

SUPPLEMENTAL INFORMATION

A new quinoline-based chemical probe inhibits the autophagy-related cysteine protease ATG4B.

AUTHORS/AFFILIATIONS

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PROTEIN PREPARATION, POCKET IDENTIFICATION AND IN SILICO SCREENING:

The crystal structures of ATG4B were obtained from the RCSB Protein Data Bank (PDB, <http://www.rcsb.org/pdb/>). ICM package (version 3.6) was used for protein preparation, pocket identification and molecular docking-based screening of small molecule databases. The structure data (sdf files) of small molecules were downloaded from ZINC (<http://zinc.docking.org>).

The protein preparation tools implemented in ICM ¹ were used to prepare the proteins for docking. Water molecules, ligands and ions were removed. Counter mutations were modeled for PDBs with mutated amino acids (catalytic residues). Hydrogens were added and global optimization was performed to find the best hydrogen bonding network. In addition, the orientations of His, Pro, Asn, Gln, Cys were optimized. The protonation states of His were also optimized.

The PocketFinder ² was applied to those crystal structures for identifying small molecule-binding pockets. This method uses only the protein structure for the prediction of cavities and clefts. The position and size of the ligand-binding pocket are determined based on a transformation of the Lennard-Jones potential by convolution with a Gaussian kernel of a certain size, a grid map of a binding potential and construction of equipotential surfaces along the maps.

A set of grid maps was pre-calculated for each pocket. The maps represent hydrogen bonding potential, van der Waals potential, hydrophobic potential and electrostatic potential. The maps were generated in a rectangular box with 0.5 Å grid spacing centered at the predicted small molecule binding site.

The docking used ICM's flexible-ligand and rigid-receptor protocol. ICM ligand docking is based on biased probability Monte Carlo optimization of the ligand coordinates in the grid maps of the receptor ³. Each small molecule is first converted to 3D and optimized using MMFF-94 force field. Then the molecule is submitted to a conformational analysis outside of

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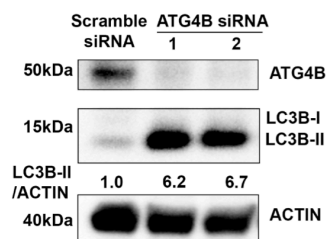
the protein pocket and a stack of low energy conformations is collected and used as starting geometries for the docking. In the docking, the ligand is placed in the binding pocket and Monte Carlo simulations and global energy optimization were conducted. The energy function includes the ligand internal strain and a weighted sum of the value from the grid maps. The top 4 best scoring poses for each ligand were kept for subsequent scoring. The ICM scoring function evaluates the full-atom complex of the selected pose and the receptor. It was derived from a benchmark dataset of experimentally determined ligand-receptor complexes. The binding score (ICM score) was calculated as a sum of weighted terms of van der Waals, electrostatic, hydrogen bonding, non-polar and polar atom solvation energy differences between bound and unbound states, ligand internal strain and its conformational entropy loss upon binding ⁴.

FIGURES

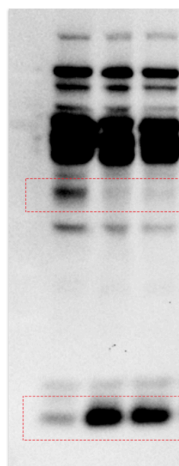
Figure S1. Full-length blots are shown next to corresponding cropped images.

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Figure 2B



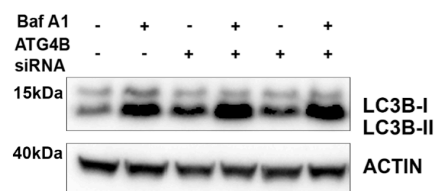
Full blot of ATG4B and LC3B



Full blot for ACTIN



Figure 3 E



Full blot for LC3B



Full blot for ACTIN

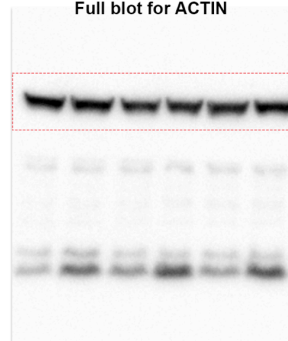
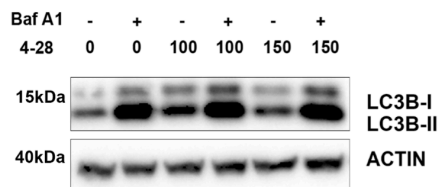


Figure 3 F



Full blot for LC3B and ACTIN

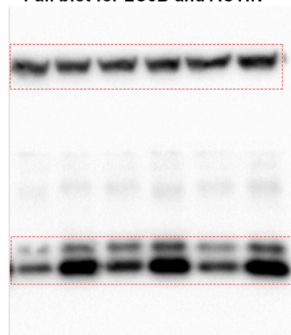
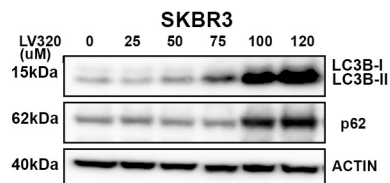
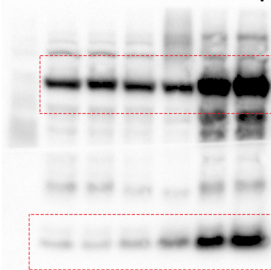


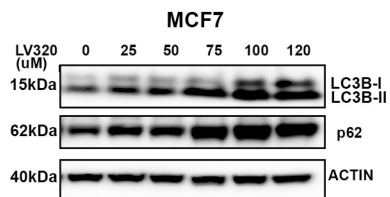
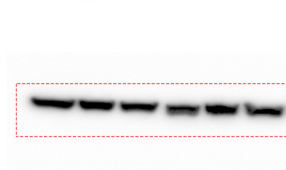
Figure 5a



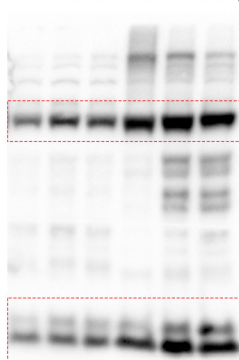
Full blot for LC3B and p62



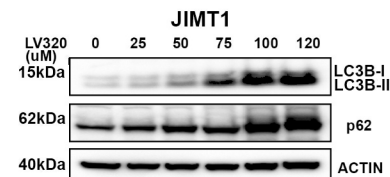
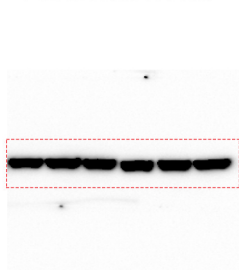
Full blot for ACTIN



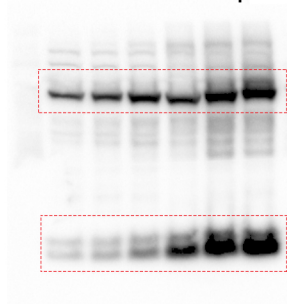
Full blot for LC3B and p62



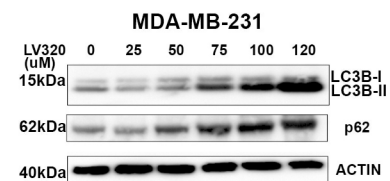
Full blot for ACTIN



Full blot for LC3B and p62



Full blot for ACTIN



Full blot for LC3B and p62



Full blot for ACTIN

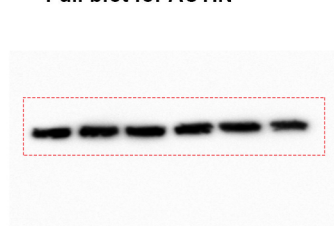
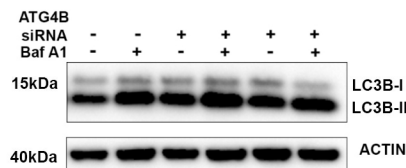
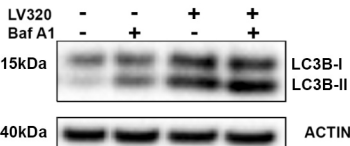
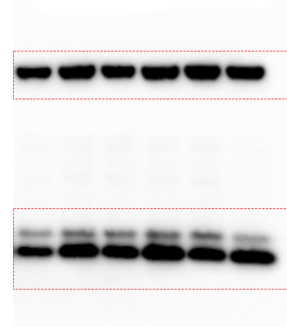


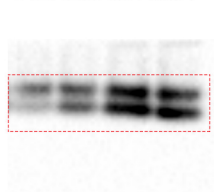
Figure 5b



Full blot for ACTIN and LC3B



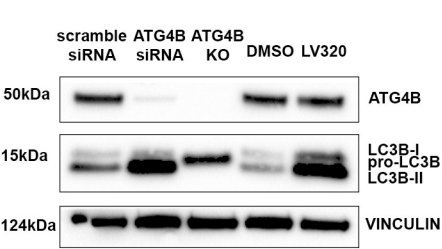
Full blot for LC3B



Full blot for ACTIN



Figure 5c



Full blot for VINCULIN, ATG4B, and LC3B

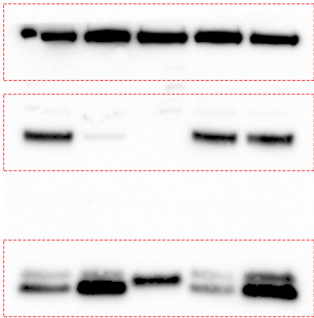
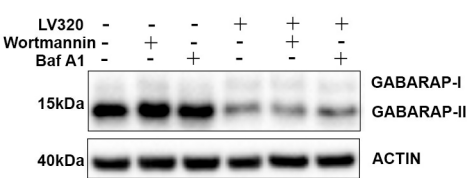
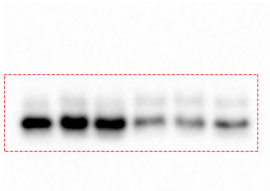


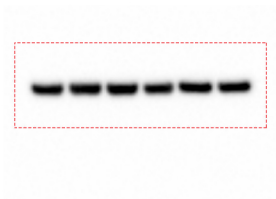
Figure 5d



Full blot for GABARAP

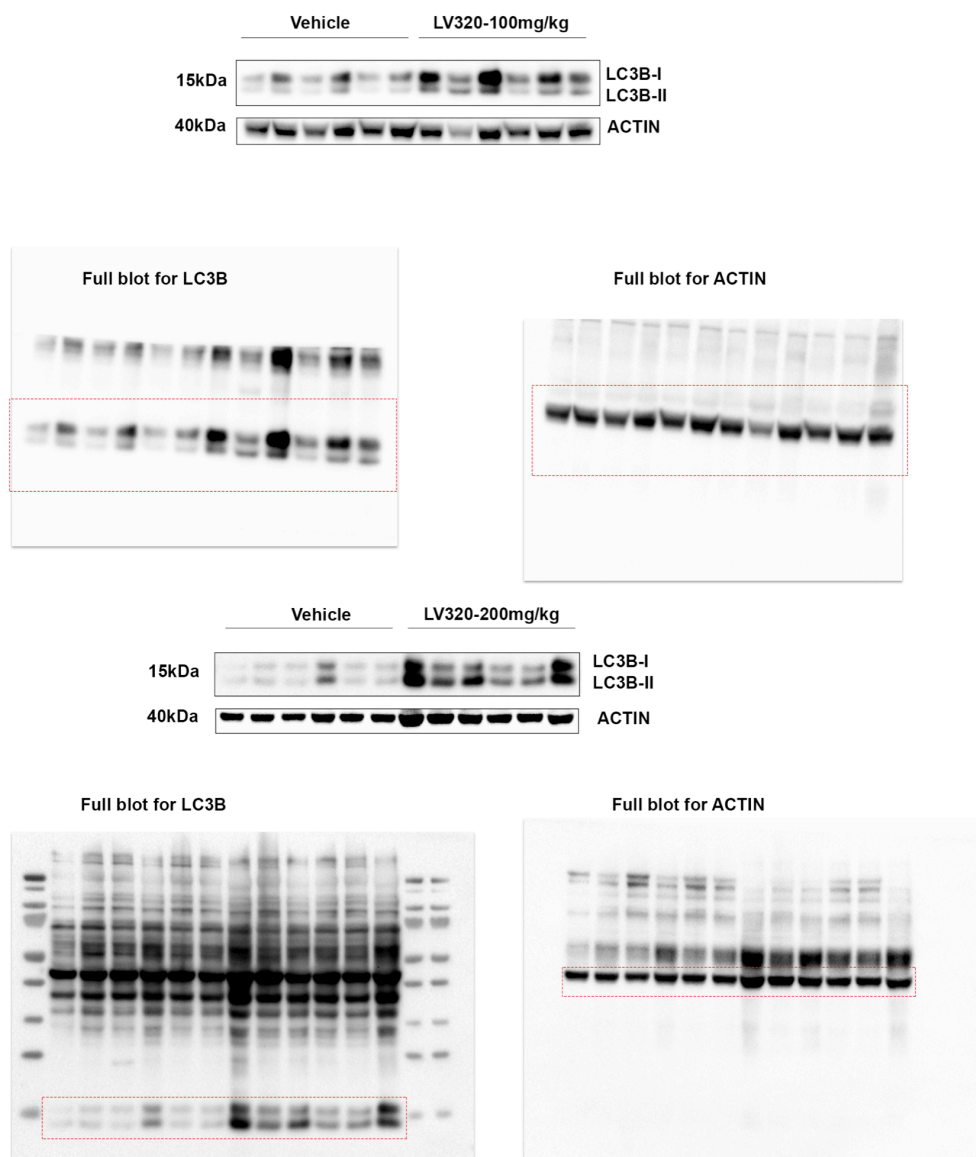


Full blot for ACTIN



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Figure 7D



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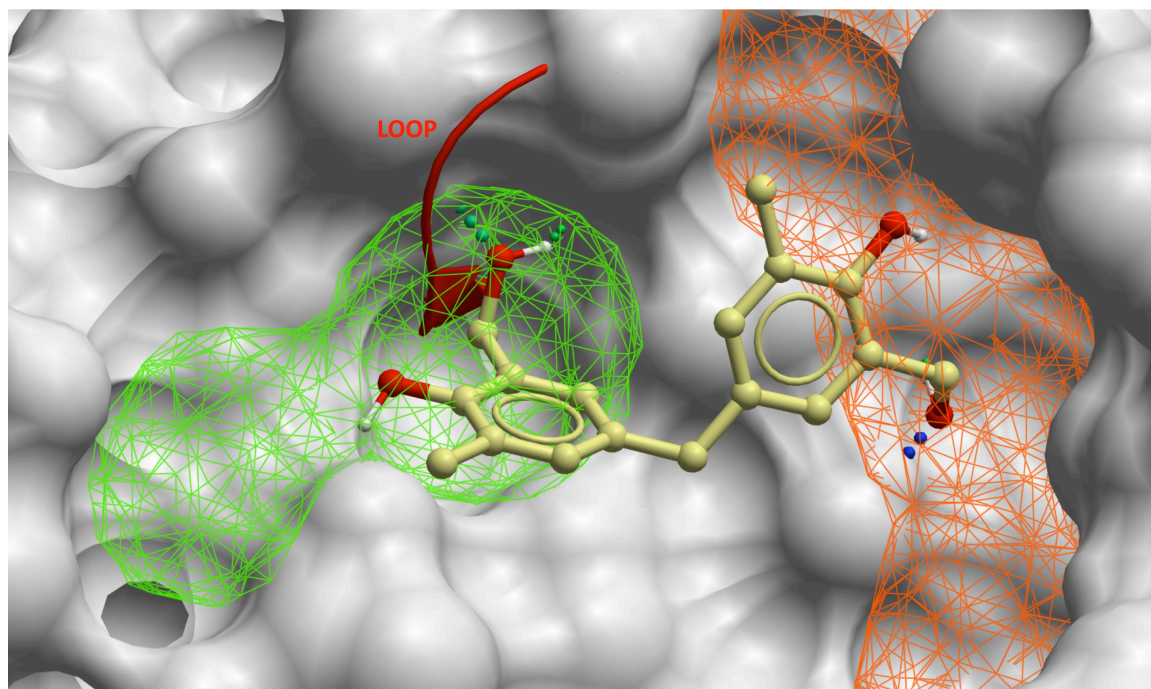


Figure S2. Binding model of compound **1-4** which binds to pocket closed#1. The predicted pocket (green) is on the back of the flexible loop (red ribbon). Another adjacent site indicated in orange. The compound binds to the ATG4B protein across the two pockets. The closed conformation of ATG4B is in grey skin model and the open (active) conformation is in red ribbon model.

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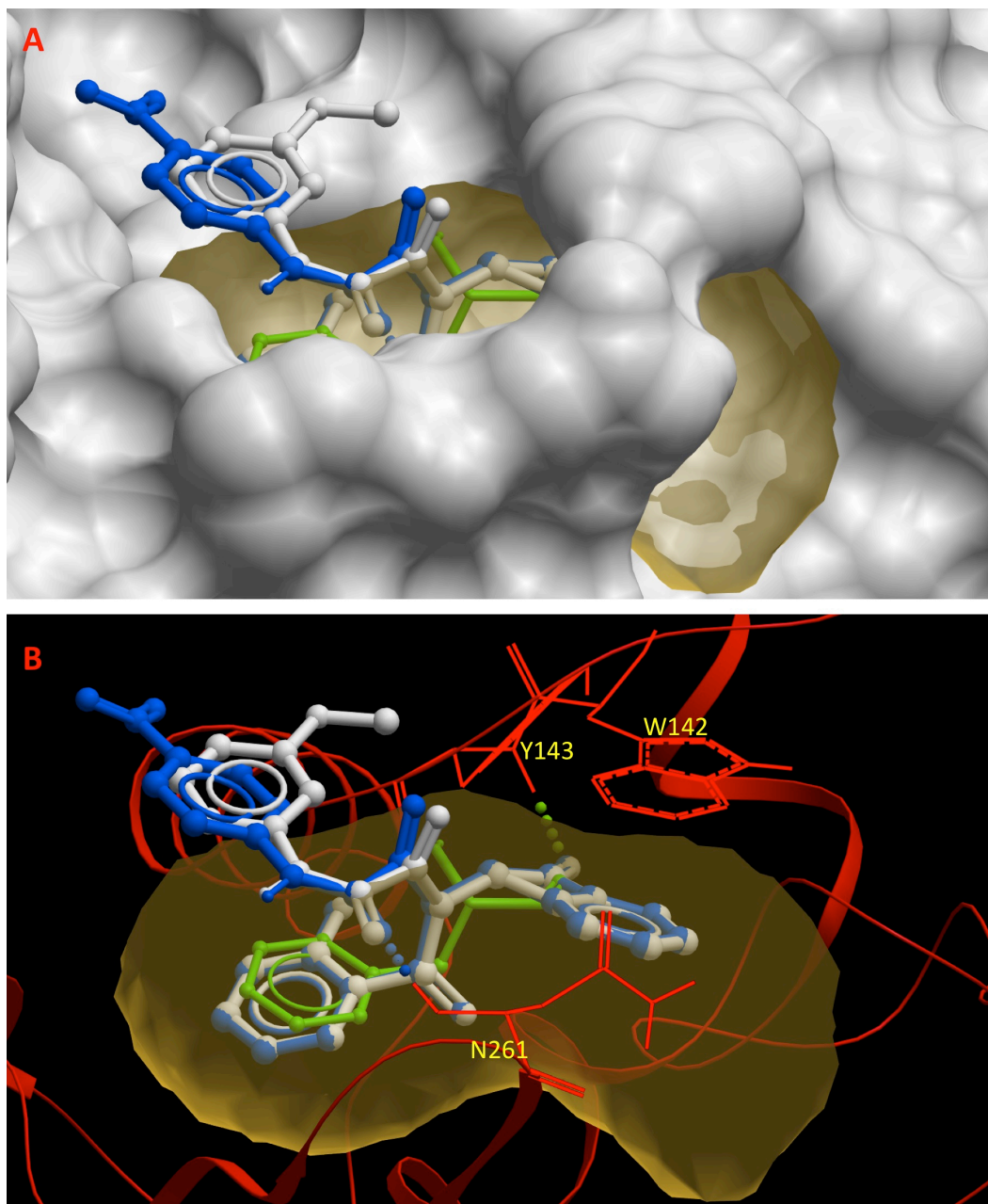


Figure S3. Binding model of compound **2-22** (blue stick model) and **3-22** (white) which are both predicted to bind to pocket open#1. These two compounds are very similar. They bind to the active site (yellow pocket) of the open conformation of ATG4B. A) Skin model shows the compounds bind into the cavity under the “bridge”. B) Ribbon model (red) of ATG4B and the key residues of interaction. Hydrogen bonds are formed with Y143 and N261. Pi-stacking is formed with W142. Part of the compounds mimics the Phe119 (green) of LC3 which is a key residue to lift the active site.

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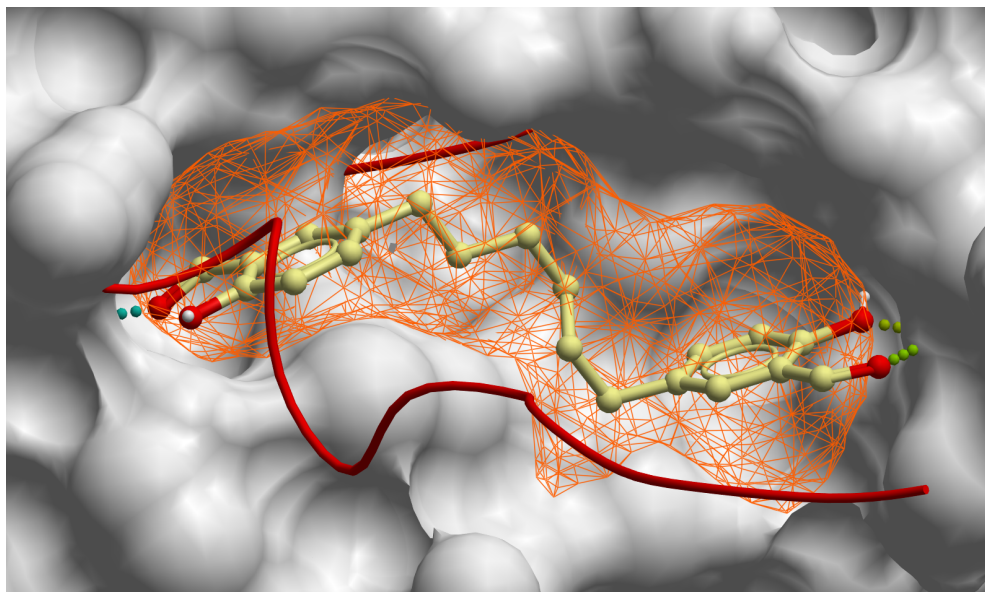
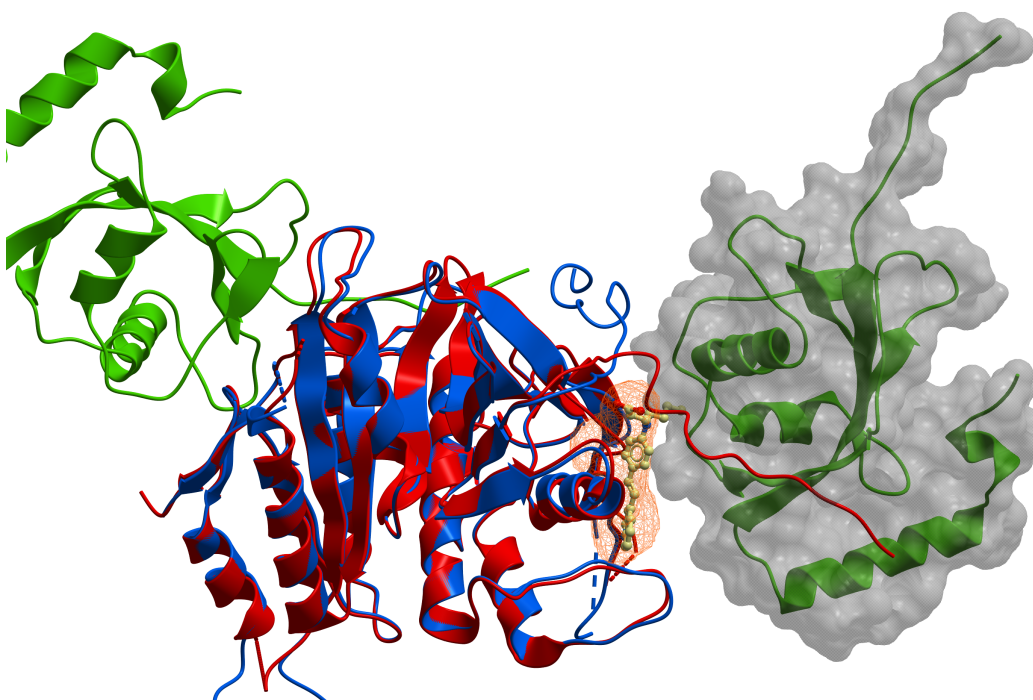


Figure S4. Binding model of compound **4-6** predicted to bind to pocket closed#2. This compound binds to the same pocket as **4-28**. Hydrogen bonds are formed at left side with F19 and the right side with Q100. The compound lies completely within the predicted pocket (orange chicken wire presentation). The ATG4B protein is in gray skin model.



