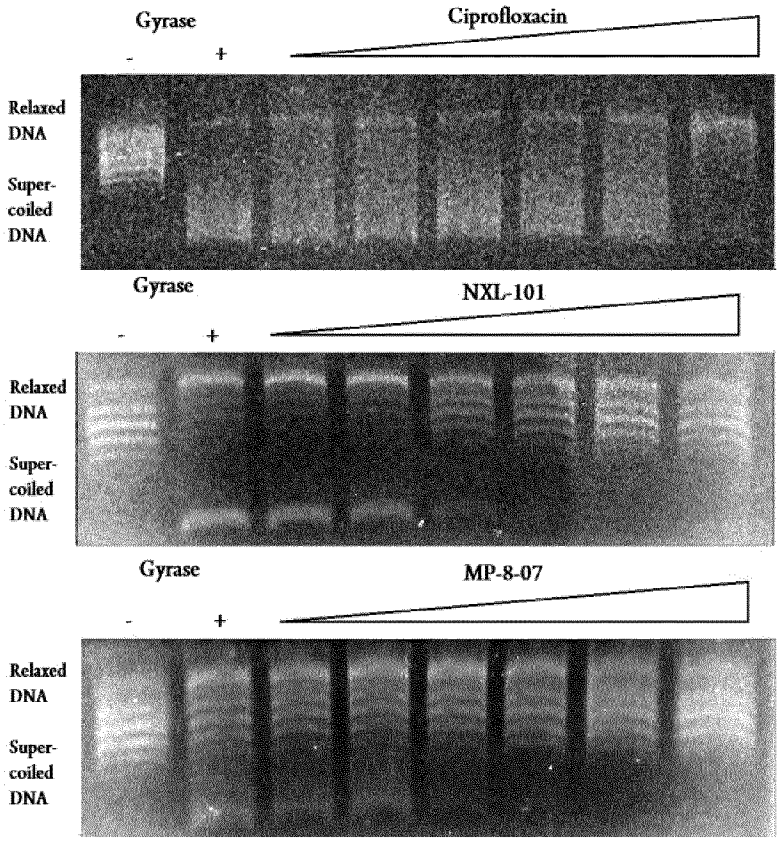
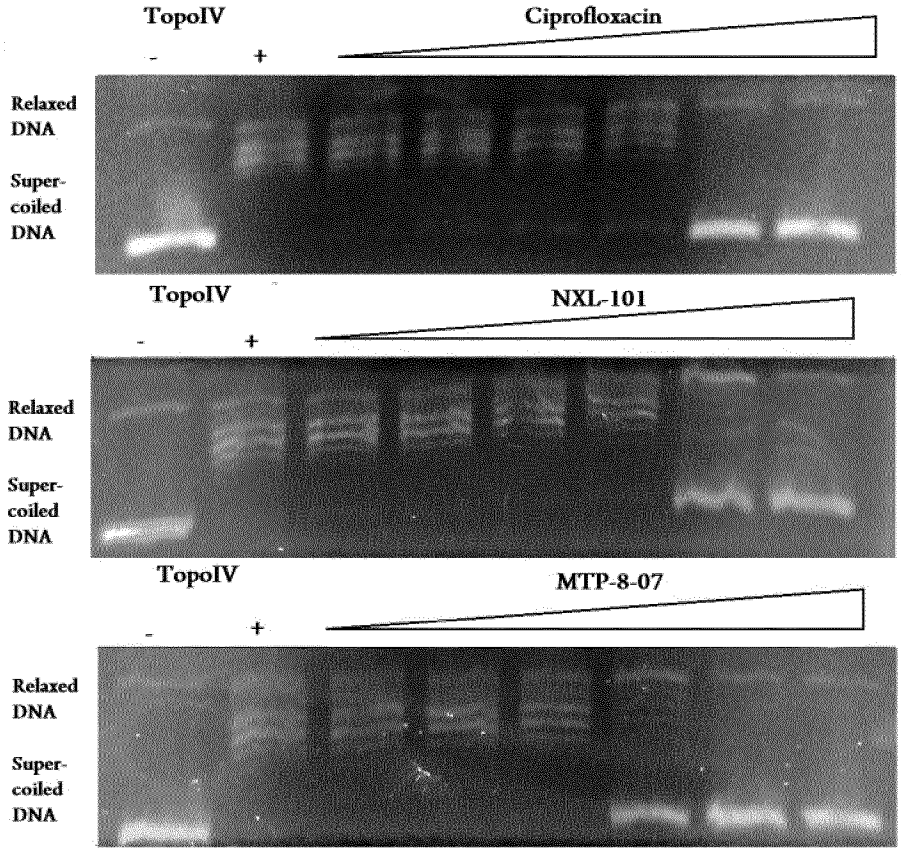

Gyrase
Ciprofloxacin
-
+
Relaxed DNA
Super-coiled DNA
Gyrase
NXL-101
-
+
Relaxed DNA
Super-coiled DNA
Gyrase
MP-8-07
-
+
Relaxed DNA
Super-coiled DNA

Fig. 2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Ciprofloxacin
-
+
Relaxed DNA
Super-coiled DNA
TopoIV
NXL-101
-
+
Relaxed DNA
Super-coiled DNA
TopoIV
MTP-8-07
-
+
Relaxed DNA
Super-coiled DNA

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/000357

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4709 A61P31/04 C07D409/14 C07D403/06
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/78748 A1 (SMITHKLINE BEECHAM PLC [GB]; DAVIES DAVID THOMAS [GB]; MARKWELL ROGER) 28 December 2000 (2000-12-28) see compounds of claim 1 as antibacterial agents and especially example 16 on p. 29 -----	1-11
Y	WO 00/43383 A1 (SMITHKLINE BEECHAM PLC [GB]; DAVIES DAVID THOMAS [GB]; HENRY CAROLINE) 27 July 2000 (2000-07-27) see compounds of claim 1 wherein Z5 is CR1a, R1a being halogen as antibacterials, -----	1-11
Y	EP 1 337 529 A2 (AVENTIS PHARMA SA [FR] NOVEXEL [FR]) 27 August 2003 (2003-08-27) see the compounds of claim 1 as bactericides, especially examples 11, 12, 31-37, 39-41, 43-45, 51-54, 56 and 57 -----	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2016	15/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Traegler-Goeldel, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

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