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Figure S5A. ATG4B active conformation is in red color and inactive conformation is in blue. LC3 is in green. The non-substrate LC3 is depicted with a transparent skin. Compound **4-28** is shown in stick model and its pocket closed #2 in thin wire.

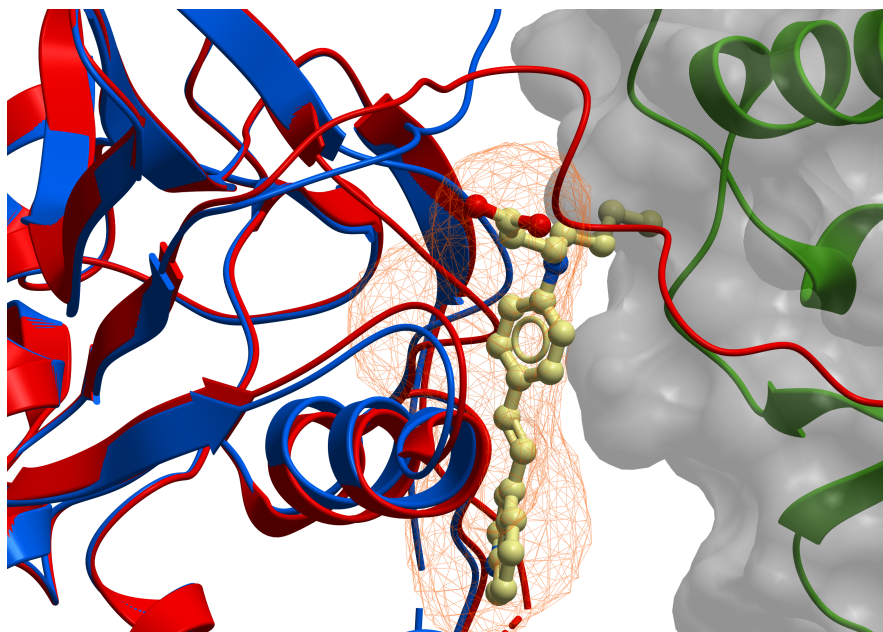


Figure S5B. Zoom in of compound **4-28** and its pocket.

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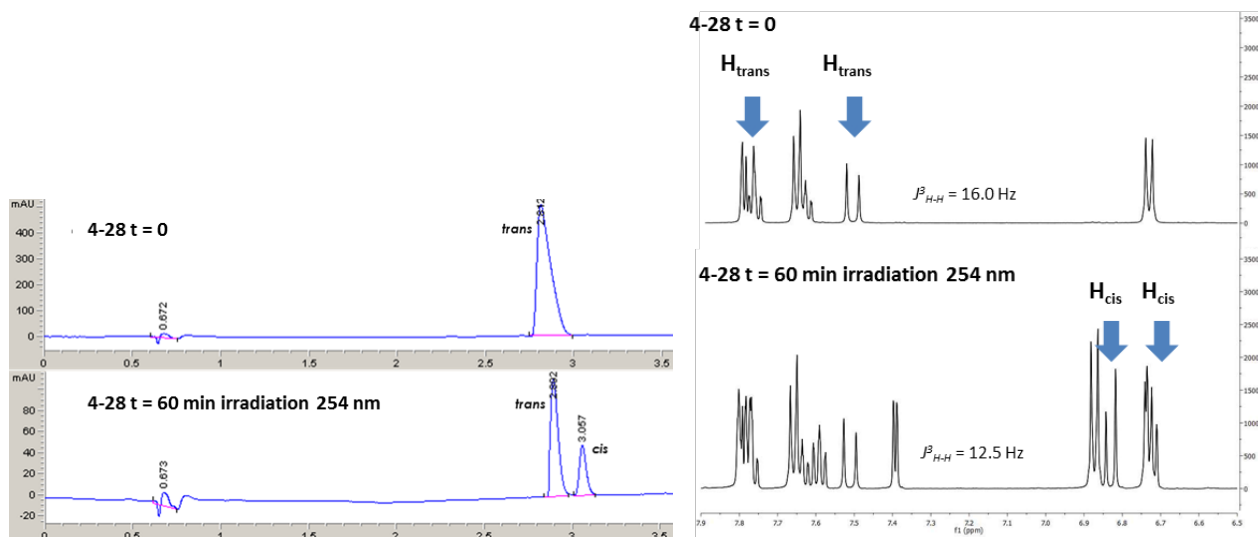


Figure S6. Instability of compound **4-28** under UV irradiation (254 nm) confirmed by HPLC (left) and NMR spectra (right)

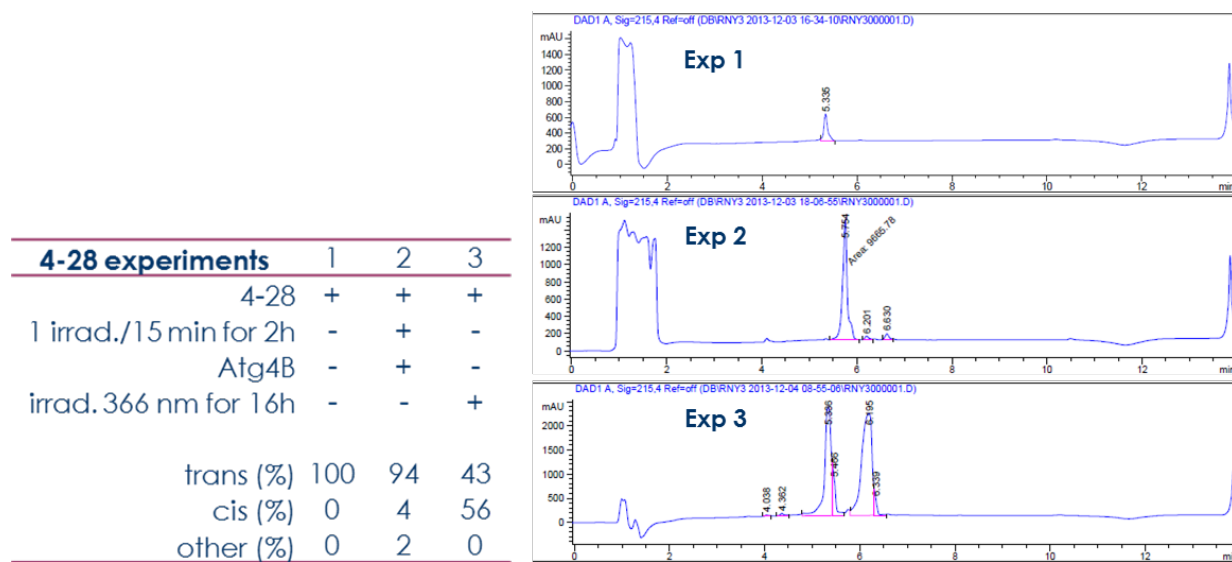


Figure S7. Integrity of compound **4-28** in the fluorimeter as analyzed by HPLC

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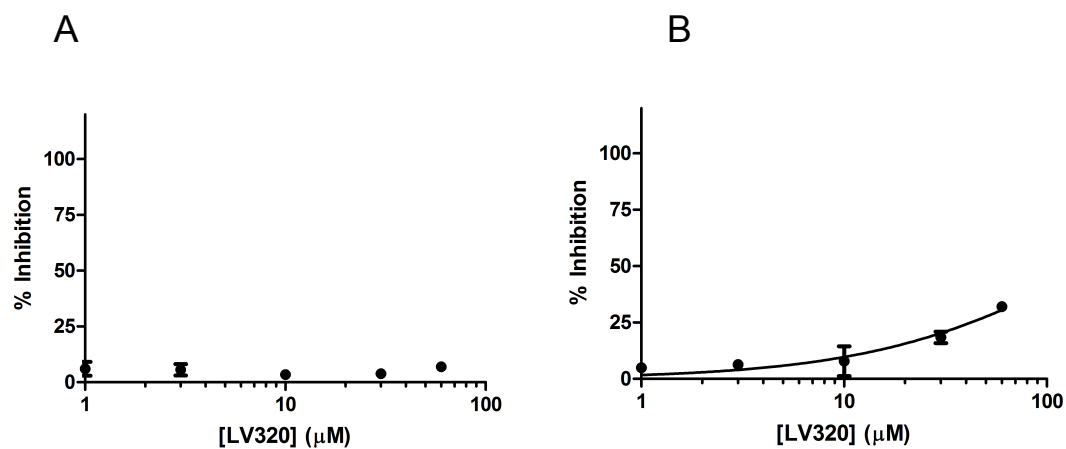


Figure S8: Inhibition curve for **LV-320** with caspase 3 (panel A) and cathepsin B (panel B)

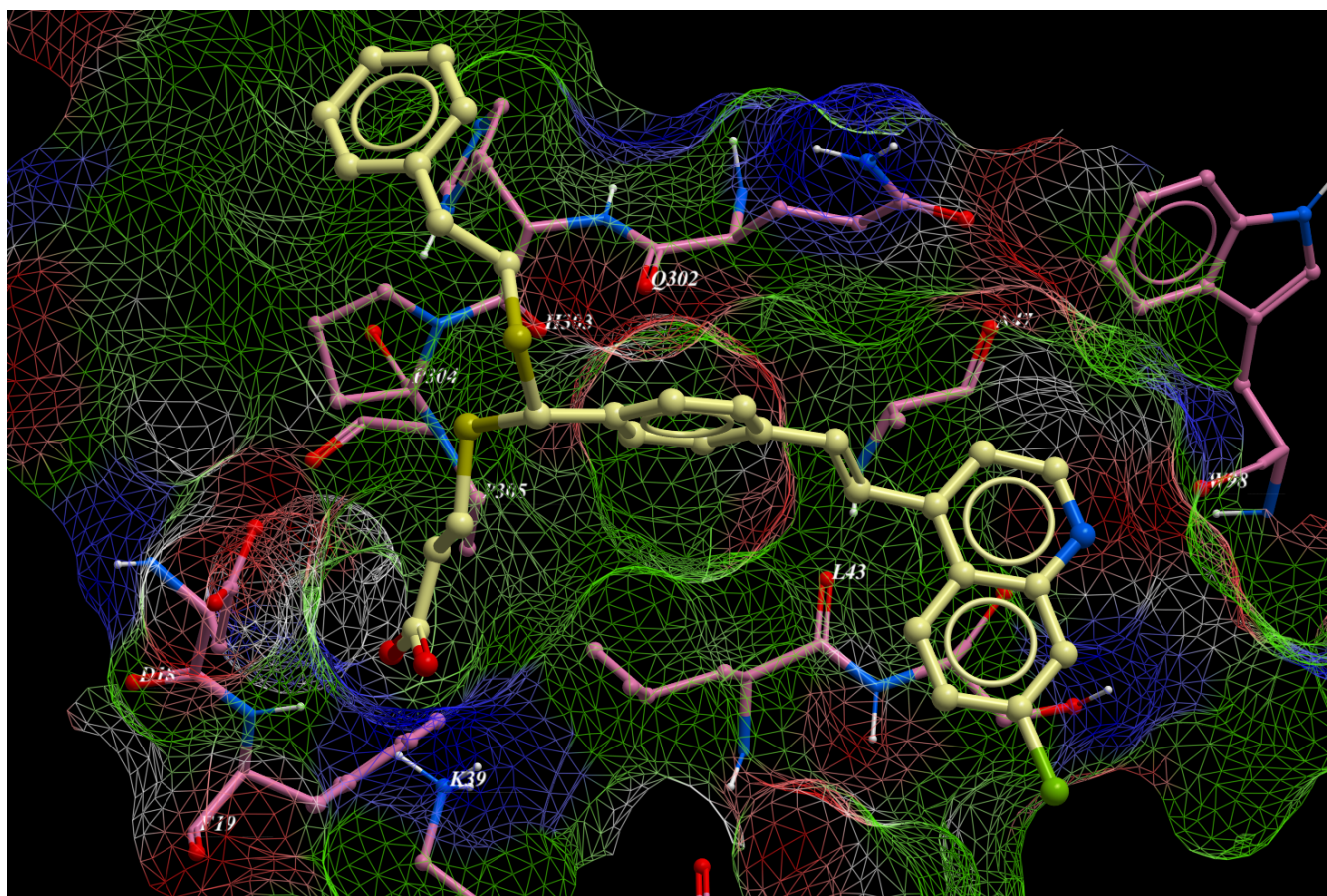


Figure S9. Representation of LV-320 binding to the putative binding site on ATG4B and the key interacting amino-acid residues

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ATG4A	1	MESVL	SKYEDQITIFTDYLEEY	PDTDEL	VWILGKQHLLKTEKSKILLSDIS
ATG4B	5	-----	TLTYD	TLRFAEF-EDF	PETSEPVWILGRKYSIFTEKDEILSDVA
ATG4A	51	ARLWFTYRRKFSP	IGGTGPSSDAGWGCMLRCGQMM	LAQALICRHLGRDWS	
ATG4B	48	SRLWFTYRKNFPA	IGGTGPTSDTGWGCMLRCGQMIFAQALVCRHLGRDWR		
ATG4A	101	WEKQKEQPKEYQR	ILQCFLDRKDCCYSIHQMAQMGVGE	GKSIGEWFGPNT	
ATG4B	98	WTQRKRQPDSYF	SVLNAFIDRKDSYYSIHQIAQMGVGE	GKSIGQWYGNT	
ATG4A	151	VAQVLKKLALFDE	WNSLAVYVSM	DNTVVEDIKKMC	RVLPLSADTAGDRP
ATG4B	148	VAQVLKKLAVFDT	WSSLAVHIAM	DNTVVMEEIR	RLCR-----
ATG4A	201	PDSLTASNQSKGT	SAYCSAWKPLLLI	VPLRLGINQIN	VPYVDAFKECFKM
ATG4B	185	-----	TSVPCSPWRPLV	LLIPLRLGLTD	INEAYVETLKHCFMM
ATG4A	251	PQSLGALGGKPN	NAYYFIGFLGDELIF	LDPHTTQTFVD	TEENGTVNDQTF
ATG4B	250	PQSLGVIGGKPN	SAHYFIGYVGEELI	YLDPHTTQPAVE---	GCFIPDES
ATG4A	301	HCLOSPQRMN	ILNLDPSVALGFFCKEEKDF	DNWCSLVQKEIL	KENLRMFE
ATG4B	300	HCQHPCRM	SIAELDPSIAVGFFCKTEDDF	NDWCQVKKLSL---	LPMFE
ATG4A	351	LVQKHPSHWPPF	VPPAKPEVTTTGA	EFIDSTEQLEEF	DLEEDFEILSV
ATG4B	351	LVEQQPDV	LNLSLDSSD	VERL-----	

Figure S10. Sequence alignment of ATG4A and ATG4B with key amino-acid residues of the binding pocket indicated in green box

SUPPLEMENTAL INFORMATION

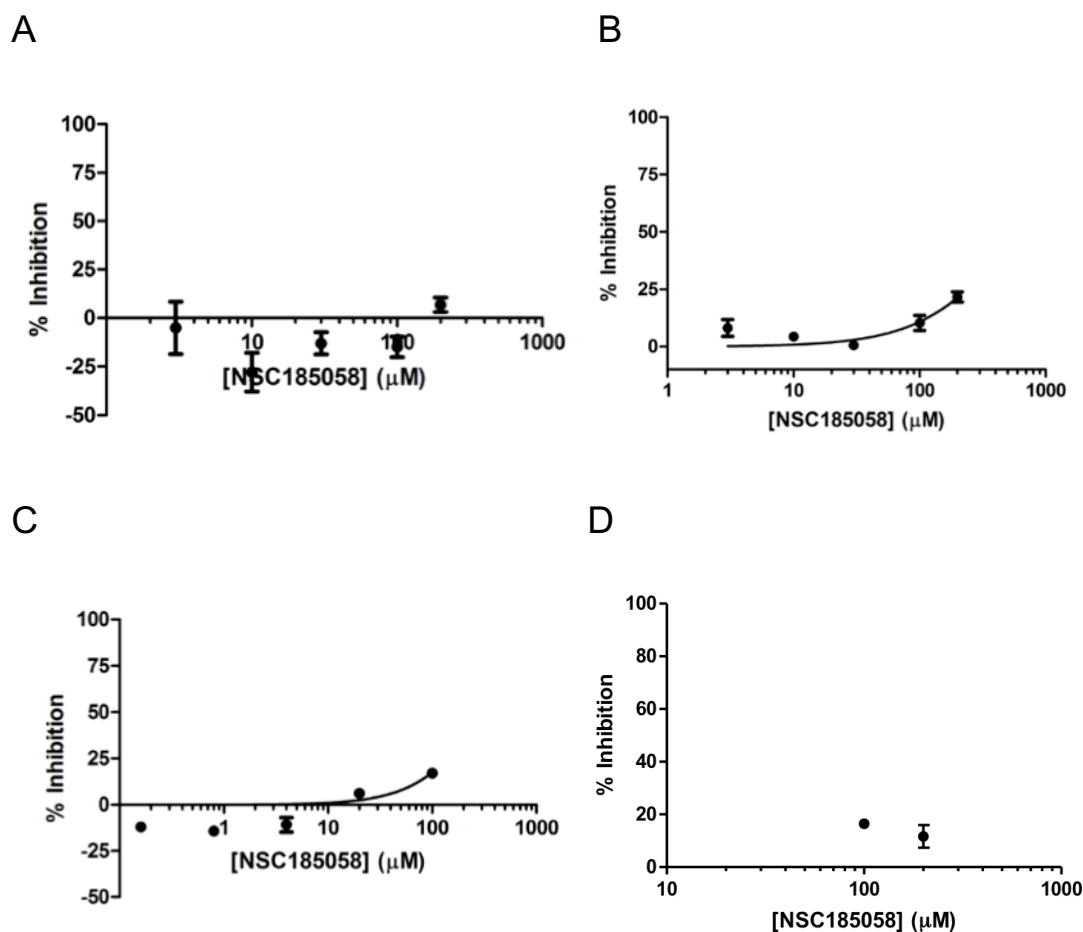


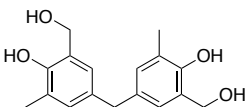
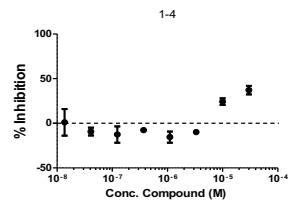
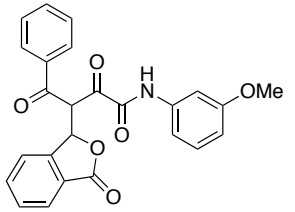
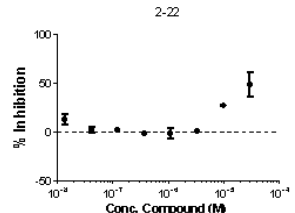
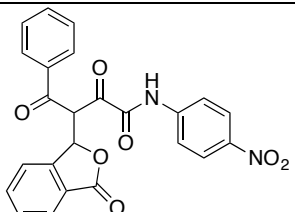
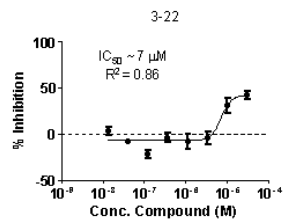
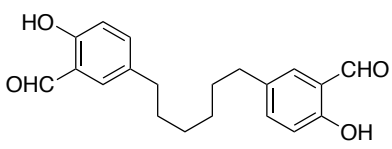
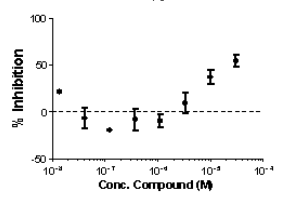
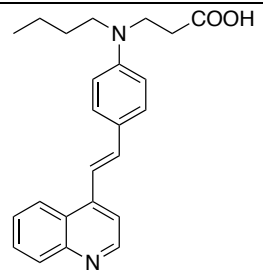
Figure S11. Inhibition of ATG4B activity observed for NSC185058 in A) the fluorescent peptide assay⁶ with TCEP; B) the fluorescent peptide assay⁶ using DTT as reducing agent; C) the FRET LC3 fluorescence assay⁵ and D) the assay with FRET LC3 as substrate monitored by mass spectrometry⁵

Atg4B-1	Sense: 5' GCCCACUACUUCAUCGGCUACGUUG 3' Antisense: 5' CAACGUAGCCGAUGAAGUAGUGGGC 3'
Atg4B-2	Sense: 5' UUCCAGAGUGUUCUCUCGACACUGC 3' Antisense: 5' GCAGUGUCGAGAGAACACUCUGGAA 3'

Figure S12: Sequences of siRNA duplexes

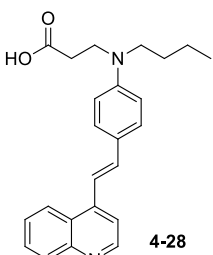
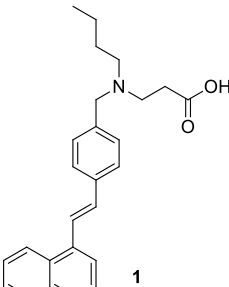
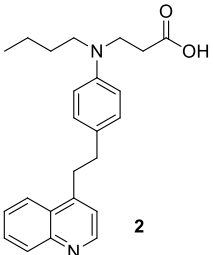
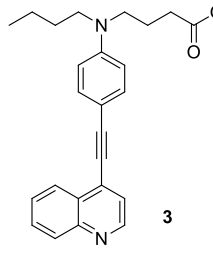
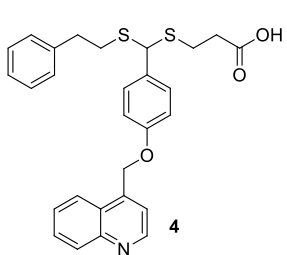
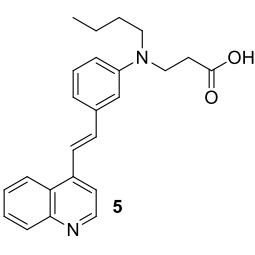
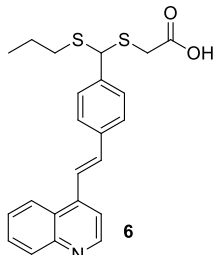
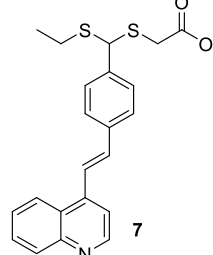
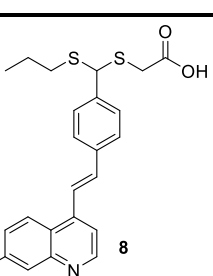
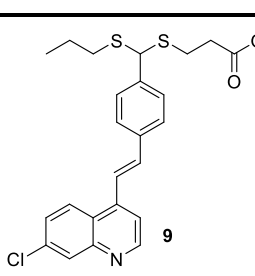
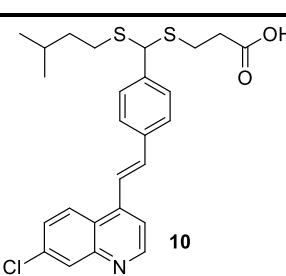
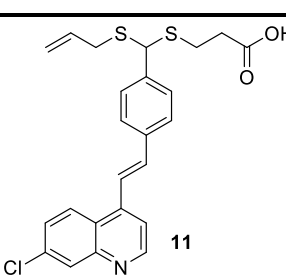
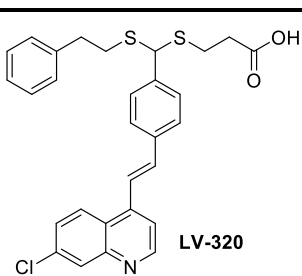
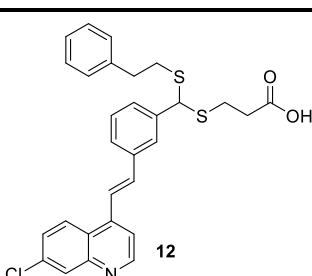
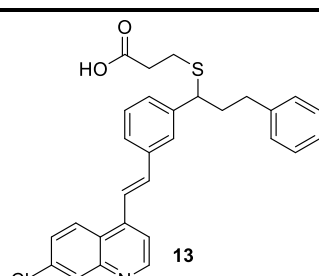
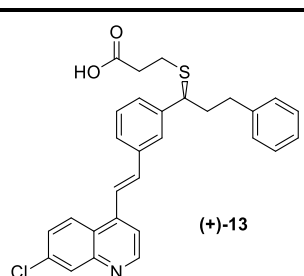
SUPPLEMENTAL INFORMATION

Tables

Screening code	NCI Code	Structure	Titration curve (FRET LC3 assay)
1-4			
2-22			
3-22			
4-6			
4-28			43% inhibition at 8 μ M

SUPPLEMENTAL INFORMATION

Table S1 : Compound hits from NCI library in silico screen that showed significant cellular effects on GFP-LC3 puncta in SKBRF3-hrGFP-LC3B cells and inhibition of ATG4B activity listed according to screening codes, NCI codes and structures with titration curve (Assays were performed in triplicate according to the method in reference 5)

Compd	 4-28	 1	 2	 3
IC ₅₀ (μM)	79 ± 9	> 200	> 200	> 200
Compd	 4	 5	 6	 7
IC ₅₀ (μM)	> 200	110 ± 6	36 ± 7	> 200
Compd	 8	 9	 10	 11
IC ₅₀ (μM)	47 ± 15	12 ± 3	29 ^a	16 ^b
Compd	 LV-320	 12	 13	 (+)-13
IC ₅₀ (μM)	24.5 (95% CL 20.7-29.1)	29 ^b	13 ± 9	9.1 ± 1.0

SUPPLEMENTAL INFORMATION

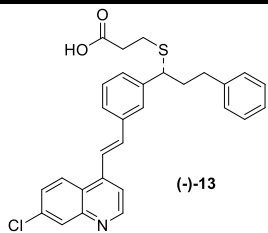
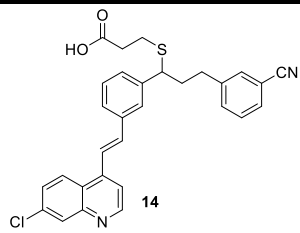
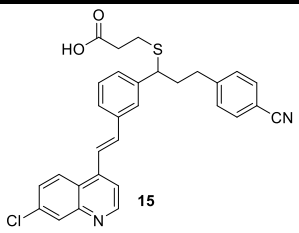
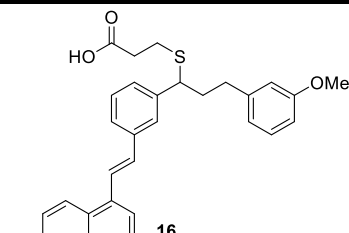
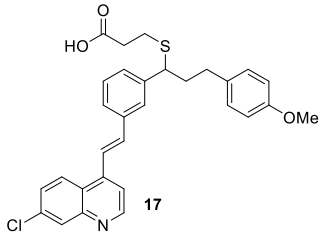
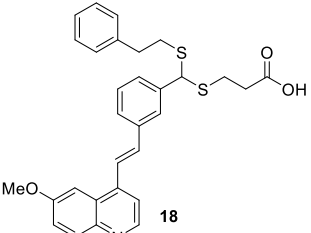
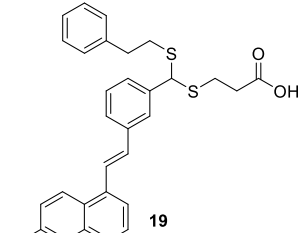
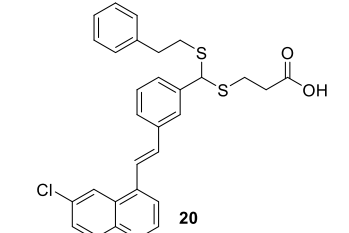
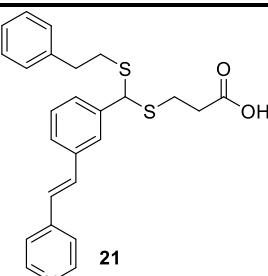
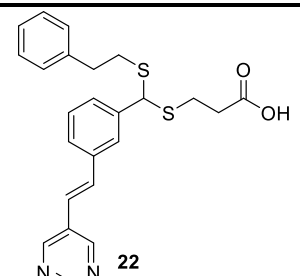
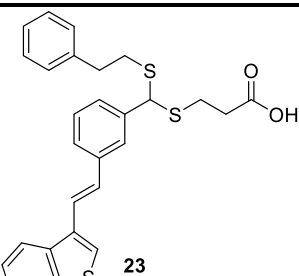
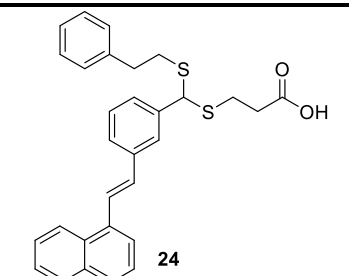
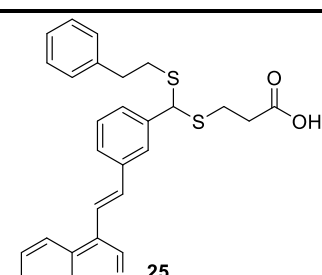
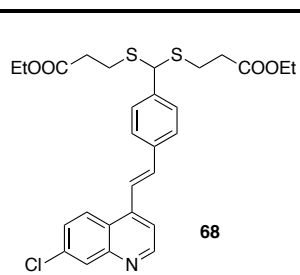
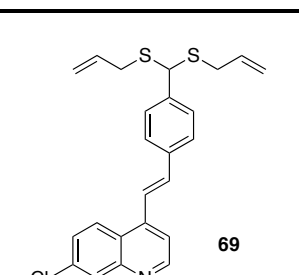
Compd	 (-)-13	 14	 15	 16
IC ₅₀ (μM)	9.4 ± 2	39 ± 9	11 ± 0.8	27 ^b
Compd	 17	 18	 19	 20
IC ₅₀ (μM)	30 ± 0.3	37 ± 21	15 ^a	30 ^a
Compd	 21	 22	 23	 24
IC ₅₀ (μM)	> 100	> 100	22 ± 2	36 ^a
Compd	 25	 68	 69	
IC ₅₀ (μM)	47 ± 12	> 100	> 100	

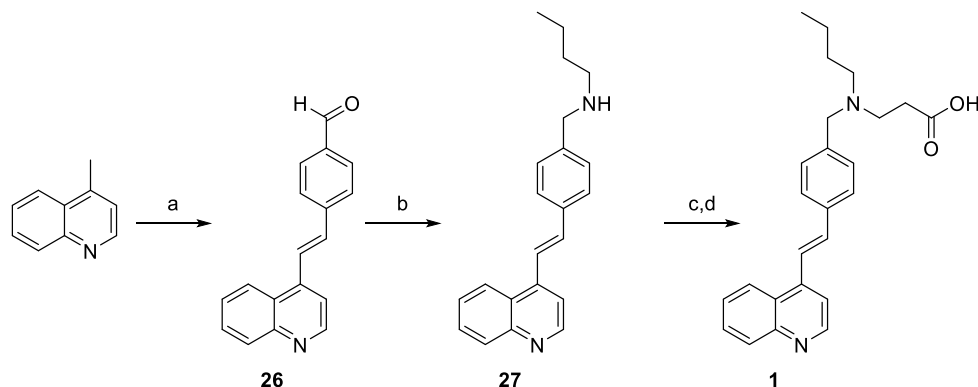
Table S2 ATG4B Inhibitory activity of **4-28** and synthesized compounds **1** to **69** and **LV-320**, related to Figure 4. Experiments are done in triplicates except where mentioned (^a n=1; ^b n=2). IC₅₀ are in μM and are represented as mean ± SD for triplicates or as mean for duplicates. Compound **13** is a racemate and **(+)-13** and **(-)-13** are depicted as ambiguous as to absolute stereochemistry as this was not determined.

SUPPLEMENTAL INFORMATION

IC₅₀ are in μM and are represented as mean $\pm$ SD for triplicates or as mean for duplicates. Compound **13** is a racemate and **(+)-13** and **(-)-13** are depicted as ambiguous as to absolute stereochemistry as this was not determined.

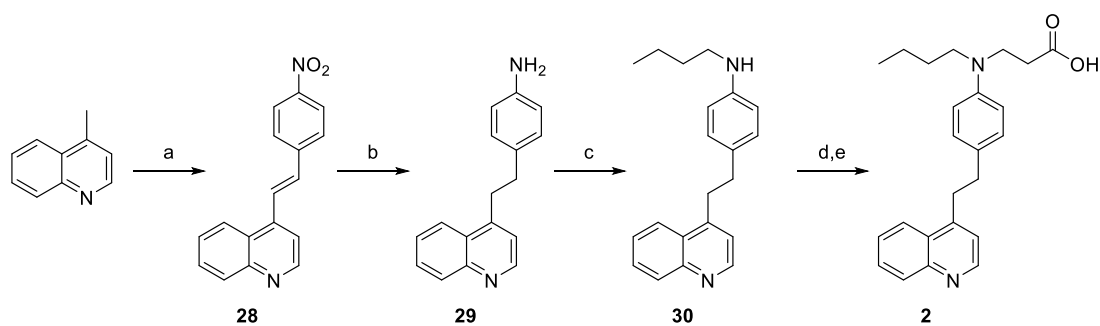
SYNTHESIS, CHARACTERIZATION OF COMPOUNDS AND SPECTRA

Scheme S1. Homologation of 4-28



Reagent and conditions: (a) terephthalaldehyde, ZnCl_2 , MW, 150 °C, 10 min, 51%; (b) *n*-butylamine, $\text{NaBH}(\text{OAc})_3$, DMF, MW, 30 min, 47%; (c) ethyl 3-bromopropionate, K_2CO_3 , DMF, MW, 90 °C, 10 h ; (d) 2N NaOH, dioxane, H_2O , 50 °C, 50%.

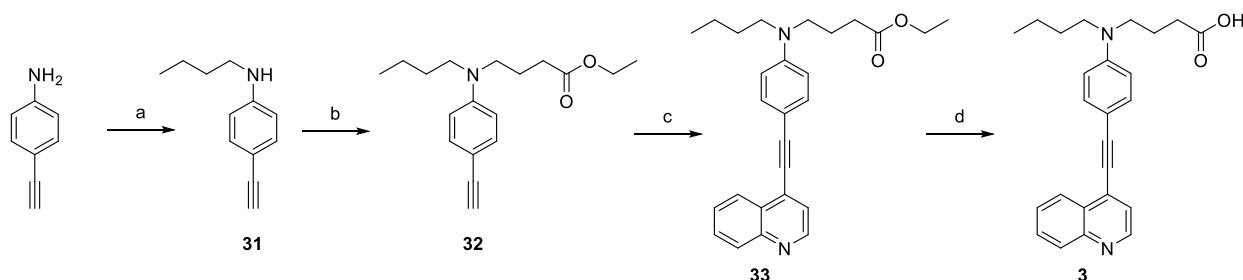
Scheme S2. Replacement of the double bond by a single bond



Reagent and conditions: (a) 4-nitrobenzaldehyde, ZnCl_2 , MW, 150 °C, 10 min, quantitative yield; (b) 10% Pd/C, H_2 , DMF, rt, 24 h, 57%; (c) butyraldehyde, $\text{NaBH}(\text{OAc})_3$, THF, rt, 2 h, 30%; (d) ethyl 3-bromopropionate, DIEA, MW, 100 °C, 2 h; (e) 2N NaOH, dioxane, H_2O , 50 °C, 10% for two steps.

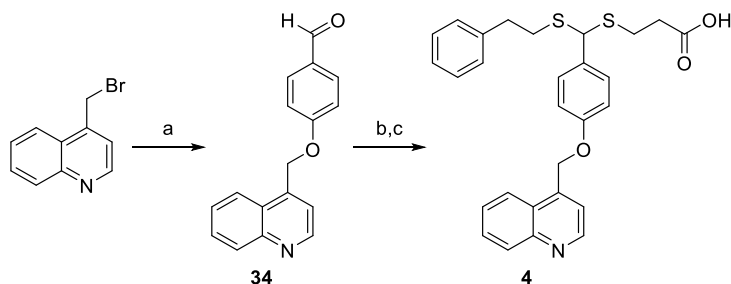
SUPPLEMENTAL INFORMATION

Scheme S3. Replacement of the double bond by a triple bond



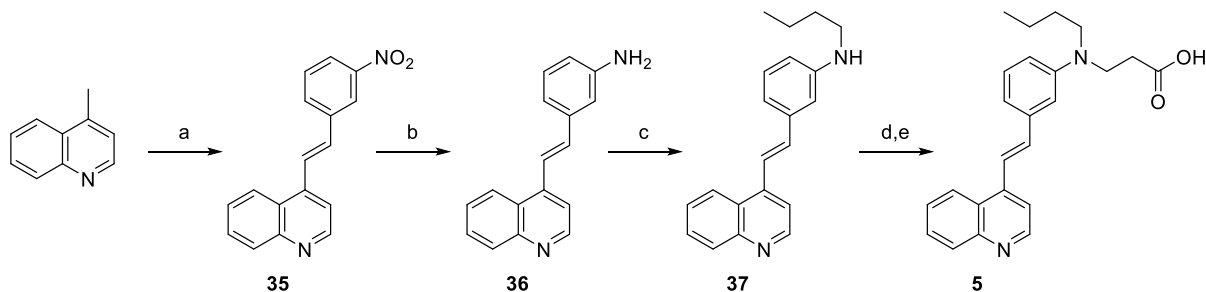
Reagent and conditions: (a) butyraldehyde, $\text{NaBH}(\text{OAc})_3$, THF, rt, 4 h, 41%; (b) ethyl 4-bromobutyrate, K_2CO_3 , DMF, MW, 90 °C, 8 h, 28%; (c) 4-bromoquinoline, Et_3N , CuI, $\text{PdCl}_2(\text{PPh}_3)_2$, DMF, MW, 60 °C, 90 min, 80%; (d) 10N NaOH, MeOH, H_2O , rt, 6 h, 59%.

Scheme S4: Synthesis of the ether analog 4



Reagent and conditions: (a) 4-hydroxybenzaldehyde, K_2CO_3 , KI, THF, rt, 48 h, 40%; (b) Ethyl 3-mercaptopropionate, 2-phenylethanethiol, PTSA, toluene, reflux, 5 h; (c) 10N NaOH, MeOH, H_2O , -10 °C to rt, 53% over two steps.

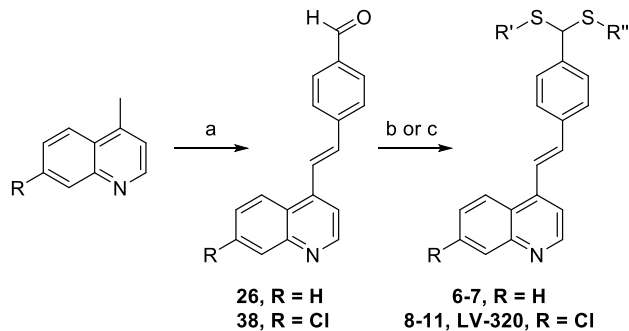
Scheme S5. Synthesis of compound 5



Reagent and conditions: (a) 3-nitrobenzaldehyde, ZnCl_2 , NMP, MW, 150 °C, 34%; (b) SnCl_2 , EtOH, reflux, 45%; (c) butyraldehyde, $\text{NaBH}(\text{OAc})_3$, AcOH, CH_2Cl_2 , rt, 38%; (d) ethyl 3-bromopropionate, K_2CO_3 , KI, DMF, 70 °C (e) 4N NaOH, dioxane, H_2O , rt, 42%.

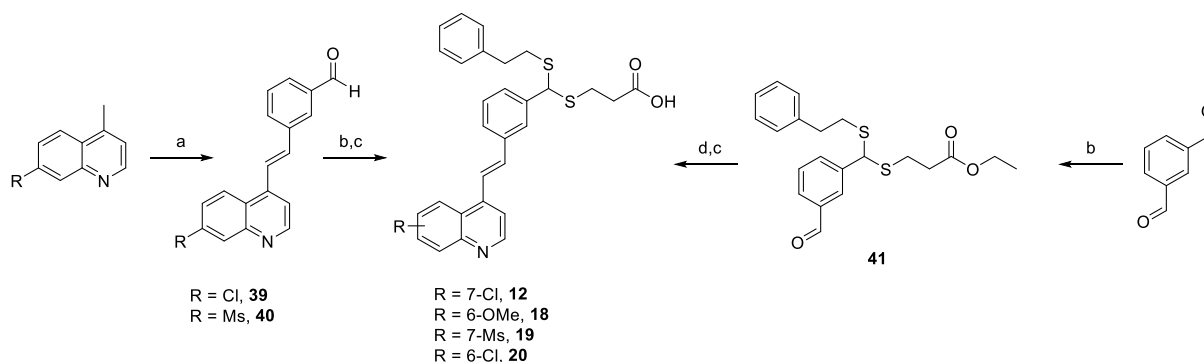
SUPPLEMENTAL INFORMATION

Scheme S6. Synthesis of the dithioacetal analogues



Reagent and conditions: (a) terephthalaldehyde, ZnCl_2 , MW, $150\text{ }^\circ\text{C}$, 20 min, yields ranging from 51% to 70%; (b) thiol 1, thiol 2, PTSA, toluene, reflux, 2 h, yields ranging from 6 to 42%; (c) (I) thiol 1, thiol 2, PTSA, toluene, reflux, 2 h (II) 2N NaOH, MeOH, rt, 2 h, 7 %.

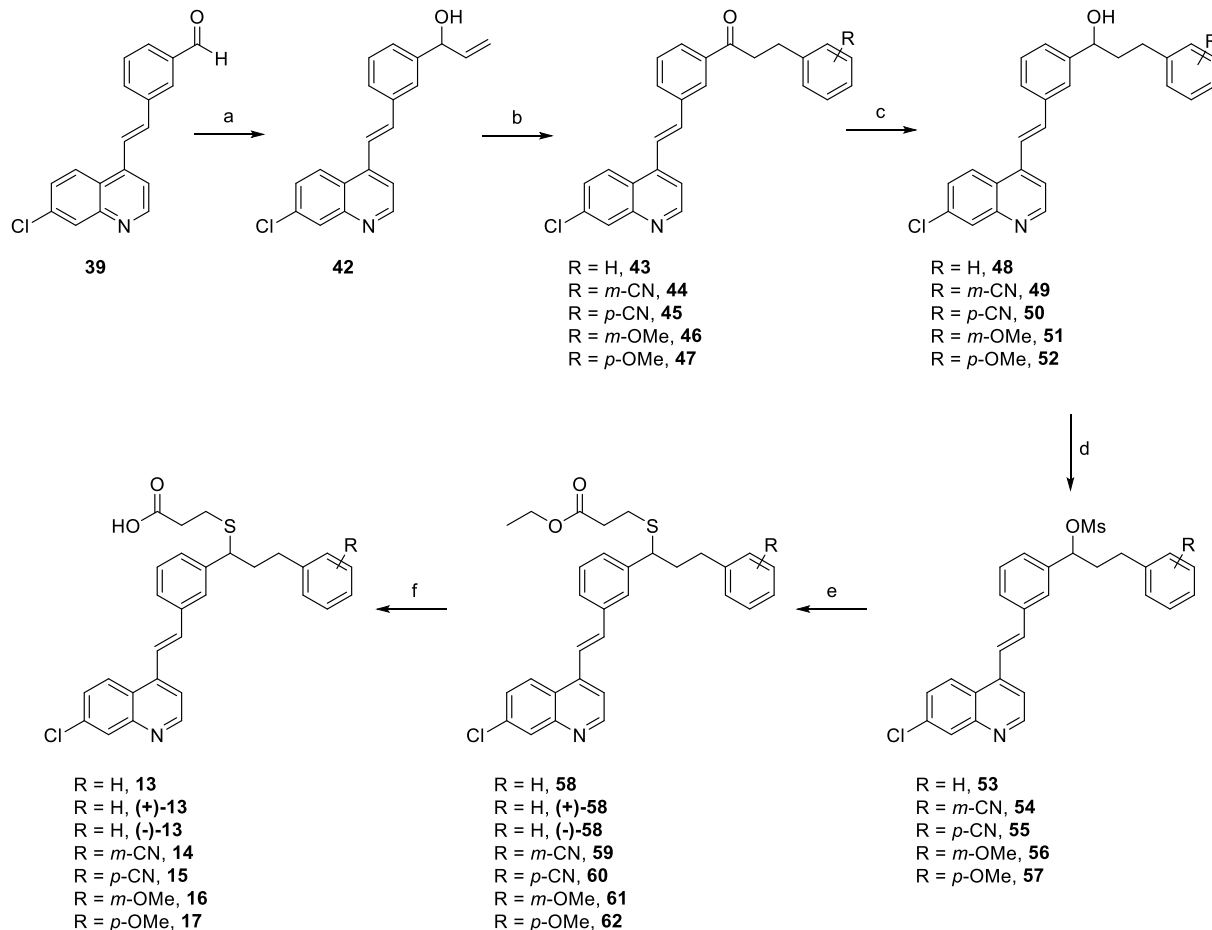
Scheme S7. Synthesis of quinoline analogs



Reagent and conditions: (a) isophthalaldehyde, ZnCl_2 , MW, $150\text{ }^\circ\text{C}$, 20 min, yields ranging from 38% to 81%; (b) ethyl 3-mercaptopropionate, 2-phenylethanethiol, PTSA, toluene, rt or reflux, 2.5 h - 3 h; (c) 2N NaOH, MeOH, H_2O , $-15\text{ }^\circ\text{C}$ - rt, 2 h, yields ranging from 7 to 36%; (d) R-substituted quinoline, Ac_2O or ZnCl_2 , MW, $150\text{ }^\circ\text{C}$ - $190\text{ }^\circ\text{C}$, 20 min - 6 h, yields ranging from 4% to 10%.

SUPPLEMENTAL INFORMATION

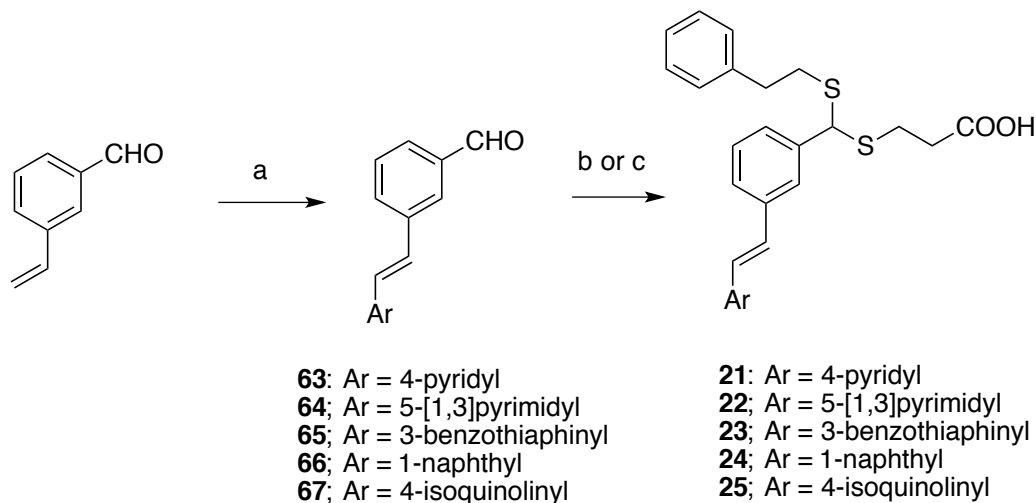
Scheme S8. Synthesis of the thioether analogs



Reagent and conditions: (a) vinyl magnesium bromide, toluene, 5 °C, 2.5 h, 52%; (b) aryl iodide, Et₃N, CH₃CN, reflux, 16 h, yields ranging from 47% to 85%; (c) NaBH₄, THF/MeOH (1:1), rt, 16 h, yields ranging from 60% to Quant.; (d) MsCl, Et₃N, toluene, 0 °C, 16 h; (e) ethyl 3-mercaptopropionate, Cs₂CO₃, CH₃CN or DMF, rt, 3 h - 16 h, yields ranging from 46% to 55%; (f) LiOH.H₂O, CH₃CN, H₂O, rt, 16 h, yields ranging from 23% to 82%.

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Scheme S9. Synthesis of analogs modulating the aromatic ring



Reagents and conditions: (a) aryl bromide, NaOAc or Et₃N, Pd(OAc)₂, P(O-tol)₃, CH₃CN or DMA, reflux, 16 h, yields ranging from 10% - 74%; (b) 3-mercaptopropionic acid, 2-phenylethanethiol, TsOH.H₂O, CH₂Cl₂, reflux, 1 h, yields ranging from 17% - 23%.

(c) (I) 3-mercaptopropionic acid, 2-phenylethanethiol, TFA, DCE, 0 °C to rt, 16 h; (II) 2N NaOH, MeOH, H₂O, -15 °C - rt, 2 h, yields ranging from 5 to 42%.

General methods and materials

All reagents, solvents and starting materials were purchased from commercial suppliers and used without further purification. ¹H NMR spectra were recorded on a Bruker Avance IITM 600 MHz, Bruker Avance IIITM 500 MHz or Bruker Avance IIITM 400 MHz spectrometer with acetone-*d*₆, CDCl₃ or DMSO-*d*₆ as the solvent. ¹³C NMR spectra are recorded at 101 or 151 MHz. All coupling constants are measured in hertz (Hz) and the chemical shifts (δ) are quoted in parts per million (ppm). Processing of the spectra was performed with MestRecTM software. The high-resolution mass spectra were recorded either in positive or negative ion-mode with an ESI or multimode ESI/APCI ion source on an AgilentTM 6210 Time-of-Flight LC/MS mass spectrometer. Purity for all final compounds was confirmed by analytical reverse-phase HPLC utilizing a Halo® C18 reverse-phase analytical column (4.6 × 50 mm, 5 mM), using UV detection (215 nM) and a gradient starting from 86 % H₂O / 14 % CH₃CN / 5 mM NH₄OAc and reaching 14 % H₂O / 86 % CH₃CN / 5 mM NH₄OAc within 6 min. Optical rotation was

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measured on a Perkin-Elmer Polarimeter 341 at 589 nm. Analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated with silica gel 60F-254 as the absorbent. The developed plates were air-dried, exposed to UV light and/or dipped in KMnO₄ solution and heated. All automated flash chromatography were performed on Biotage Isolera Flash Purification Systems using commercial silica gel cartridges.

General procedures

Procedure A: Heck coupling with 3-vinylbenzaldehyde and halogen-substituted aryl Aldehyde (1.0 mmol) in CH₃CN (0.55 mL) was treated with halogen-aryl (1.1 mmol), triethylamine (1.5 – 2.5 mmol), and palladium acetate (0.02 mmol). The mixture was heated at reflux under nitrogen for 14 h. The reaction mixture was diluted with EtOAc and H₂O. The separated organic layer was washed with water and brine, dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (hexanes:EtOAc; 10:0 to 25:75).

Procedure B: Asymmetric dithioacetal formation with TFA

Syntheses generally followed procedures previously reported by Gauthier³ and Zamboni.⁴ The aldehyde (1.0 mmol) was solubilized in 1,2-DCE (10.0 mL) and TFA (5.0 mL) at 0 °C. The 3-mercaptopropionic acid (1.1 mmol) and 2-phenylethanethiol (1.1 mmol) were added and the reaction mixture was stirred at room temperature for 16 h. The crude reaction mixture was purified by reverse phase chromatography (water:MeOH; 1:0 to 0:1) to afford the dithioacetal.

Procedure C: Asymmetric dithioacetal formation with TsOH.H₂O

Syntheses followed procedures previously reported by Gauthier³ and Zamboni.⁴ The aldehyde (1.0 mmol) and TsOH.H₂O (1.1 mmol) were solubilized in CH₂Cl₂ (0.5 mL). Thiol 1 (1.1 mmol) and Thiol 2 (1.1 mmol) were added and the reaction mixture was stirred at 50 °C for 1 h. The reaction mixture was diluted with 12.5 mL of a MeOH:water:HCl:DMF (4:4:1:4) solution. The crude reaction mixture was purified by reverse phase chromatography (H₂O:MeOH; 9:1 to 0:1) to afford the dithioacetal.

Procedure D: Reduction of ketone with NaBH₄

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A mixture of ketone (1.0 mmol), tetrahydrofuran (2.3 mL) and ethanol (2.3 mL) was added to sodium borohydride (0.5 mmol) at 5 °C. The colorless reaction mixture was stirred at room temperature for 1 h, and then acidified with a 10% aqueous solution of citric acid. The mixture was extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to afford the alcohol with a purification step if needed.

Procedure E: Mesylation of alcohol

Alcohol (1.0 mmol) in toluene (6.4 mL) was cooled at -10 °C. Triethylamine (1.8 mmol) was added followed by the dropwise addition of methanesulfonyl chloride (2.5 mmol). The reaction mixture was stirred at 0 °C for 16 h. The reaction mixture was diluted in CH₂Cl₂ and 10% citric acid. The aqueous layer was washed with CH₂Cl₂. The collected organic layer was washed with 10% citric acid and saturated aqueous Na₂CO₃ solution, dried over Na₂SO₄ and concentrated to afford the mesylated alcohol, which was used without further purification in the next step.

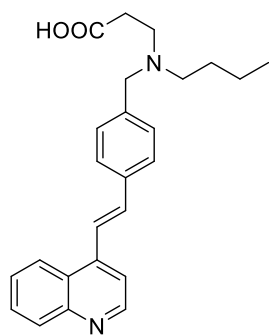
Procedure F: Thiolation of mesylated alcohol

The mesylate (1.0 mmol) in CH₃CN or DMF (10 mL) was degassed by purging three times with vacuum and nitrogen. Ethyl 3-mercaptopropionate (1.5 mmol) was added at room temperature followed by addition of Cs₂CO₃ (1.8 mmol). The reaction mixture was stirred at room temperature for 3 h – 16 h. The solids were filtered and washed with CH₃CN. The filtrate was evaporated to dryness to give a yellow oil. The crude product was purified by flash chromatography on silica gel (toluene/EtOAc 10:0 to 75:25 (v/v) in 30 min) to afford the thioether.

Procedure G: Saponification of ethyl 3-(thioether)propanoate

To a solution (CH₃CN:H₂O; 3:2, 26 mL) of ester (1.0 mmol) at 0 °C was added lithium hydroxide monohydrate (3.0 mmol). The mixture was stirred for 16 h. The aqueous layer was acidified with acetic acid until pH 3 and extracted twice with ethyl acetate. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (hexanes to toluene/EtOAc:CH₃COOH; 1:0:0:0 to 0:1:1:0.01) to afford the acid.

SUPPLEMENTAL INFORMATION



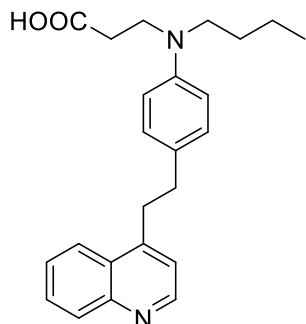
(E)-3-(butyl(4-(2-(quinolin-4-yl)vinyl)benzyl)amino)propanoic acid (**1**)

Compound **26** (259 mg, 1 mmol), *n*-butylamine (143 μ L, 1.5 mmol) and NaHB(OAc)₃ (422 mg, 2 mmol) were combined under inert atmosphere. DMF (2 mL) was added and the mixture was stirred under microwave irradiation for 30 min. The reaction was quenched with 2M NaOH and extracted with EtOAc. The organic phase was washed with 2M NaOH, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (CH₂Cl₂:MeOH:TEA; 99:1:1 to 90:10:1) to yield *(E)*-*N*-(4-(2-(quinolin-4-yl)vinyl)benzyl)butan-1-amine (**27**) as a brown oil (150 mg) which was used directly in the following reaction

To a solution of **27** (65 mg, 0.205 mmol) in (DMF, 0.5 mL) was added ethyl 3-bromopropionate (131 mg, 1.025 mmol) and K₂CO₃ (140 mg, 1.02 mmol). The mixture was stirred under microwave irradiation at 90 °C for 10 h. The mixture was filtered and the solvent removed under reduced pressure. The crude ester was purified by preparative reverse phase chromatography (CH₃CN:H₂O; 20:80 to 100:0). The ester was dissolved in dioxane (0.5 mL) and 2N NaOH solution (20 μ L) was added. The reaction was stirred at 50 °C for 14 h. The solvent was removed under reduced pressure. The residue was dissolved in an acetonitrile/H₂O/formic acid solution (1:1:0.01 (v/v), 5 mL) and purified by preparative reverse phase chromatography (CH₃CN:H₂O; 20:80 to 100:0) to afford **1** as a yellow solid (40 mg, 50%). ¹H NMR (DMSO-*d*₆) δ (ppm): 8.89 (d, 1H, *J* = 3.8 Hz), 8.53 (d, 1H, *J* = 7.9 Hz), 8.08 (d, 1H, *J* = 16.2 Hz), 8.04 (d, 1H, *J* = 6.9 Hz), 7.85 (d, 1H, *J* = 4.6 Hz), 7.79 (ddd, 1H, *J* = 6.7, 5.0, 1.3 Hz), 7.79 (d, 2H, *J* = 4.9 Hz), 7.66 (ddd, 1H, *J* = 8.2, 6.8, 1.1 Hz), 7.59 (d, 1H, *J* = 16.1 Hz), 7.38 (d, 2H, *J* = 7.5 Hz), 3.60 (s, 2H), 2.71 (s, 2H), 2.39 (d, 4H, *J* = 8.2 Hz), 1.42 (s, 2H), 1.25 (dd, 2H, *J* = 14.4, 7.2 Hz), 0.83 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (DMSO-*d*₆) δ (ppm): 174.3, 150.8,

SUPPLEMENTAL INFORMATION

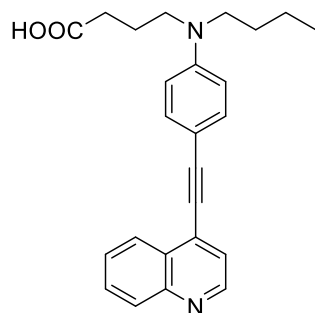
148.9, 142.8, 140.7, 135.7, 135.5, 130.1, 130.0, 129.6, 127.9, 127.1, 126.4, 124.7, 122.4, 117.1, 57.8, 53.0, 49.5, 32.4, 29.0, 20.5, 14.4.



3-(butyl(4-(2-(quinolin-4-yl)ethyl)phenyl)amino)propanoic acid (2)

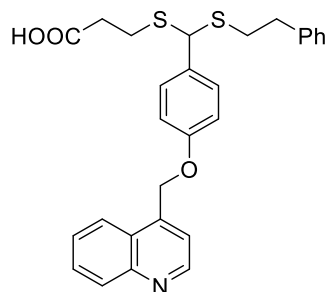
To a solution of **30** (40 mg, 0.131 mmol) in DIEA (90 μ L, 0.353 mmol) was added ethyl 3-bromopropionate3-ethoxy-3-oxopropyl benzoate (168 μ L, 1.31 mmol). The mixture was stirred under microwave irradiation at 100 $^{\circ}$ C for 2 h. The mixture was diluted with EtOAc and washed with water, saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The crude ester was purified by flash chromatography on a silica gel column (MeOH:CH₂Cl₂; 1:99 to 10:90). The ester was dissolved in dioxane (7.5 mL) and 2N NaOH solution (300 μ L) was added. The reaction was stirred at 50 $^{\circ}$ C for 14 h. The solvent was removed under reduced pressure. The residue was dissolved in an acetonitrile/H₂O/formic acid solution (1:1:0.01 (v/v), 5 mL) and purified by preparative reverse phase chromatography (CH₃CN:H₂O:formic acid; 30:70:0.1 to 50:50:0.1) to afford **2** as a yellow oil (21%). ¹H NMR (DMSO-*d*₆) δ (ppm): 8.79 (d, 1H, *J* = 4.4 Hz), 8.21 (d, 1H, *J* = 8.4 Hz), 8.03 (d, 1H, *J* = 8.4 Hz), 7.76 (t, 1H, *J* = 7.6 Hz), 7.64 (t, 1H, *J* = 7.6 Hz), 7.39 (d, 1H, *J* = 4.4 Hz), 7.09 (d, 2H, *J* = 8.1 Hz), 6.60 (d, 2H, *J* = 8.1 Hz), 3.51 (t, 2H, *J* = 7.1 Hz), 3.36 – 3.30 (m, 2H), 3.24 (t, 2H, *J* = 7.6 Hz), 2.88 (dd, 2H, *J* = 9.6, 6.5 Hz), 2.46 – 2.39 (m, 2H), 1.47 (p, 2H, *J* = 7.5 Hz), 1.31 (h, 2H, *J* = 7.4 Hz), 0.91 (t, 3H, *J* = 7.3 Hz).

SUPPLEMENTAL INFORMATION



4-(butyl(4-(quinolin-4-ylethynyl)phenyl)amino)butanoic acid (3)

To a solution of **33** (17 mg, 0.041 mmol) in MeOH (0.4 mL) was added a 10N NaOH solution (50 μ L). The reaction was stirred at rt for 6 h. The mixture was diluted with H₂O (10 mL) and purified by reverse phase chromatography (CH₃CN:H₂O:HOAc; 30:70:0.1 to 50:50:0.1) to afford **3** as yellow crystals (10 mg, 59%). ¹H NMR (DMSO-d₆) δ (ppm): 8.80 (d, 1H, *J* = 4.5 Hz), 8.32 (d, 1H, *J* = 8.2 Hz), 8.02 (d, 1H, *J* = 8.4 Hz), 7.82 (t, 1H, *J* = 7.6 Hz), 7.72 (t, 1H, *J* = 7.5 Hz), 7.59 (d, 1H, *J* = 4.5 Hz), 7.48 (d, 2H, *J* = 8.7 Hz), 6.73 (d, 2H, *J* = 8.8 Hz), 3.33 – 3.22 (m, 4H), 1.96 (t, 2H, *J* = 7.0 Hz), 1.67 (dd, 2H, *J* = 15.0, 7.5 Hz), 1.53 – 1.43 (m, 2H), 1.34 – 1.23 (m, 2H), 0.88 (t, 3H, *J* = 7.3 Hz).

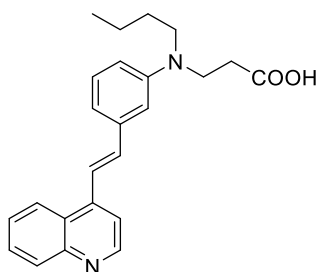


3-(((phenethylthio)(4-(quinolin-4-ylmethoxy)phenyl)methyl)thio)propanoic acid (4)

To a solution of **34** (30 mg, 0.114 mmol) and TsOH.H₂O (26 mg, 0.139 mmol) in toluene (1 mL) was added ethyl 3-mercaptopropionate (43 μ L, 0.342 mmol) and 2-phenylethanethiol (45 μ L, 0.342 mmol). The mixture was stirred at reflux for 5 h. The mixture was diluted with EtOAc, washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and the filtrate concentrated under reduced pressure. The crude dithioacetal was then purified by flash chromatography on a silica gel column (EtOAc:hexanes; 20:80 to 50:50). The dithioacetal was dissolved in MeOH (200 μ L), 10N NaOH (50 μ L) was added and the reaction was stirred at rt for 14 h. The mixture was diluted with H₂O and washed with Et₂O. The aqueous phase was

SUPPLEMENTAL INFORMATION

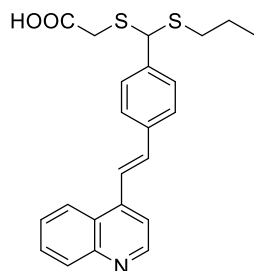
acidified to pH 5 and extracted with EtOAc. The organic phase was concentrated under reduced pressure and the residue was purified by reverse phase chromatography (H₂O:CH₃CN:HOAc; 100:0:0.1 to 50:50:0.1) to afford **4** as white crystals (17 mg, 53%). ¹H NMR (DMSO-d₆) δ 8.91 (d, 1H, *J* = 4.3 Hz), 8.17 (d, 1H, *J* = 8.3 Hz), 8.08 (d, 1H, *J* = 8.4 Hz), 7.80 (t, 1H, *J* = 7.6 Hz), 7.69 – 7.66 (m, 1H), 7.65 (d, 1H, *J* = 4.4 Hz), 7.38 (d, 1H, *J* = 8.5 Hz), 7.27 (t, 1H, *J* = 7.5 Hz), 7.26 (d, 1H, *J* = 7.2 Hz), 7.19 (t, 1H, *J* = 6.6 Hz), 7.18 (d, 2H, *J* = 7.6 Hz), 7.10 (d, 2H, *J* = 8.5 Hz), 5.66 (s, 2H), 5.12 (s, 1H), 2.85 – 2.74 (m, 3H), 2.72 – 2.63 (m, 2H), 2.62 – 2.55 (m, 1H), 2.08 (t, 2H, *J* = 7.8 Hz). ¹³C NMR (DMSO-d₆) δ (ppm): 158.3, 151.4, 148.5, 143.2, 141.4, 134.7, 130.5, 130.4, 129.8, 129.4, 129.2, 127.7, 127.0, 126.5, 124.9, 120.4, 115.6, 67.1, 52.4, 36.2, 34.2, 30.4.



(E)-3-(butyl(3-(2-(quinolin-4-yl)vinyl)phenyl)amino)propanoic acid (**5**)

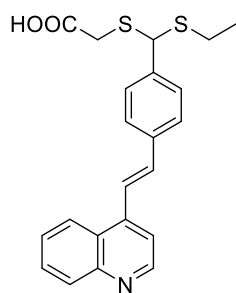
Compound **37** (33 mg, 0.109 mmol), K₂CO₃ (155 mg, 1.12 mmol) and KI (36 mg, 0.217 mmol) were suspended in DMF (0.2 mL) under an inert atmosphere. Ethyl 3-bromopropionate (155 μL, 0.112 mmol) was added and the reaction was stirred at 70 °C for 48 h. The mixture was diluted with MeOH (2 mL), 4M NaOH (0.2 mL) was added and the reaction was stirred at rt for 48 h. The solvent was removed under reduced pressure and the residue was purified by reverse phase chromatography (H₂O:MeOH:HOAc; 95:5:0.1 to 5:95; :0.1) to afford **5** as a yellow powder (18 mg, 42%). ¹H NMR (D₂O) δ (ppm): 8.03 (d, 1H, *J* = 3.7 Hz), 7.52 (d, 1H, *J* = 8.2 Hz), 7.19 (dd, 2H, *J* = 15.5, 7.9 Hz), 6.82 (t, 1H, *J* = 7.0 Hz), 6.74 (d, 2H, *J* = 14.2 Hz), 6.64 (d, 1H, *J* = 3.8 Hz), 6.49 (d, 1H, *J* = 15.9 Hz), 6.34 (d, 1H, *J* = 7.4 Hz), 6.24 (s, 2H), 3.26 (s, 2H), 2.75 (s, 2H), 2.25 – 2.14 (m, 2H), 1.03 (s, 2H), 0.91 (dd, 2H, *J* = 13.9, 7.0 Hz), 0.53 (t, 3H, *J* = 7.1 Hz).

SUPPLEMENTAL INFORMATION



(E)-2-(((propylthio)(4-(2-(quinolin-4-yl)vinyl)phenyl)methyl)thio)acetic acid (**6**)

Compound **26** (129.5 mg, 0.5 mmol) and TsOH·H₂O (570 mg, 0.75 mmol) were dissolved in toluene (10 mL) and 4Å molecular sieves were added. Sodium propane-1-thiolate (196 mg, 2 mmol) and 2-mercaptoacetic acid (70 mg, 1 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (CH₂Cl₂:MeOH:AcOH; 99:1:0.5 to 90:10:0.5) to afford **6** as a yellow solid (13 mg, 6%). ¹H NMR (DMSO-d₆) δ (ppm): 8.89 (d, 1H, *J* = 4.6 Hz), 8.52 (d, 1H, *J* = 8.4 Hz), 8.10 (d, 1H, *J* = 16.1 Hz), 8.04 (d, 1H, *J* = 8.4 Hz), 7.85 (d, 1H, *J* = 4.6 Hz), 7.83 (d, 2H, *J* = 8.1 Hz), 7.81 – 7.78 (t, 1H, *J* = 7.6 Hz), 7.66 (t, 1H, *J* = 7.6 Hz), 7.59 (d, 1H, *J* = 16.1 Hz), 7.48 (d, 2H, *J* = 8.0 Hz), 5.23 (s, 1H), 3.36 (d, 1H, *J* = 15.2 Hz), 3.21 (d, 1H, *J* = 15.2 Hz), 2.67 – 2.61 (m, 1H), 2.56 – 2.51 (m, 1H), 1.63 – 1.50 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (DMSO-d₆) δ (ppm): 171.7, 151.1, 149.2, 143.0, 141.4, 137.1, 135.4, 130.4, 130.3, 128.9, 128.6, 127.5, 126.7, 125.0, 123.6, 117.6, 53.0, 35.1, 34.7, 23.0, 14.2.

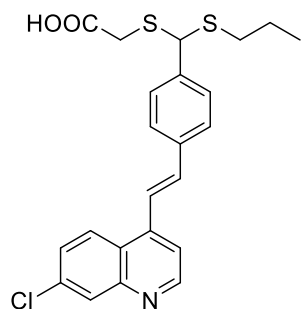


(E)-2-(((ethylthio)(4-(2-(quinolin-4-yl)vinyl)phenyl)methyl)thio)acetic acid (**7**)

Compound **26** (129.5 mg, 0.5 mmol) and TsOH·H₂O (570 mg, 0.75 mmol) were dissolved in toluene (10 mL) and 4Å molecular sieves were added. Sodium ethanethiolate (168 mg, 2 mmol) and 2-mercaptoacetic acid (53 mg, 0.75 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The reaction mixture was concentrated

SUPPLEMENTAL INFORMATION

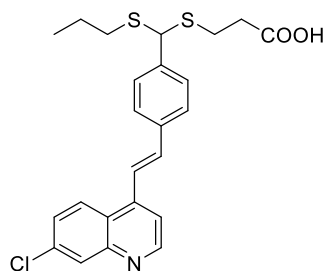
under reduced pressure. The residue was purified by flash chromatography on a silica gel column (CH₂Cl₂:MeOH:AcOH; 99:1:0.5 to 90:10:0.5) to afford **7** as a yellow solid (30 mg, 42%). ¹H NMR (DMSO-d₆) δ (ppm): 8.20 (d, 1H, *J* = 5.7 Hz), 7.91 (d, 1H, *J* = 8.6 Hz), 7.39 (d, 1H, *J* = 5.7 Hz), 7.35 (d, 1H, *J* = 8.5 Hz), 7.30 (d, 1H, *J* = 16.0 Hz), 7.13 (t, 1H, *J* = 7.7 Hz), 7.06 (d, 1H, *J* = 16.0 Hz), 6.98 (d, 2H, *J* = 8.1 Hz), 6.97 – 6.94 (t, 1H), 6.55 (d, 2H, *J* = 8.2 Hz), 4.30 (s, 1H), 2.38 (d, 1H, *J* = 15.2 Hz), 2.23 (d, 1H, *J* = 15.2 Hz), 1.68 (tt, 1H, *J* = 14.8, 7.4 Hz), 1.61 – 1.54 (m, 1H), 0.21 (t, 3H, *J* = 7.4 Hz). ¹³C NMR (CDCl₃) δ (ppm): 175.7, 155.6, 149.3, 147.0, 145.3, 144.7, 140.3, 138.5, 133.8, 133.7, 133.0, 130.8, 130.3, 127.3, 125.8, 121.5, 56.6, 38.9, 30.8, 19.3.



(E)-2-(((4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)(propylthio)methyl)thio)acetic acid (8)

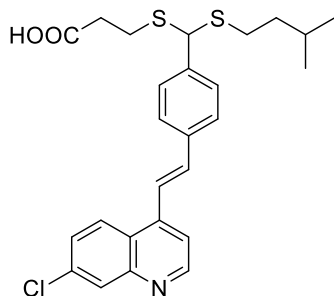
Compound **38** (120 mg, 0.41 mmol) and TsOH.H₂O (467 mg, 2.46 mmol) were dissolved in toluene (10 mL) and 4Å molecular sieves were added. Sodium propane-1-thiolate (161 mg, 1.64 mmol) and 2-mercaptoacetic acid (43 mg, 0.615 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The reaction mixture was concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (CH₂Cl₂:MeOH:AcOH; 99:1:0.5 to 90:10:0.5) to afford **8** as yellow crystals (25 mg, 39%). ¹H NMR (DMSO-d₆) δ (ppm): δ 9.07 (d, 1H, *J* = 5.2 Hz), 8.78 (d, 1H, *J* = 9.2 Hz), 8.20 (d, 1H, *J* = 1.8 Hz), 8.18 (d, 1H, *J* = 16.2 Hz), 8.14 (d, 1H, *J* = 5.0 Hz), 7.90 (d, 2H, *J* = 8.2 Hz), 7.85 (m, 2H), 7.51 (d, 2H, *J* = 8.2 Hz), 5.24 (s, 1H), 3.37 (d, 1H, *J* = 15.2 Hz), 3.22 (d, 1H, *J* = 15.2 Hz), 2.69 – 2.61 (m, 1H), 2.57 – 2.52 (m, 1H), 1.62 – 1.50 (m, 2H), 0.91 (t, 3H, *J* = 7.3 Hz). ¹³C NMR (DMSO-d₆) δ (ppm): ¹³C NMR (600 MHz, DMSO) δ 171.3, 149.1, 142.0, 138.5, 136.6, 136.2, 128.8, 128.6, 128.5, 127.6, 125.3, 125.0, 122.0, 117.4, 52.6, 34.5, 34.3, 22.6, 13.7.

SUPPLEMENTAL INFORMATION



(E)-3-(((4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)(propylthio)methyl)thio)propanoic acid (9**)**

Compound **38** (100 mg, 0.34 mmol) and TsOH.H₂O (126 mg, 0.68 mmol) were dissolved in toluene (20 mL) and 4Å molecular sieves were added. Sodium propane-1-thiolate (161 mg, 1.64 mmol) and 2-mercaptoacetic acid (43 mg, 0.615 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. Upon cooling, the material crystallised and was filtered. The precipitate was purified by flash chromatography on a silica gel column (CH₂Cl₂:MeOH:AcOH 99:1:0.5 to 90:10:0.5). The fraction containing the product was then further purified by HPLC reverse phase with a gradient from H₂O:CH₃CN:HCOOH 40:60:0.1 to 60:40:0.1 to afford **9** as yellow crystals (10%). ¹H NMR (DMSO-*d*₆) δ (ppm): 9.04 (d, 1H, *J* = 5.0 Hz), 8.75 (d, 1H, *J* = 9.1 Hz), 8.21 – 8.14 (m, 2H), 8.09 (d, 1H, *J* = 4.9 Hz), 7.89 (d, 2H, *J* = 7.9 Hz), 7.85 – 7.77 (m, 2H), 7.54 (d, 2H, *J* = 8.0 Hz), 5.27 (s, 1H), 2.72 (ddt, 2H, *J* = 57.4, 13.6, 7.1 Hz), 2.62 – 2.48 (m, 4H), 1.55 (ddt, 2H, *J* = 14.2, 11.1, 7.0 Hz), 0.91 (t, 3H, *J* = 7.3 Hz).

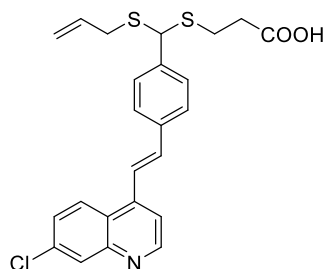


(E)-3-(((4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)(isopentylthio)methyl)thio)propanoic acid (10**)**

Compound **38** (100 mg, 0.34 mmol) and TsOH.H₂O (126 mg, 0.68 mmol) were dissolved in toluene (25 mL) and 4Å molecular sieves were added. 3-methylbutane-1-thiol (106 mg, 0.85 mmol) and ethyl 3-mercaptopropanoate (107 mg, 0.85 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The mixture was diluted with

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EtOAc and the organic phase was washed with saturated $\text{NaHCO}_{3(\text{aq})}$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc/hexanes). The ester was dissolved in methanol (0.5 mL) and 2N NaOH solution (1 mL) was added. The reaction was stirred at -15°C for 40 h. The mixture was diluted with H_2O and purified on a reverse phase Sep-pak column (20 g) (MeOH: H_2O ; 60:40) to afford **10** as a white solid (10 mg, 7%). ^1H NMR (DMSO-d_6) δ (ppm): 8.77 (d, 1H, $J = 4.7$ Hz), 8.38 (d, 1H, $J = 9.1$ Hz), 7.97 (d, 1H, $J = 2.0$ Hz), 7.88 (d, 1H, $J = 16.2$ Hz), 7.78 (d, 1H, $J = 4.7$ Hz), 7.69 (d, 2H, $J = 8.1$ Hz), 7.61 (dd, 1H, $J = 9.0, 2.0$ Hz), 7.49 (d, 1H, $J = 16.0$ Hz), 7.44 (d, 2H, $J = 8.1$ Hz), 5.03 (s, 1H), 2.65 (dt, 1H, $J = 13.0, 7.7$ Hz), 2.59 – 2.54 (m, 1H), 2.45 (tt, 2H, $J = 12.7, 6.4$ Hz), 2.18 (t, 2H, $J = 7.7$ Hz), 1.52 – 1.44 (m, 1H), 1.30 (q, 2H, $J = 7.4$ Hz), 0.74 (d, 3H, $J = 6.6$ Hz), 0.72 (d, 3H, $J = 6.6$ Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 178.0, 152.8, 149.5, 144.7, 143.4, 137.1, 137.0, 136.3, 129.7, 129.2, 129.0, 128.7, 127.6, 125.9, 123.2, 118.7, 53.3, 39.2, 39.0, 31.4, 30.4, 28.3, 23.5, 23.5.

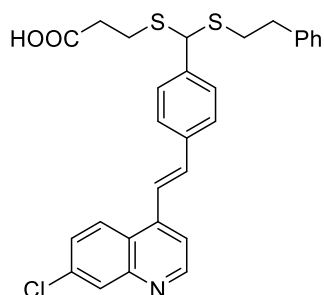


(E)-3-(((allylthio)(4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)methyl)thio)propanoic acid (11)

Compound **38** (100 mg, 0.34 mmol) and $\text{TsOH}\cdot\text{H}_2\text{O}$ (126 mg, 0.68 mmol) were dissolved in toluene (15 mL) and $4\text{\AA}$ molecular sieves were added. Allyl thiol (84 μL , 1.02 mmol) and ethyl 3-mercaptopropanoate (129 mg, 1.02 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The mixture was diluted with EtOAc and the organic phase was washed with saturated $\text{NaHCO}_{3(\text{aq})}$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexanes; 20:80 to 60:40). The ester was dissolved in a solution of H_2O /dioxane (1:1 v/v, 5 mL) and 2N NaOH solution (0.3 mL) was added. The reaction was stirred at 0°C for 1 h. The mixture was quenched with 1M HCl and extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel column (MeOH/ H_2O) to afford **11** as yellow crystals (29%). ^1H

SUPPLEMENTAL INFORMATION

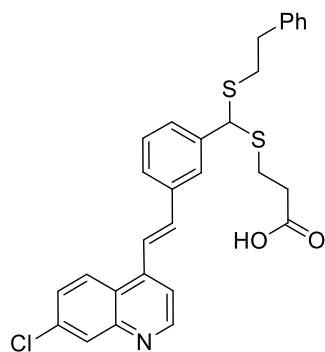
NMR (DMSO- d_6) δ (ppm): 9.10 (d, 1H, J = 5.3 Hz), 8.81 (d, 1H, J = 9.1 Hz), 8.26 – 8.16 (m, 3H), 7.92 (d, 2H, J = 8.0 Hz), 7.90 – 7.85 (m, 2H), 7.54 (d, 2H, J = 8.1 Hz), 5.82 (ddt, 1H, J = 17.1, 10.1, 7.1 Hz), 5.20 – 5.10 (m, 3H), 3.32 (dd, 1H, J = 13.6, 7.3 Hz), 3.18 (dd, 1H, J = 13.6, 7.0 Hz), 2.77 (dt, 1H, J = 13.8, 7.2 Hz), 2.67 (dt, 1H, J = 13.5, 7.1 Hz), 2.57 – 2.48 (m, 2H).



(E)-3-(((4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid (**LV-320**)

Compound **38** (1.21 g, 4.10 mmol) and TsOH.H₂O (0.86 g, 4.51 mmol) were suspended in CH₂Cl₂ (2.5 mL). 3-mercaptopropionic acid (0.393 mL, 4.51 mmol) and 2-phenylethanethiol (0.604 mL, 4.51 mmol) were added and the reaction was stirred at 50 °C for 1 h. The mixture was diluted with 1:1 water-methanol (4 mL, acidified with a drop of 1 M HCl; add THF dropwise until the system became homogeneous). The solution was directly loaded onto a C18 cartridge (BioTage KP-C18, 50g), and purified with a 50-100% MeOH-water linear gradient. The pure fractions were combined and concentrated by rotary evaporation to remove MeOH. The resulting precipitate was filtered and dried to give **LV-320** as a white solid (0.75 g, 35%). Purity = 100%; t_r = 2.94 min; MS (ESI⁺): m/z = 520 [M+H]⁺; HRMS m/z calculated for C₂₉H₂₇ClNO₂S₂⁺ [M+H]⁺ 520.1166, found 520.1147. ¹H NMR (DMSO- d_6) δ (ppm): 9.13 (d, 1H, J = 5.4 Hz), 8.86 (d, 1H, J = 9.2 Hz), 8.31 (d, 1H, J = 1.9 Hz), 8.25 (d, 1H, J = 5.5 Hz), 8.22 (d, 1H, J = 16.1 Hz), 7.95 (d, 1H, J = 14.1 Hz), 7.93 (d, 2H, J = 8.1 Hz), 7.90 (dd, 1H, J = 9.2, 2.0 Hz), 7.54 (d, 2H, J = 8.2 Hz), 7.28 (dd, 2H, J = 9.7, 5.4 Hz), 7.20 (d, 2H, J = 7.2 Hz), 7.22 – 7.18 (t, 1H), 5.29 (s, 1H), 2.88 – 2.81 (m, 2H), 2.79 – 2.72 (m, 2H), 2.69 – 2.63 (m, 3H), 2.53 (t, 1H, J = 7.4 Hz). ¹³C NMR (DMSO- d_6) δ (ppm): 173.4, 147.5, 143.1, 140.8, 140.0, 137.6, 135.9, 129.2, 129.1, 129.0, 128.8, 128.6, 127.9, 126.7, 125.1, 121.5, 117.4, 52.1, 35.6, 34.7, 33.8, 27.6. HRMS: calcd for C₂₉H₂₆ClNO₂S₂ 519.1093, observed 520.1204 (ESI⁺, [M+H]⁺), 518.1009 (ESI⁻, [M-H]⁻); Elemental analysis: calcd for C₂₉H₂₆ClNO₂S₂: C 66.97, H 5.04, N 2.69, S 12.33, Cl 6.82; found C 66.74, H 5.00, N 2.79, S 12.10, Cl 6.89.

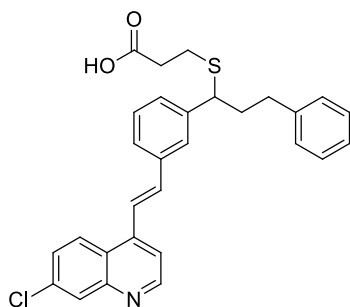
SUPPLEMENTAL INFORMATION



(E)-3-(((3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid (**12**)

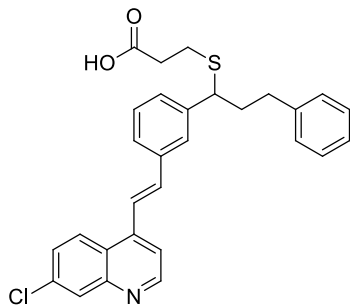
Compound **39** (40 mg, 0.136 mmol) and TsOH.H₂O (5.2 mg, 0.2 mmol) were dissolved in toluene (1 mL) and 4Å molecular sieves were added. 2-phenylethane-1-thiol (12 mg, 0.09 mmol) and ethyl 3-mercaptopropanoate (11.4 mg, 0.09 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO_{3(aq)} and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc/hexanes). The ester was dissolved in a solution of H₂O/dioxane (1:1 v/v, 5 mL) and 2N NaOH solution (0.3 mL) was added. The reaction was stirred at -15 °C for 24 h. The mixture was quenched with 1M HCl and extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on a C18 reverse phase column (CH₃CN:H₂O;0:100 to 50:50) to afford **12** as white crystals (5 mg, 7%). ¹H NMR (DMSO-d₆) δ (ppm): 8.92 (d, 1H, *J* = 4.6 Hz), 8.61 (d, 1H, *J* = 9.0 Hz), 8.09 (t, 2H, *J* = 8.0 Hz), 7.93 (d, 1H, *J* = 4.6 Hz), 7.85 (s, 1H), 7.78 (d, 1H, *J* = 6.1 Hz), 7.69 (d, 1H, *J* = 9.0 Hz), 7.64 (d, 1H, *J* = 16.0 Hz), 7.47 – 7.41 (m, 2H), 7.25 (t, 2H, *J* = 7.4 Hz), 7.20 (d, 2H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.2 Hz), 5.22 (s, 1H), 2.83 (t, 3H, *J* = 10.2 Hz), 2.76 – 2.68 (m, 2H), 2.68 – 2.60 (m, 2H), 2.08 (t, 2H, *J* = 7.9 Hz). ¹³C NMR (DMSO-d₆) δ (ppm): 173.6, 152.1, 149.3, 143.0, 142.5, 140.9, 136.9, 136.0, 134.6, 129.4, 129.0, 128.8, 128.6, 128.5, 127.5, 127.1, 127.1, 126.7, 125.0, 122.7, 117.6, 52.5, 39.3, 35.8, 33.9, 30.3.

SUPPLEMENTAL INFORMATION



(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropyl)thio)propanoic acid (**13**)

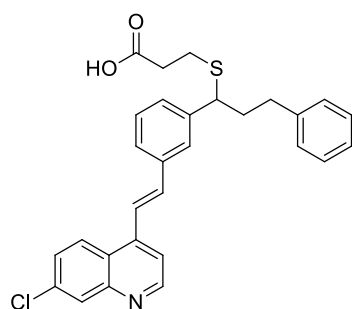
To a solution (THF/EtOH 2/1, 0.22 mL) of **58** (0.051 g, 0.10 mmol, 1.0 eq.) was added aqueous NaOH (2M, 0.15 mL). After stirring 72 h at room temperature, the mixture was neutralized with aqueous 1M HCl until pH = 5 and extracted two times with CH₂Cl₂. The organic layers were pooled, dried over Na₂SO₄ and concentrated under reduced pressure to give a yellow oil (0.031 g). The crude product was purified by chromatography on 4 g C18 column (H₂O:MeOH; 95:5 to 0:10) to afford after lyophilization **13** as a white amorphous solid (0.011 g, 23%). Purity = 98%; tr = 3.00 min; MS (ESI⁺): m/z = 488 [M+H]⁺; HRMS m/z calculated for C₂₉H₂₇ClNO₂S⁺ [M+H]⁺ 488.1451, found 488.1470. ¹H NMR (DMSO-*d*₆) δ (ppm): 8.92 (d, 1H, *J* = 5.0 Hz), 8.64 (d, 1H, *J* = 9.0 Hz), 8.10 (d, 1H, *J* = 16.0 Hz), 8.09 (d, 1H, *J* = 2.0 Hz), 7.92 (d, 1H, *J* = 5.0 Hz), 7.78 (s, 1H), 7.76 (d, 1H, *J* = 7.5 Hz), 7.69 (dd, 1H, *J* = 2.0 and 9.0 Hz), 7.66 (d, 1H, *J* = 16.0 Hz), 7.43 (t, 1H, *J* = 7.5 Hz), 7.34 (d, 1H, *J* = 7.5 Hz), 7.30-7.27 (m, 2H), 7.19-7.09 (m, 3H), 3.88 (t, 1H, *J* = 7.5 Hz), 2.68-2.62 (m, 1H), 2.57-2.53 (m, 1H), 2.45 (t, 2H, *J* = 8.0 Hz), 2.20-2.14 (m, 2H), 2.10-1.99 (m, 2H). ¹³C NMR (DMSO-*d*₆) δ (ppm): 174.8, 152.0, 149.3, 144.2, 143.1, 141.8, 136.8, 136.3, 134.5, 129.3, 128.8, 128.7, 128.6, 128.4, 127.6, 127.4, 127.1, 126.3, 124.9, 122.4, 117.5, 48.6, 38.9, 38.0, 33.7, 28.5.



(+)-(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropyl)thio)propanoic acid ((+)-**13**)

SUPPLEMENTAL INFORMATION

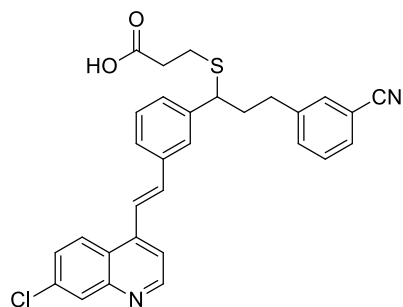
Obtained according to general procedure G from **(+)-58**. Yellow oil (0.077 g, 52%). Purity = 98%; tr = 2.99 min; MS (ESI+): m/z = 488 [M+H]⁺; HRMS m/z calculated for C₂₉H₂₇ClNO₂S⁺ [M+H]⁺ 488.1451, found 488.1464. ¹H NMR (CDCl₃) δ (ppm): 8.71 (d, 1H, J = 4.5 Hz), 8.00-7.97 (m, 2H), 7.72 (s, 1H), 7.63 (d, 1H, J = 16.5 Hz), 7.51-7.45 (m, 2H), 7.40-7.28 (m, 6H + CDCl₃), 7.23-7.20 (m, 3H), 3.94 (t, 1H, J = 7.5 Hz), 2.78-2.70 (m, 4H), 2.60-2.48 (m, 2H), 2.34-2.24 (m, 2H). ¹³C NMR (CDCl₃) δ (ppm): 175.4, 149.6, 147.1, 144.0, 143.4, 141.2, 136.3, 136.3, 135.8, 129.4, 128.6, 128.5, 127.6, 127.1, 127.0, 126.5, 126.1, 125.1, 124.4, 121.7, 116.5, 49.3, 37.7, 34.8, 33.7, 26.2. [α]₂₀^D = + 0.56° (c = 0.5 g/100 mL in MeOH/DMSO (1:1)).



(-)-(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropyl)thio)propanoic acid ((-)-13)

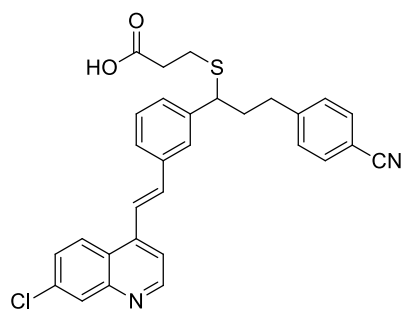
Obtained according to general procedure G from **(-)-58**. Yellow oil (0.077 g, 52%). Purity = 99%; tr = 3.00 min; MS (ESI+): m/z = 488 [M+H]⁺; HRMS m/z calculated for C₂₉H₂₇ClNO₂S⁺ [M+H]⁺ 488.1451, found 488.1461. ¹H NMR (CDCl₃) δ (ppm): 8.71 (br s, 1H), 8.00-7.98 (m, 2H), 7.72 (s, 1H), 7.63 (d, 1H, J = 16.0 Hz), 7.51-7.45 (m, 2H), 7.40-7.29 (m, 6H + CDCl₃), 7.23-7.20 (m, 3H), 3.94 (t, 1H, J = 7.5 Hz), 2.80-2.70 (m, 4H), 2.60-2.47 (m, 2H), 2.34-2.22 (m, 2H). ¹³C NMR (CDCl₃) δ (ppm): 175.4, 149.6, 147.1, 144.0, 143.4, 141.2, 136.3, 136.3, 135.8, 129.4, 128.6, 128.5, 127.6, 127.1, 127.0, 126.5, 126.1, 125.1, 124.4, 121.7, 116.5, 49.3, 37.7, 34.8, 33.7, 26.2. [α]₂₀^D = - 0.41° (c = 0.5 g/100 mL in MeOH/DMSO (1:1)).

SUPPLEMENTAL INFORMATION



(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-cyanophenyl)propyl)thio)propanoic acid (**14**)

Obtained according to general procedure G from **59**. Yellow oil (0.171 g, 82%). Purity = 92%; tr = 2.88 min; MS (ESI⁺): m/z = 513 [M+H]⁺; HRMS m/z calculated for C₃₀H₂₆ClN₂O₂S⁺ [M+H]⁺ 513.1398, found 513.1409. ¹H NMR (CDCl₃) δ (ppm): 8.71 (d, 1H, *J* = 4.4 Hz), 8.00 (d, 1H, *J* = 2.0 Hz), 7.98 (d, 1H, *J* = 9.0 Hz), 7.71 (s, 1H), 7.64 (d, 1H, *J* = 16.1 Hz), 7.56-7.30 (m, 10H), 3.92 (t, 1H, *J* = 7.4 Hz), 2.87-2.66 (m, 4H), 2.63-2.45 (m, 2H), 2.30-2.25 (m, 2H). ¹³C NMR (CDCl₃) δ (ppm): 175.2, 149.5, 147.0, 144.2, 143.0, 142.6, 136.5, 136.2, 135.9, 133.0, 132.0, 129.9, 129.5, 129.3, 128.5, 127.6, 127.2, 126.9, 126.5, 125.1, 124.4, 121.9, 118.9, 116.6, 112.5, 49.2, 37.5, 34.8, 33.3, 26.2.

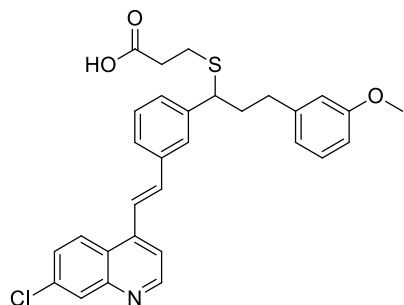


(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-cyanophenyl)propyl)thio)propanoic acid (**15**)

Obtained according to general procedure G from **60**. White solid (0.054 g, 25%). Purity = 92%; tr = 3.17 min; MS (ESI⁺): m/z = 513 [M+H]⁺; HRMS m/z calculated for C₃₀H₂₆ClN₂O₂S⁺ [M+H]⁺ 513.1398, found 513.1384. ¹H NMR (CDCl₃) δ (ppm): 8.75 (d, 1H, *J* = 3.9 Hz), 8.14 (s, 1H), 8.05 (d, 1H, *J* = 9.4 Hz), 7.73 (s, 1H), 7.69 (d, 1H, *J* = 15.9 Hz), 7.60 (d, 2H, *J* = 8.1 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 7.49-7.47 (m, 2H), 7.43 (d, 1H, *J* = 8.8 Hz), 7.41-7.35 (m, 2H), 7.31 (d, 2H, *J* = 8.1 Hz), 3.92 (t, 1H, *J* = 7.4 Hz), 2.85-2.72 (m, 4H), 2.59-2.50 (m, 2H), 2.31-2.24

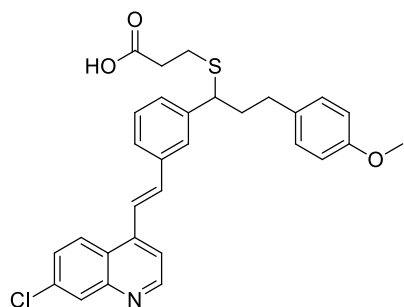
SUPPLEMENTAL INFORMATION

(m, 2H). ^{13}C NMR (CDCl_3) δ (ppm): 174.0, 146.3, 145.5, 142.6, 137.0, 135.7, 134.4, 131.9, 131.8, 129.6, 129.1, 128.8, 128.8, 128.3, 127.7, 127.0, 126.1, 124.7, 123.9, 121.1, 118.5, 115.9, 109.6, 48.7, 36.8, 34.1, 33.4, 25.7.



(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-methoxyphenyl)propyl)thio)propanoic acid (16**)**

Obtained according to general procedure G from **61**. Yellow oil (0.162 g, 69%). Purity = 91%; tr = 3.03 min; MS (ESI⁺): m/z = 518 [M+H]⁺; HRMS m/z calculated for $\text{C}_{30}\text{H}_{29}\text{ClNO}_3\text{S}^+$ [M+H]⁺ 518.1551, found 518.1559. ^1H NMR (CDCl_3) δ (ppm): 8.70 (d, 1H, J = 4.8 Hz), 8.02 (d, 1H, J = 1.5 Hz), 8.00 (d, 1H, J = 9.0 Hz), 7.73 (s, 1H), 7.64 (d, 1H, J = 16.1 Hz), 7.55-7.43 (m, 2H), 7.43-7.18 (m, 6H + CDCl_3), 6.82-6.74 (m, 3H), 3.94 (t, 1H, J = 7.4 Hz), 3.81 (s, 3H), 2.78-2.53 (m, 5H), 2.53-2.45 (m, 1H), 2.28 (m, 2H). ^{13}C NMR (CDCl_3) δ (ppm): 175.3, 159.7, 149.4, 146.9, 144.3, 143.4, 142.8, 136.5, 136.3, 135.9, 129.4, 129.4, 128.7, 127.7, 127.1, 126.9, 126.5, 125.1, 124.4, 121.7, 120.9, 116.5, 114.3, 111.3, 55.2, 49.3, 37.6, 34.8, 33.7, 26.2.

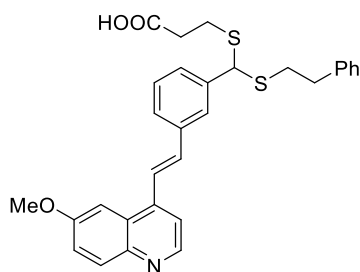


(E)-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-methoxyphenyl)propyl)thio)propanoic acid (17**)**

Obtained according to general procedure G from **62** as a white solid (0.086 g, 44%). Purity = 92%; tr = 3.17 min; MS (ESI⁺): m/z = 518 [M+H]⁺; HRMS m/z calculated for $\text{C}_{30}\text{H}_{29}\text{ClNO}_3\text{S}^+$

SUPPLEMENTAL INFORMATION

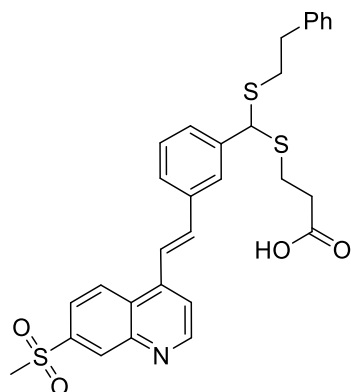
$[M+H]^+$ 518.1551, found 518.1536. ^1H NMR (CDCl_3) δ (ppm): 8.70 (d, 1H, $J = 4.5$ Hz), 8.01-7.98 (m, 2H), 7.72 (s, 1H), 7.63 (d, 1H, $J = 16.0$ Hz), 7.51-7.45 (m, 2H), 7.40-7.34 (m, 3H), 7.31 (d, 1H, $J = 16.0$ Hz), 7.12 (d, 2H, $J = 8.6$ Hz), 6.86 (d, 2H, $J = 8.6$ Hz), 3.93 (s, 1H), 3.81 (s, 3H), 2.82-2.62 (m, 4H), 2.59-2.44 (m, 2H), 2.33-2.20 (m, 2H). ^{13}C NMR (CDCl_3) δ (ppm): 174.4, 157.5, 148.4, 145.9, 144.4, 143.0, 136.4, 135.7, 132.7, 128.9, 128.9, 128.8, 128.7, 128.3, 127.4, 126.7, 126.1, 124.7, 123.9, 121.1, 115.9, 113.4, 54.8, 48.7, 37.4, 34.2, 32.2, 25.6.



(E)-3-(((3-(2-(6-methoxyquinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid
(**18**)

Compound **41** (100 mg, 0.271 mmol) and 6-methoxy-4-methylquinoline (93 mg, 0.542 mmol) were dissolved in acetic anhydride (0.35 mL). The reaction mixture was stirred under microwave irradiation at 180 °C for 4 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated $\text{NaHCO}_3(\text{aq})$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 10:90 to 50:50). The ester was dissolved in MeOH (0.5 mL) and 30N NaOH solution (25 μL) was added. The reaction was stirred at -15 °C for 48 h. The mixture was quenched with 1M HCl and extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by reverse phase chromatography to afford **18** as pale yellow crystals (14 mg, 10%). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 8.73 (d, 1H, $J = 4.6$ Hz), 8.06 (d, 1H, $J = 16.1$ Hz), 7.96 (d, 1H, $J = 9.2$ Hz), 7.84 (t, 2H, $J = 4.5$ Hz), 7.80 (s, 1H), 7.73 (d, 1H, $J = 2.7$ Hz), 7.58 (d, 1H, $J = 16.1$ Hz), 7.48 – 7.42 (m, 3H), 7.28 – 7.16 (m, 5H), 5.24 (s, 1H), 3.99 (s, 3H), 2.88 – 2.79 (m, 3H), 2.77 – 2.62 (m, 3H), 2.10 (dd, 2H, $J = 15.6, 7.8$ Hz).

SUPPLEMENTAL INFORMATION



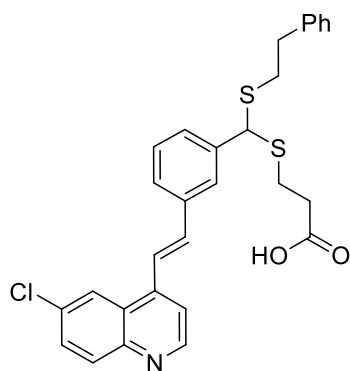
(E)-3-(((3-(2-(7-(methylsulfonyl)quinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid (19**)**

4-methyl-7-(methylsulfonyl)quinoline (35 mg, 0.158 mmol, 1 eq.), isophthalaldehyde (61.7 mg, 0.158 mmol) and zinc chloride (6.4 mg, 0.047 mmol) were dissolved in NMP (0.2 mL) and the mixture was stirred under microwave irradiation at 150 °C for 3 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated $\text{NaHCO}_{3(\text{aq})}$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column ($\text{MeOH}:\text{CH}_2\text{Cl}_2$; 1:99 to 5:95) to afford (E)-3-(2-(7-(methylsulfonyl)quinolin-4-yl)vinyl)benzaldehyde (**40**) as yellow crystals (20 mg, 38%) which was used directly in the next reaction.

Compound **40** (15 mg, 0.045 mmol) was dissolved in 1,1,2,2-tetrachloroethane (0.5 mL) and TFA (100 μL). 2-phenylethane-1-thiol (6 mg, 0.045 mmol) and ethyl 3-mercaptopropanoate (6 mg, 0.045 mmol) were added and the reaction mixture was stirred at rt for 6 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated $\text{NaHCO}_{3(\text{aq})}$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column ($\text{EtOAc}:\text{hexane}$; 15:85 to 70:30). The ester was dissolved in MeOH (0.5 mL) and 30N NaOH solution (80 μL) was added. The reaction was stirred at -15 °C for 16 h. The mixture was quenched with 1M HCl and extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by reverse phase chromatography ($\text{CH}_3\text{CN}:\text{H}_2\text{O}:\text{formic acid}$; 40:60:0.1 to 80:20:0.1) to afford **19** as white crystals (20%). ^1H NMR ($\text{DMSO}-d_6$) δ (ppm): 9.06 (d, 1H, J = 4.6 Hz), 8.86 (d, 1H, J = 8.8 Hz), 8.55 (d, 1H, J = 1.8 Hz), 8.14 (d, 1H, J = 16.1 Hz), 8.09 (m, 2H), 7.86 (s, 1H), 7.81 (d, 1H, J = 6.6 Hz), 7.70 (d, 1H, J = 16.0 Hz), 7.45 (s, 1H), 7.45 (d, 1H, J = 3.0 Hz), 7.25 (t, 2H, J = 7.4 Hz), 7.21 (d, 2H, J = 7.1 Hz), 7.17 (t, 1H, J = 7.3 Hz), 5.24 (s, 1H), 3.38 (s, 3H), 2.83 (t,

SUPPLEMENTAL INFORMATION

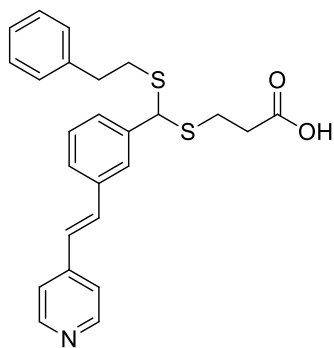
2H, $J = 9.7$ Hz), 2.76 – 2.69 (m, 1H), 2.67 (dd, 1H, $J = 7.7, 4.5$ Hz), 2.62 (dt, 2H, $J = 12.7, 7.8$ Hz), 2.07 (t, 2H, $J = 7.8$ Hz). ^{13}C NMR (DMSO- d_6) δ (ppm): 173.2, 152.7, 147.7, 143.1, 142.5, 141.7, 140.9, 136.8, 136.5, 129.6, 129.4, 129.0, 128.8, 128.7, 128.7, 128.7, 127.6, 127.1, 126.6, 123.1, 122.5, 119.5, 52.4, 43.8, 35.7, 33.9, 30.3.



(E)-3-(((3-(2-(6-chloroquinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid (**20**)

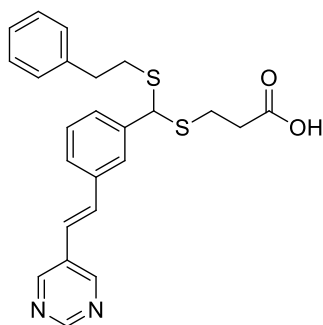
Compound **41** (65 mg, 0.16 mmol) and 6-methoxy-4-methylquinoline (57 mg, 0.32 mmol) were dissolved in acetic anhydride (1 mL). The reaction mixture was stirred under microwave irradiation at 150 °C for 6 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated $\text{NaHCO}_{3(\text{aq})}$ and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 25:75 to 55:45). The ester was dissolved in MeOH (0.5 mL) and 30N NaOH solution (50 μL) was added. The reaction was stirred at -15 °C for 24 h. The mixture was quenched with 1M HCl and extracted with EtOAc. The solvent was removed under reduced pressure and the residue was purified by reverse phase C18 chromatography to ($\text{CH}_3\text{CN}:\text{H}_2\text{O}$; 50:50) afford **20** as white crystals (3 mg, 4%). ^1H NMR (DMSO- d_6) δ (ppm): 8.90 (d, 1H, $J = 4.6$ Hz), 8.66 (s, 1H), 8.10 (d, 1H, $J = 16.0$ Hz), 8.05 (d, 1H, $J = 9.0$ Hz), 7.96 (d, 1H, $J = 4.6$ Hz), 7.86 (d, 1H, $J = 5.8$ Hz), 7.83 (s, 1H), 7.80 (d, 1H, $J = 9.1$ Hz), 7.63 (d, 1H, $J = 15.9$ Hz), 7.44 (s, 1H), 7.43 (d, 1H, $J = 6.1$ Hz), 7.25 (t, 2H, $J = 7.4$ Hz), 7.20 (d, 2H, $J = 7.7$ Hz), 7.17 (t, 1H, $J = 7.2$ Hz), 5.22 (s, 1H), 2.82 (t, 4H, $J = 7.8$ Hz), 2.68 (m, 2H), 2.05 (t, 2H, $J = 7.9$ Hz). ^{13}C NMR (DMSO- d_6) δ (ppm): 151.2, 147.3, 142.5, 142.3, 141.0, 137.0, 136.0, 132.2, 132.0, 130.5, 129.4, 129.0, 128.8, 128.5, 127.9, 126.7, 123.8, 122.7, 118.1, 52.5, 35.8, 33.9, 30.4.

SUPPLEMENTAL INFORMATION



(E)-3-(((phenethylthio)(3-(2-(pyridin-4-yl)vinyl)phenyl)methyl)thio)propanoic acid (21**)**

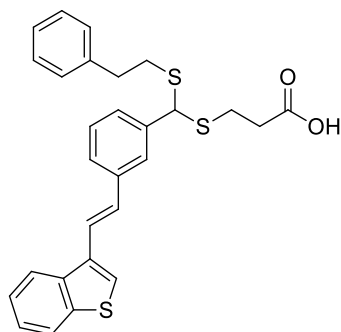
Obtained according to general procedure B from **63**. White solid (0.057 g, 33%). Purity = 97%; tr = 2.62 min; MS (ESI+): m/z = 436 [M+H]⁺; HRMS m/z calculated for C₂₅H₂₆NO₂S₂⁺ [M+H]⁺ 436.1399, found 436.1412. ¹H NMR (DMSO-*d*₆) δ (ppm): 8.56 (dd, 2H, *J* = 1.6 and 4.6 Hz), 7.71 (s, 1H), 7.65–7.53 (m, 4H), 7.41 (dd, 2H, *J* = 1.6 and 4.6 Hz), 7.31–7.13 (m, 6H), 5.25 (s, 1H), 2.90–2.60 (m, 6H), 2.58–2.45 (m, 2H + DMSO-*d*₆). ¹³C NMR (DMSO-*d*₆) δ (ppm): 173.4, 150.5, 144.6, 141.9, 140.7, 136.9, 133.1, 129.5, 129.0, 128.8, 128.3, 126.9, 126.7, 121.4, 52.3, 35.6, 34.7, 33.8, 27.6.



(E)-3-(((phenethylthio)(3-(2-(pyrimidin-5-yl)vinyl)phenyl)methyl)thio)propanoic acid (22**)**

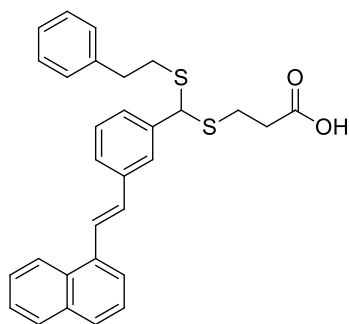
Obtained according to general procedure B from **64**. White solid (0.070 g, 42%). Purity = 99%; tr = 2.57 min; MS (ESI+): m/z = 437 [M+H]⁺; HRMS m/z calculated for C₂₄H₂₅N₂O₂S₂⁺ [M+H]⁺ 437.1352, found 437.1348. ¹H NMR (DMSO-*d*₆) δ (ppm): 12.33 (s, 1H), 9.08 (d, 3H, *J* = 2.3 Hz), 7.69 (s, 1H), 7.59–7.56 (m, 2H), 7.44–7.39 (m, 2H), 7.29–7.24 (m, 3H), 7.22–7.17 (m, 3H), 5.25 (s, 1H), 2.89–2.72 (m, 5H), 2.69–2.63 (m, 1H), 2.57–2.46 (m, 2H + DMSO-*d*₆). ¹³C NMR (DMSO-*d*₆) δ (ppm): 173.4, 157.4, 154.9, 141.8, 137.1, 132.4, 131.2, 129.5, 128.2, 126.7, 126.4, 122.5, 52.4, 34.6, 27.6.

SUPPLEMENTAL INFORMATION



(E)-3-(((3-(2-(benzo[b]thiophen-3-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid **(23)**

Obtained according to general procedure C from **65**. White solid (0.054 g, 23%). Purity = 90%; tr = 3.13 min; MS (ESI⁻): m/z = 489 [M-H]⁻; HRMS m/z calculated for C₂₈H₂₅O₂S₃⁻ [M-H]⁻ 489.1022, found 489.1036. ¹H NMR (DMSO-*d*₆) δ (ppm): 8.24 (d, 1H, *J* = 7.6 Hz), 8.09 (s, 1H), 8.04 (d, 1H, *J* = 7.4 Hz), 7.71 (s, 1H), 7.67 (d, 1H, *J* = 7.4 Hz), 7.61 (d, 1H, *J* = 16.5 Hz), 7.50–7.34 (m, 6H), 7.29–7.25 (m, 2H), 7.23–7.17 (m, 2H), 5.25 (s, 1H), 2.89–2.81 (m, 2H), 2.80–2.62 (m, 4H), 2.59–2.42 (m, 2H + DMSO). ¹³C NMR (DMSO-*d*₆) δ (ppm): 173.4, 141.7, 140.8, 140.3, 137.9, 137.8, 133.9, 129.9, 129.4, 129.0, 128.8, 127.3, 126.7, 126.3, 126.2, 125.2, 125.0, 123.6, 123.5, 122.7, 121.3, 52.4, 35.6, 34.9, 33.8, 27.7.

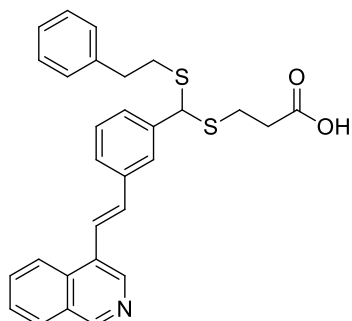


(E)-3-(((3-(2-(naphthalen-1-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid **(24)**

Obtained according to general procedure B from **66**. White solid (0.018 g, 5%). Purity = 97%; tr = 3.12 min; MS (ESI⁻): m/z = 483 [M-H]⁻; HRMS m/z calculated for C₃₀H₂₇O₂S₂⁻ [M-H]⁻ 483.1458, found 483.1452. ¹H NMR (CD₃CN) δ (ppm): 8.35 (d, 1H, *J* = 8.2 Hz), 8.04 (d, 1H, *J* = 16.1 Hz), 7.98–7.94 (m, 1H), 7.89 (t, 2H, *J* = 8.4 Hz), 7.73 (s, 1H), 7.68–7.54 (m, 4H), 7.46–7.39 (m, 2H), 7.38–7.21 (m, 6H), 5.06 (s, 1H), 2.96–2.70 (m, 6H), 2.69–2.49 (m, 2H). ¹³C NMR (CD₃CN) δ (ppm): 173.7, 142.9, 142.0, 139.4, 136.1, 135.2, 132.6, 132.5, 130.5, 130.0, 129.9,

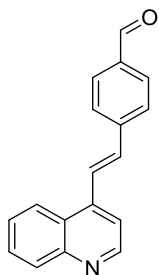
SUPPLEMENTAL INFORMATION

129.8, 129.5, 128.5, 127.7, 127.7, 127.6, 127.4, 127.3, 127.2, 125.1, 124.9, 54.0, 36.9, 35.2, 35.1, 28.7.



(E)-3-(((3-(2-(isoquinolin-4-yl)vinyl)phenyl)(phenethylthio)methyl)thio)propanoic acid (**25**)

Obtained according to general procedure B from **67**. White solid (0.055 g, 21%). Purity = 98%; tr = 2.71 min; MS (ESI⁺): m/z = 486 [M+H]⁺; HRMS m/z calculated for C₂₉H₂₈NO₂S₂⁺ [M+H]⁺ 486.1556, found 486.1548. ¹H NMR (DMSO-*d*₆) δ (ppm): 9.27 (s, 1H), 8.89 (s, 1H), 8.43 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 8.1 Hz), 7.98 (d, 1H, *J* = 16.3 Hz), 7.88 (ddd, 1H, *J* = 8.3, 6.9 and 1.2 Hz), 7.80–7.77 (m, 3H), 7.48–7.39 (m, 3H), 7.36–7.07 (m, 5H), 5.27 (s, 1H), 2.90–2.64 (m, 6H), 2.56 (t, 2H, *J* = 6.9 Hz). ¹³C NMR (DMSO-*d*₆) δ (ppm): 172.9, 151.7, 141.3, 140.3, 140.0, 137.2, 132.9, 132.2, 130.8, 129.0, 128.5, 128.3, 128.1, 127.8, 127.7, 127.5, 127.2, 126.3, 126.2, 123.0, 122.6, 51.9, 35.2, 34.2, 33.3, 27.2.

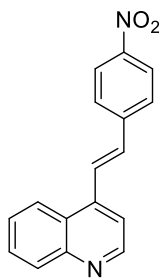


(E)-4-(2-(quinolin-4-yl)vinyl)benzaldehyde (**26**)

Lepidine (1 mL, 7.54 mmol), terephthalaldehyde (3.04 g, 22.7 mmol) and ZnCl₂ (463 mg, 3.41 mmol) were combined and stirred under microwave irradiation at 150 °C for 20 min. The mixture was then dissolved in DMF, diluted with EtOAc and the organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 20:80 to 75:25) to afford **26** as a white solid (1 g, 51%). ¹H NMR (DMSO-*d*₆) δ

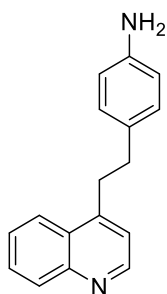
SUPPLEMENTAL INFORMATION

(ppm): 10.04 (s, 1H), 8.92 (d, 1H, $J = 4.6$ Hz), 8.56 (d, 1H, $J = 8.4$ Hz), 8.30 (d, 1H, $J = 16.2$ Hz), 8.06 (m, 3H), 7.97 (m, 2H), 7.89 (d, 1H, $J = 4.6$ Hz), 7.80 (m, 1H), 7.69 (d, 1H, $J = 16.1$ Hz), 7.68 (t, 1H, $J = 7.5$ Hz).



(E)-4-(4-nitrostyryl)quinoline (**28**)

Lepidine (0.5 mL, 3.79 mmol), 4-nitrobenzaldehyde (1.14 g, 7.57 mmol) and ZnCl_2 (231 mg, 1.70 mmol) were combined and stirred under microwave irradiation at 150 °C for 20 min. The resultant solid was triturated in boiling MeOH and filtered to give **28** as a yellow powder (1.04 g, quant). ^1H NMR (DMSO-d_6) δ (ppm): 8.94 (d, 1H, $J = 4.6$ Hz), 8.58 (d, 1H, $J = 8.3$ Hz), 8.36 (d, 1H, $J = 16.2$ Hz), 8.29 (d, 2H, $J = 8.8$ Hz), 8.13 (t, 2H, $J = 9.3$ Hz), 8.07 (d, 1H, $J = 8.3$ Hz), 7.91 (d, 1H, $J = 4.6$ Hz), 7.84 – 7.80 (m, 1H), 7.75 (d, 1H, $J = 16.2$ Hz), 7.70 (dd, 1H, $J = 11.2$, 4.0 Hz). ^{13}C NMR (DMSO-d_6) δ (ppm): 150.8, 148.8, 147.5, 143.6, 141.9, 133.4, 130.1, 130.1, 129.0, 127.6, 127.3, 126.3, 124.7, 124.5, 117.7.

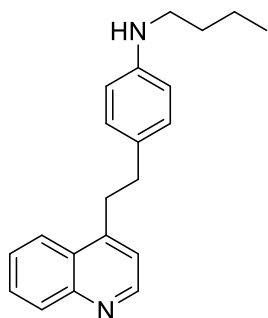


4-(2-(quinolin-4-yl)ethyl)aniline (**29**)

Compound **28** (0.8 g, 2.85 mmol) was dissolved in DMF (20 mL) and AcOH (150 μL). Pd/C (10%, 80 mg, 0.28 mmol) was added, the reaction was put under an atmosphere of H_2 and stirred at rt for 24 h. The mixture was diluted in EtOAc and washed with saturated NaHCO_3 and brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated under

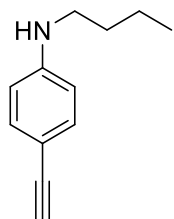
SUPPLEMENTAL INFORMATION

reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 50:50 to 100:0) to afford **29** (400 mg, 57%). ^1H NMR (DMSO- d_6) δ (ppm): 8.76 (d, 1H, J = 4.3 Hz), 8.19 (d, 1H, J = 8.3 Hz), 8.02 (d, 1H, J = 8.3 Hz), 7.75 (t, 1H, J = 7.5 Hz), 7.63 (t, 1H, J = 7.5 Hz), 7.32 (d, 1H, J = 4.2 Hz), 6.92 (d, 2H, J = 8.0 Hz), 6.49 (d, 2H, J = 8.1 Hz), 4.86 (s, 2H), 3.32 – 3.24 (m, 2H), 2.87 – 2.79 (m, 2H). ^{13}C NMR (DMSO- d_6) δ (ppm): 150.6, 148.3, 148.0, 147.2, 130.2, 129.5, 129.3, 128.5, 127.5, 126.9, 124.4, 121.6, 114.5, 35.5, 34.2.



N-butyl-4-(2-(quinolin-4-yl)ethyl)aniline (**30**)

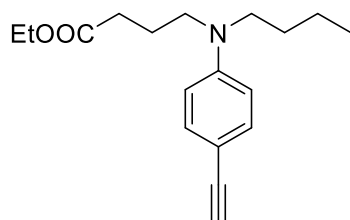
Compound **29** (100 mg, 0.405 mmol) and butyraldehyde (0.38 g, 0.448 mmol) were dissolved in THF (5 mL) under inert conditions. $\text{NaBH}(\text{OAc})_3$ (141 mg, 0.672 mmol) was added and the reaction was stirred at rt for 2 h. The reaction was quenched with saturated NaHCO_3 and extracted with EtOAc. The organic phase was washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The resultant oil was purified by flash chromatography on a silica gel column (EtOAc:hexane; 40:60 to 100:0) to afford **30** as white crystals (75 mg, 30%). ^1H NMR (DMSO- d_6) δ (ppm): 8.76 (d, 1H, J = 4.4 Hz), 8.20 (d, 1H, J = 7.9 Hz), 8.02 (d, 1H, J = 7.8 Hz), 7.82 – 7.71 (m, 1H), 7.63 (ddd, 1H, J = 8.2, 6.9, 1.2 Hz), 7.34 (d, 1H, J = 4.4 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.51 (dd, 2H, J = 31.7, 8.3 Hz), 5.33 (s, 1H), 3.31 – 3.26 (m, 2H), 2.95 (d, 2H, J = 3.2 Hz), 2.89 – 2.81 (m, 2H), 1.51 (dt, 2H, J = 14.7, 7.2 Hz), 1.37 (dq, 2H, J = 14.4, 7.3 Hz), 0.91 (t, 3H, J = 7.3 Hz).



SUPPLEMENTAL INFORMATION

N-butyl-4-ethynylaniline (**31**)

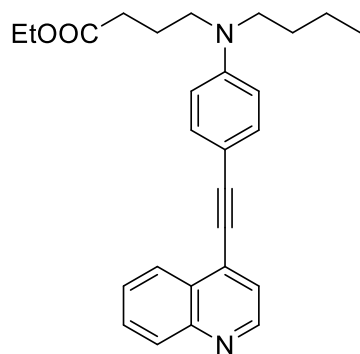
4-ethynylaniline (250 mg, 2.14 mmol) and butyraldehyde (192 mg, 2.14 mmol) were dissolved in THF (2 mL) under inert conditions and the reaction was stirred at rt for 3 h. NaBH(OAc)₃ (901 mg, 4.27 mmol) was added and the reaction was stirred at rt for 1 h. The reaction was quenched with saturated NaHCO₃ and extracted with EtOAc. The organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The resultant oil was purified by flash chromatography on a silica gel column (EtOAc:hexane; 0:100 to 10:90) to afford **31** as a yellow oil (150 mg, 41%). ¹H NMR (DMSO-d₆) δ (ppm): 7.16 (d, 2H, *J* = 8.7 Hz), 6.51 (d, 2H, *J* = 8.8 Hz), 3.79 (s, 1H), 3.00 (dd, 2H, *J* = 12.5, 7.0 Hz), 1.52 (m, 2H), 1.37 (dq, 2H, *J* = 14.1, 7.1 Hz), 0.91 (t, 3H, *J* = 7.3 Hz).



Ethyl 4-(butyl(4-ethynyl)phenyl)amino)butanoate (**32**)

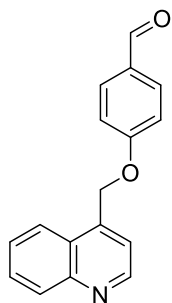
Compound **31** (55 mg, 0.32 mmol) and ethyl 4-bromobutanoate (227 mg, 1.6 mmol) were dissolved in DMF (0.5 mL). K₂CO₃ (130 mg, 0.95 mmol) was added and the reaction was stirred under microwave irradiation at 90 °C for 8 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 0:100 to 15:85) to afford **32** as a yellow oil (25 mg, 28%). ¹H NMR (500 MHz, DMSO) δ 7.24 (d, 2H, *J* = 8.9 Hz), 6.64 (d, 2H, *J* = 9.0 Hz), 4.07 (q, 2H, *J* = 7.1 Hz), 3.32 – 3.23 (m, 4H), 2.40 – 2.33 (m, 2H), 1.79 – 1.70 (m, 2H), 1.48 (dt, 2H, *J* = 15.0, 7.5 Hz), 1.36 – 1.27 (m, 2H), 1.19 (t, 3H, *J* = 7.1 Hz), 0.92 (t, 3H, *J* = 7.3 Hz).

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Ethyl 4-(butyl(4-(quinolin-4-ylethynyl)phenyl)amino)butanoate (33)

Compound **32** (8 mg, 0.03 mmol), 4-bromoquinoline (6.5 mg, 0.031 mmol) and triethylamine (7.8 μ L, 0.06 mmol) were dissolved in DMF (0.4 mL) under inert conditions. CuI (1.8 mg, 0.005 mmol) and $\text{PdCl}_2(\text{PPh}_3)_2$ (2 mg, 0.003 mmol) were added and the reaction was stirred under microwave irradiation at 60 $^\circ\text{C}$ for 1.5 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 25:75 to 55:45) to afford **33** (9.3 mg, 80%). ^1H NMR (DMSO-d_6) δ (ppm): 8.87 (d, 1H, J = 4.5 Hz), 8.39 – 8.33 (m, 1H), 8.06 (d, 1H, J = 8.3 Hz), 7.86 – 7.81 (t, 1H), 7.75 – 7.71 (t, 1H), 7.62 (d, 1H, J = 4.5 Hz), 7.53 (d, 2H, J = 8.9 Hz), 6.77 (d, 2H, J = 9.0 Hz), 4.08 (q, 2H, J = 7.1 Hz), 3.39 – 3.34 (m, 4H), 2.38 (t, 2H, J = 6.7 Hz), 1.84 – 1.74 (m, 2H), 1.57 – 1.48 (m, 2H), 1.38 – 1.29 (m, 2H), 1.19 (t, 3H, J = 7.1 Hz), 0.93 (t, 3H, J = 7.4 Hz).

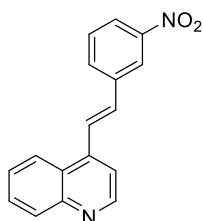


4-(quinolin-4-ylmethoxy)benzaldehyde (34)

4-hydroxybenzaldehyde (80.5 mg, 0.66 mmol), 4-(bromomethyl)quinoline (50 mg, 0.22 mmol) and K_2CO_3 (120 mg, 0.88 mmol) were dissolved in THF (2 mL) and H_2O (150 μ L). KI (73 mg, 0.44 mmol) was added and the reaction was stirred at rt for 48 h. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO_3 and brine, dried over

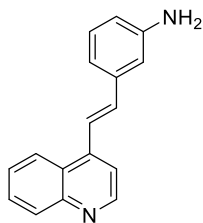
SUPPLEMENTAL INFORMATION

Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexane; 35:65 to 65:35) to afford **34** as a white powder (23.2 mg, 40%). ¹H NMR (DMSO-d₆) δ (ppm): 9.92 (s, 1H), 8.95 (d, J = 4.3 Hz, 1H), 8.21 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H), 7.94 (d, J = 8.7 Hz, 2H), 7.84 (dd, J = 11.2, 4.1 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.69 (d, J = 4.3 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 5.84 (s, 2H). ¹³C NMR (DMSO-d₆) δ (ppm): 192.26, 163.83, 151.3, 148.51, 142.54, 132.74, 131.05, 130.54, 130.47, 127.79, 126.34, 124.84, 120.31, 116.36, 67.47



(E)-4-(3-nitrostyryl)quinoline (**35**)

Lepidine (143 mg, 1.0 mmol) and 3-nitrobenzaldehyde (166 mg, 1.1 mmol) were dissolved in NMP (0.47 mL). ZnCl₂ (136 mg, 1.0 mmol) was added and the reaction was stirred under microwave irradiation at 150 °C for 20 min. The mixture was diluted with a solution of NH₃-H₂O/NH₄Cl/H₂O (1:1:10, v/v/v) and extracted with CH₂Cl₂. The organic phase was washed with a solution of saturated NH₄Cl/NH₃-H₂O (10:1, v/v), saturated NaHCO_{3(aq)} and then concentrated under reduced pressure. The residue was purified by flash chromatography (hexane:EtOAc; 90:10 to 10:90) then triturated in MTBE/hexanes (1:1) to afford **35** as a yellow solid (92 mg, 34%). MS (ESI⁺): m/z = 277.

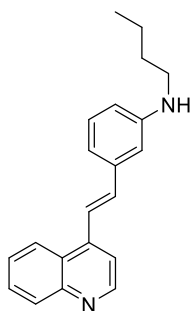


(E)-3-(2-(quinolin-4-yl)vinyl)aniline (**36**)

Compound **35** (22 mg, 0.08 mmol) and SnCl₂·2H₂O (230 mg, 0.93 mmol) were suspended in EtOH (1 mL) and the reaction was stirred at reflux for 14 h. The solvent was removed under reduced pressure. The residue was dissolved in 0.1M HCl and purified by reverse phase

SUPPLEMENTAL INFORMATION

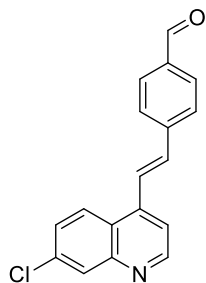
chromatography (H₂O, MeOH) to afford **36** as an amorphous solid (8.9 mg, 45%). ¹H NMR (MeOD-d₄) δ (ppm): 8.89 (d, 1H, *J* = 5.6 Hz), 8.60 (dd, 1H, *J* = 8.7, 1.2 Hz), 8.19 – 8.08 (m, 2H), 8.07 – 7.96 (m, 2H), 7.86 (ddd, 1H, *J* = 8.4, 6.9, 1.3 Hz), 7.72 (d, 1H, *J* = 16.0 Hz), 7.36 – 7.23 (m, 3H), 6.95 (dt, 1H, *J* = 6.2, 2.4 Hz). ¹³C NMR (MeOD-d₄) δ (ppm): 152.4, 145.9, 145.3, 142.4, 142.2, 138.2, 134.5, 131.0, 130.0, 127.7, 126.0, 124.2, 122.0, 121.6, 120.3, 117.8, 117.3, 49.5, 49.5, 49.3, 49.3, 49.2, 49.0, 48.8, 48.7, 48.5.



(E)-N-butyl-3-(2-(quinolin-4-yl)vinyl)aniline (**37**)

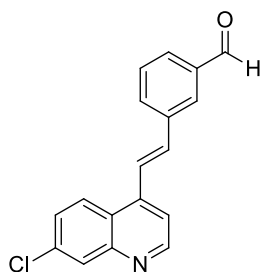
Compound **36** (20 mg, 0.081 mmol) and NaBH(OAc)₃ (20.7 mg, 0.097 mmol) were dissolved in CH₂Cl₂ (0.8 mL). AcOH (10 μL, 0.162 mmol) and butyraldehyde (5.6 mg, 0.077 mmol) were added and the reaction was stirred at rt for 1 h. The reaction was quenched with 1M HCl and the organic phase was separated. The aqueous phase was extracted with CH₂Cl₂, and the combined organic phases were concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (hexane:EtOAc; 90:10 to 10:90) to afford **37** as a yellow oil (9.8 mg, 40%). ¹H NMR (CDCl₃) δ (ppm): 8.89 (d, 1H, *J* = 4.6 Hz), 8.22 (dd, 1H, *J* = 8.5, 0.9 Hz), 8.15 (dd, 1H, *J* = 8.4, 0.6 Hz), 7.74 (ddd, 2H, *J* = 12.3, 8.8, 8.3 Hz), 7.59 (ddd, 2H, *J* = 8.4, 6.8, 1.7 Hz), 7.28 (d, 1H, *J* = 16.0 Hz), 7.23 (t, 1H, *J* = 7.8 Hz), 6.98 (d, 1H, *J* = 7.6 Hz), 6.86 – 6.80 (m, 1H), 6.62 (ddd, 1H, *J* = 8.1, 2.3, 0.7 Hz), 3.26 – 3.13 (m, 2H), 1.65 (ddd, 2H, *J* = 14.6, 8.3, 6.5 Hz), 1.47 (dq, 2H, *J* = 14.7, 7.4 Hz), 0.99 (t, 3H, *J* = 7.4 Hz). ¹³C NMR (CDCl₃) δ (ppm): 150.1, 149.1, 148.5, 143.6, 137.6, 136.2, 130.0, 129.8, 129.5, 126.6, 126.6, 123.7, 122.5, 117.2, 116.3, 113.6, 111.2, 43.8, 31.8, 20.5, 14.1.

SUPPLEMENTAL INFORMATION



(E)-4-(2-(7-chloroquinolin-4-yl)vinyl)benzaldehyde (**38**)

7-chloro-4-methylquinoline (150 mg, 0.85 mmol), terephthalaldehyde (340 mg, 2.54 mmol) and ZnCl_2 (51.8 mg, 0.381 mmol) were combined and stirred under microwave irradiation at 150 °C for 20 min. The mixture was then dissolved in DMF, diluted with EtOAc and the organic phase was washed with saturated NaHCO_3 and brine, dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc/hexane; 20:80 to 100:0) to afford **38** as yellow crystals (150 mg, 60%). ^1H NMR (DMSO-d_6) δ (ppm): 10.04 (s, 1H), 8.96 (d, 1H, J = 4.7 Hz), 8.64 (d, 1H, J = 9.1 Hz), 8.30 (d, 1H, J = 16.2 Hz), 8.11 (d, 1H, J = 2.2 Hz), 8.08 (d, 2H, J = 8.3 Hz), 7.98 (d, 2H, J = 8.3 Hz), 7.95 (d, 1H, J = 4.7 Hz), 7.73 (d, 1H, J = 16.1 Hz), 7.71 (dd, 1H, J = 9.0, 2.3 Hz).

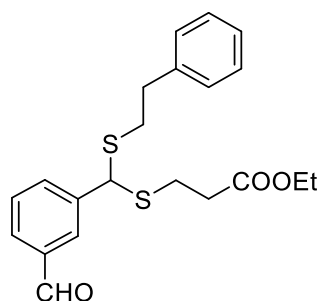


(E)-3-(2-(7-chloroquinolin-4-yl)vinyl)benzaldehyde (**39**)

7-Chloro-4-methylquinoline (4.01 g, 22.6 mmol, 1 eq.), isophthalaldehyde (5.75 g, 42.9 mmol, 1.9 eq.) and zinc chloride (1.38 g, 10.15 mmol, 0.45 eq.) were added neat to a 10-20 mL microwave vessel. The compounds were heated in the sealed microwave vessel until dissolution. The dark brown reaction mixture was heated under microwave irradiation at 150 °C for 20 min. The obtained solid product was dissolved in DMF and poured in EtOAc. This solution was washed twice with brine and saturated aqueous NaHCO_3 solution (1:1) and one time with brine to remove the zinc chloride salt. The organic phase was dried over

SUPPLEMENTAL INFORMATION

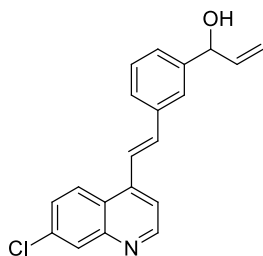
Na₂SO₄ and concentrated under reduced pressure to give a yellowish residue. The crude product was purified by flash chromatography on 120 g silica gel column (hexane/EtOAc 80:20 to 0:10 (v/v) in 30 min) to afford **39** as a yellowish amorphous solid (5.35 g, 81%). MS (ESI⁺): *m/z* = 294 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.08 (s, 1H), 8.90 (d, 1H, *J* = 4.5 Hz), 8.15-8.13 (m, 3H), 7.86-7.81 (m, 3H), 7.62-7.58 (m, 2H), 7.54 (dd, 1H, *J* = 2.0 and 9.0 Hz), 7.36 (d, 1H, *J* = 16 Hz). ¹³C NMR (CDCl₃) δ (ppm): 192.2, 151.4, 149.3, 142.9, 137.5, 137.2, 135.7, 134.5, 133.2, 130.6, 129.9, 129.2, 127.9, 127.7, 125.1, 124.9, 124.5, 117.6.



Ethyl 3-(((3-formylphenyl)(phenethylthio)methyl)thio)propanoate (41)

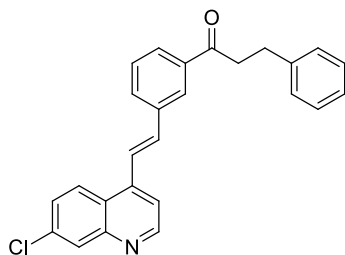
Isophthalaldehyde (500 mg, 3.73 mmol) and TsOH.H₂O (212 mg, 2.24 mmol) were dissolved in toluene (15 mL) and 4Å molecular sieves were added. 2-phenylethane-1-thiol (1.19 mL, 8.95 mmol) and ethyl 3-mercaptopropanoate (1.13 mL, 8.95 mmol) were added and the reaction mixture was stirred at reflux for 1.5 h under inert conditions. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO_{3(aq)} and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexanes; 0:100 to 20:80) to afford **41** as an amorphous solid. ¹H NMR (DMSO-*d*₆) δ (ppm): 10.02 (s, 1H), 7.96 (s, 1H), 7.85 (d, 1H, *J* = 7.6 Hz), 7.76 (d, 1H, *J* = 7.8 Hz), 7.61 (t, 1H, *J* = 7.7 Hz), 7.27 (t, 2H, *J* = 7.4 Hz), 7.19 (t, 1H, *J* = 8.6 Hz), 7.18 (d, 2H, *J* = 7.5 Hz), 5.37 (s, 1H), 4.04 (q, 2H, *J* = 7.1 Hz), 2.87 – 2.79 (m, 3H), 2.79 – 2.71 (m, 2H), 2.65 (dt, 1H, *J* = 18.5, 6.3 Hz), 2.60 (dd, 2H, *J* = 11.9, 6.8 Hz), 1.15 (t, 3H, *J* = 7.1 Hz).

SUPPLEMENTAL INFORMATION



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)prop-2-en-1-ol (**42**)

A suspension of the aldehyde **39** (3.00 g, 10.20 mmol, 1 eq.) in toluene (24 mL) at 0 °C was degassed by purging three times with vacuum and nitrogen. Vinylmagnesium bromide (1.0 M in THF, 10.8 mL, 10.8 mmol, 1.2 eq.) was added dropwise over 20 min while the internal temperature was maintained at < 10 °C. The brown reaction mixture was stirred at 0–5 °C for 2.5 h and quenched by slowly adding 10% aqueous ammonium acetate (25 mL). This two-phase mixture was stirred for 1 h to ensure the solvolysis of the magnesium salts. The separated organic layer was washed with water (2 X 25 mL), dried over Na₂SO₄ and concentrated in vacuo to give an orange residue. The crude product was purified by flash chromatography on 80 g silica gel column (hexane:EtOAc; 10:0 to 50:50) to afford the **42** as a colorless oil (1.71 g, 52%). MS (ESI⁺): *m/z* = 322 [M+H]⁺. ¹H NMR (CDCl₃) δ (ppm): 8.87 (d, 1H, *J* = 4.5 Hz), 8.16–8.12 (m, 2H), 7.74 (d, 1H, *J* = 16.0 Hz), 7.67 (s, 1H), 7.58 (d, 1H, *J* = 4.5 Hz), 7.56–7.53 (m, 2H), 7.46–7.40 (m, 2H), 7.35 (d, 1H, *J* = 16.0 Hz), 6.17–6.10 (m, 1H), 5.45 (td, 1H, *J* = 1.5 and 17.0 Hz), 5.33 (d, 1H, *J* = 6.0 Hz), 5.29 (td, 1H, *J* = 1.5 and 10.0 Hz). ¹³C NMR (CDCl₃) δ (ppm): 151.1, 149.0, 147.5, 143.4, 143.2, 140.1, 136.6, 135.7, 135.4, 129.2, 128.9, 127.5, 127.1, 126.6, 125.0, 125.0, 122.5, 117.2, 115.6, 75.2.

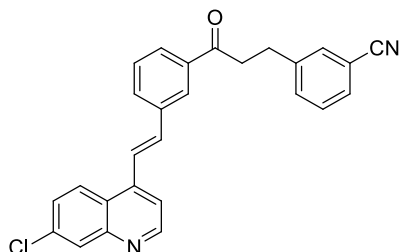


(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropan-1-one (**43**)

Obtained according to general procedure A from **42** and 4-iodobenzene. Yellow oil (0.270 g, 73%). MS (ESI⁺): *m/z* = 398 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.92 (d, 1H, *J* = 4.5 Hz), 8.22 (s, 1H), 8.17–8.15 (m, 2H), 7.95 (d, 1H, *J* = 7.5 Hz), 7.83–7.80 (m, 2H), 7.60–7.53 (m, 3H),

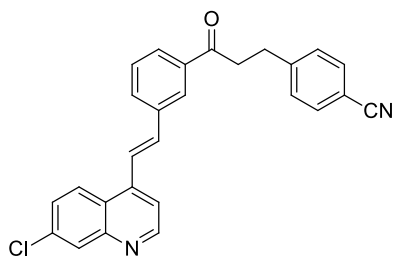
SUPPLEMENTAL INFORMATION

7.39-7.25 (m, 6H), 3.39 (t, 2H, $J = 7.8$ Hz), 3.14 (t, 2H, $J = 7.8$ Hz). ^{13}C NMR (CDCl_3) δ (ppm): 198.9, 151.2, 149.1, 142.7, 141.1, 137.5, 136.8, 135.4, 134.7, 131.5, 129.2, 129.0, 128.6, 128.5, 128.4, 127.6, 126.5, 126.3, 124.9, 124.7, 123.7, 117.3, 40.7, 30.1.



(E)-3-(3-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-oxopropyl)benzonitrile (44)

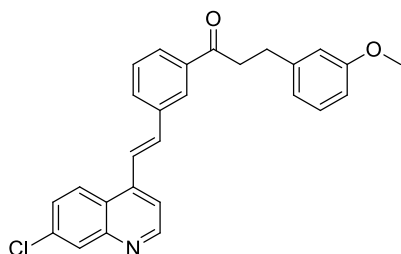
Obtained according to general procedure A from **42** and 3-iodobenzonitrile. Colorless oil (0.079 g, 69%). MS (ESI⁺): $m/z = 423$ $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3) δ (ppm): 8.91 (d, 1H, $J = 4.0$ Hz), 8.21 (s, 1H), 8.17-8.15 (m, 2H), 7.95 (d, 1H, $J = 7.5$ Hz), 7.84-7.80 (m, 2H), 7.60-7.52 (m, 6H), 7.43 (t, 1H, $J = 8.0$ Hz), 7.37 (d, 1H, $J = 16.0$ Hz), 3.40 (t, 2H, $J = 7.5$ Hz), 3.17 (t, 2H, $J = 7.5$ Hz). ^{13}C NMR (CDCl_3) δ (ppm): 198.0, 151.2, 149.1, 142.6, 142.6, 137.2, 137.0, 135.4, 134.6, 133.2, 132.0, 131.6, 130.0, 129.3, 129.0, 128.3, 127.6, 126.5, 124.9, 124.7, 123.9, 118.9, 117.4, 112.6, 39.8, 29.4.



(E)-4-(3-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-oxopropyl)benzonitrile (45)

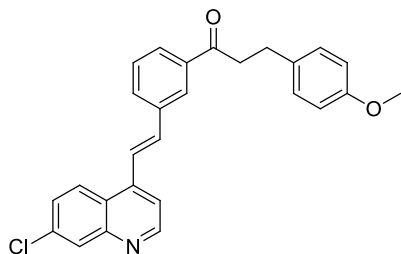
Obtained according to general procedure A from **42** and 4-iodobenzonitrile. White solid (0.347 g, 59%). MS (ESI⁺): $m/z = 423$ $[\text{M}+\text{H}]^+$; ^1H NMR (CDCl_3) δ (ppm): 8.92 (d, 1H, $J = 4.5$ Hz), 8.21 (s, 1H), 8.17-8.15 (m, 2H), 7.94 (d, 1H, $J = 7.5$ Hz), 7.85-7.82 (m, 2H), 7.63-7.55 (m, 5H), 7.42 (d, 2H, $J = 7.0$ Hz), 7.38 (d, 1H, $J = 16.0$ Hz), 3.41 (t, 2H, $J = 7.5$ Hz), 3.20 (t, 2H, $J = 7.5$ Hz). ^{13}C NMR (CDCl_3) δ (ppm): 197.9, 151.2, 149.1, 146.8, 142.7, 137.2, 137.0, 135.5, 134.6, 132.4, 131.7, 129.4, 129.3, 129.0, 128.3, 127.7, 126.5, 124.9, 124.7, 124.0, 118.9, 117.4, 110.2, 39.6, 29.9.

SUPPLEMENTAL INFORMATION



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-methoxyphenyl)propan-1-one (46)

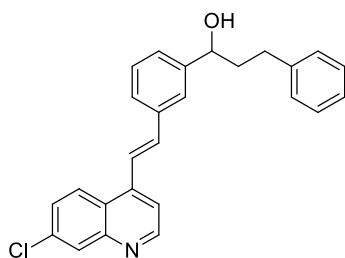
Obtained according to general procedure A from **42** and 3-iodoanisole. Colorless oil (0.090 g, 85%). MS (ESI⁺): m/z = 428 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.92 (d, 1H, J = 4.5 Hz), 8.22 (s, 1H), 8.18-8.15 (m, 2H), 7.95 (d, 1H, J = 8.0 Hz), 7.84-7.81 (m, 2H), 7.61-7.55 (m, 3H), 7.37 (d, 1H, J = 16.0 Hz), 7.26 (t, 1H, J = 8.0 Hz), 6.89 (d, 1H, J = 8.0 Hz), 6.87-6.86 (m, 1H), 6.80 (dd, 1H, J = 2.5 and 8.0 Hz), 3.83 (s, 3H), 3.39 (t, 2H, J = 7.5 Hz), 3.11 (t, 2H, J = 7.5 Hz). ¹³C NMR (CDCl₃) δ (ppm): 198.9, 159.8, 151.2, 149.2, 142.8, 142.7, 137.5, 136.9, 135.4, 134.7, 131.5, 129.6, 129.2, 129.0, 128.4, 127.6, 126.5, 124.9, 124.7, 123.8, 120.8, 117.4, 114.4, 111.4, 55.2, 40.6, 30.2.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-methoxyphenyl)propan-1-one (47)

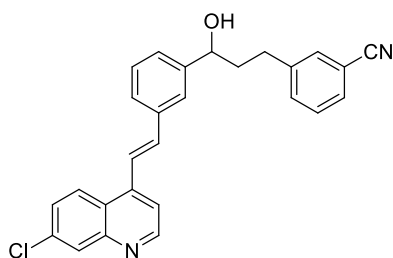
Obtained according to general procedure A from **42** and 4-iodoanisole. White solid (0.501 g, 47%). MS (ESI⁺): m/z = 428 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.90 (d, 1H, J = 4.0 Hz), 8.20 (s, 1H), 8.16-8.13 (m, 2H), 7.94 (d, 1H, J = 7.6 Hz), 7.82-7.78 (m, 2H), 7.59-7.51 (m, 3H), 7.36 (d, 1H, J = 16.4 Hz), 7.22 (d, 2H, J = 8.2 Hz), 6.87 (d, 2H, J = 8.2 Hz), 3.81 (s, 3H), 3.35 (t, 2H, J = 7.6 Hz), 3.07 (t, 2H, J = 7.6 Hz). ¹³C NMR (CDCl₃) δ (ppm): 199.1, 158.1, 151.2, 149.1, 142.7, 137.5, 136.8, 135.4, 134.7, 133.1, 131.4, 129.4, 129.4, 129.2, 129.0, 128.4, 127.6, 126.5, 124.9, 123.7, 117.3, 114.0, 55.3, 40.9, 29.3.

SUPPLEMENTAL INFORMATION



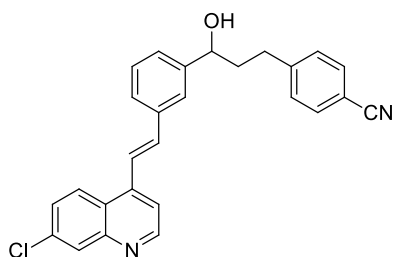
(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropan-1-ol (48)

Obtained from **43** according to general procedure D with no purification step. Yellow oil (0.121 g, 81%). MS (ESI⁺): m/z = 400 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.90 (d, 1H, J = 4.5 Hz), 8.19-8.15 (m, 2H), 7.77 (d, 1H, J = 16.5 Hz), 7.65 (s, 1H), 7.61 (d, 1H, J = 4.5 Hz), 7.56-7.55 (m, 2H), 7.44 (t, 1H, J = 4.5 Hz), 7.38-7.22 (m, 7H + CDCl₃), 4.80 (dd, 1H, J = 5.5 and 8.0 Hz), 2.84-2.77 (m, 2H), 2.26-2.19 (m, 1H), 2.08-2.15 (m, 1H).



(E)-3-(3-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-hydroxypropyl)benzonitrile (49)

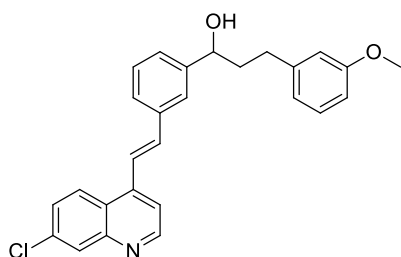
Obtained from **44** according to general procedure D with no purification step. Yellow oil (0.021 g, quantitative). MS (ESI⁺): m/z = 425 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.87 (br s, 1H), 8.17-8.12 (m, 2H), 7.75 (d, 1H, J = 16.0 Hz), 7.62-7.59 (m, 2H), 7.56-7.33 (m, 9 H), 4.78 (dd, 1H, J = 5.5 and 8.0 Hz), 2.89-2.80 (m, 2H), 2.24-2.16 (m, 1H), 2.12-2.05 (m, 1H). ¹³C NMR (CDCl₃) δ (ppm): 151.0, 148.9, 145.2, 143.2, 136.6, 135.6, 135.4, 133.1, 132.0, 129.8, 129.2, 129.2, 128.8, 127.6, 126.7, 126.6, 125.0, 124.5, 122.6, 119.0, 117.2, 112.4, 73.3, 40.2, 31.6.



(E)-4-(3-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-hydroxypropyl)benzonitrile (50)

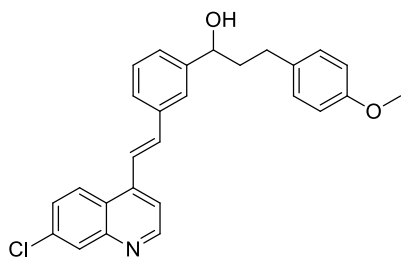
SUPPLEMENTAL INFORMATION

Obtained according to general procedure D from **45**. The crude product was purified by flash chromatography on a silica gel column (hexanes:EtOAc; 90:10 to 30:70) to afford **50** as a yellow oil (0.307 g, 88%). MS (ESI+): m/z = 425 $[M+H]^+$; ^1H NMR (CDCl_3) δ (ppm): 8.84 (d, 1H, J = 3.6 Hz), 8.13 (d, 1H, J = 9.2 Hz), 8.09 (d, 1H, J = 2.0 Hz), 7.73 (d, 1H, J = 16.0 Hz), 7.60-7.53 (m, 6H), 7.44 (t, 1H, J = 7.6 Hz), 7.37-7.30 (m, 4H), 4.79 (dd, 1H, J = 5.6 and 8.0 Hz), 2.94-2.79 (m, 2H), 2.26-2.19 (m, 1H), 2.10-2.06 (m, 1H). ^{13}C NMR (CDCl_3) δ (ppm): 151.0, 149.0, 147.5, 145.3, 143.1, 136.6, 135.6, 135.4, 132.2, 129.3, 129.2, 129.2, 128.8, 127.5, 126.6, 126.6, 124.9, 124.5, 122.5, 119.0, 117.2, 109.8, 73.3, 40.0, 32.3.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-methoxyphenyl)propan-1-ol (**51**)

Obtained from **46** according to general procedure D with no purification step. Colorless oil (0.006 g, 60%). MS (ESI+): m/z = 430 $[M+H]^+$; ^1H NMR (CDCl_3) δ (ppm): 8.89 (d, 1H, J = 4.8 Hz), 8.17 (d, 1H, J = 8.8 Hz), 8.13 (d, 1H, J = 2.0 Hz), 7.76 (d, 1H, J = 16.4 Hz), 7.60 (s, 1H), 7.59-7.46 (m, 3H), 7.44 (t, 1H, J = 8.0 Hz), 7.39-7.18 (m, 3H), 6.86-6.76 (m, 3H), 4.80-4.77 (dd, 1H, J = 5.6 and 7.2 Hz), 3.82 (s, 3H), 2.86-2.67 (m, 2H), 2.27-2.17 (m, 1H), 2.15-2.13 (m, 1H).

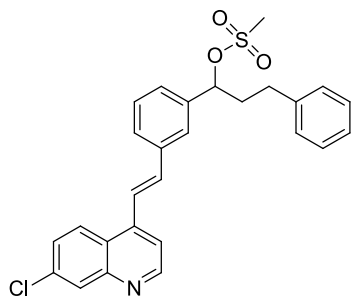


(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-methoxyphenyl)propan-1-ol (**52**)

Obtained according to general procedure D from **47**. The crude product was purified by flash chromatography on a silica gel column (hexanes:EtOAc; 90:10 to 50:50) to afford **52** as a colorless oil (0.180 g, 75%). MS (ESI+): m/z = 430 $[M+H]^+$; ^1H NMR (CDCl_3) δ (ppm): 8.86 (s,

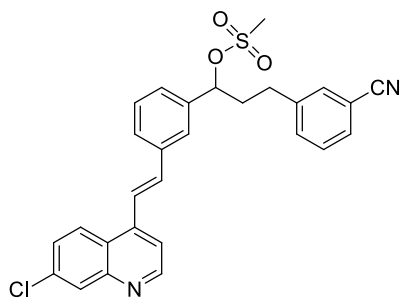
SUPPLEMENTAL INFORMATION

¹H), 8.15 (d, 1H, *J* = 9.2 Hz), 8.11 (d, 1H, *J* = 2.0 Hz), 7.74 (d, 1H, *J* = 16.0 Hz), 7.63 (s, 1H), 7.59-7.52 (m, 3H), 7.43 (t, 1H, *J* = 7.6 Hz), 7.37 (d, 1H, *J* = 7.6 Hz), 7.34 (d, 1H, *J* = 16.0 Hz), 7.16 (d, 2H, *J* = 8.4 Hz), 6.87 (d, 2H, *J* = 8.4 Hz), 4.80-4.77 (m, 1H), 3.81 (s, 3H), 2.78-2.69 (m, 2H), 2.24-2.14 (m, 1H), 2.12-2.03 (m, 1H). ¹³C NMR (CDCl₃) δ (ppm): 157.9, 151.1, 149.0, 145.7, 143.2, 136.4, 135.7, 135.3, 133.6, 129.3, 129.3, 129.1, 128.8, 127.5, 126.7, 126.5, 125.0, 124.5, 122.3, 117.2, 113.9, 73.5, 55.3, 40.8, 31.2.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropyl methanesulfonate (**53**)

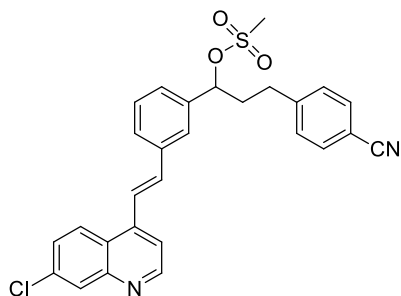
Obtained according to general procedure E from **48**. Yellow oil (0.096 g, quantitative). MS (ESI⁺): *m/z* = 478 [M+H]⁺.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-cyanophenyl)propyl methanesulfonate (**54**)

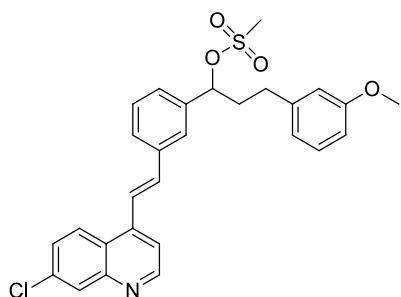
Obtained according to general procedure E from **49**. Yellow oil (0.482 g, quantitative). MS (ESI⁺): *m/z* = 503 [M+H]⁺.

SUPPLEMENTAL INFORMATION



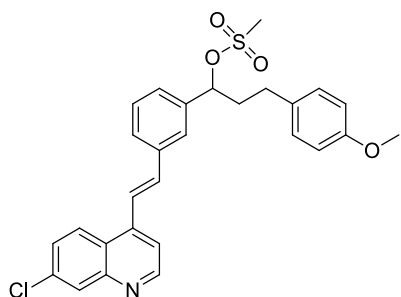
(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-cyanophenyl)propyl methanesulfonate
(55)

Obtained according to general procedure E from **50**. Yellow oil (0.494 g, quantitative). MS (ESI⁺): m/z = 503 [M+H]⁺.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-methoxyphenyl)propyl methanesulfonate
(56)

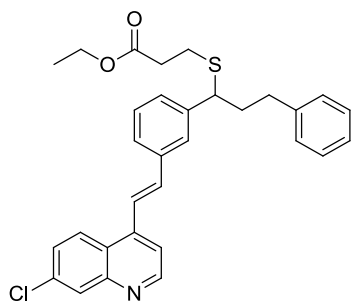
Obtained according to general procedure E from **51**. Yellow oil (0.496 g, quantitative). MS (ESI⁺): m/z = 508 [M+H]⁺.



(E)-1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-methoxyphenyl)propyl methanesulfonate
(57)

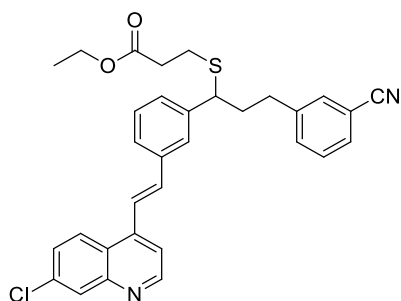
Obtained according to general procedure E from **52**. Yellow oil (0.370 g, quantitative). MS (ESI⁺): m/z = 508 [M+H]⁺.

SUPPLEMENTAL INFORMATION



(E)-ethyl 3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-phenylpropyl)thio)propanoate (**58**)

Obtained according to general procedure F from **53**. Colorless oil (0.491 g, 47%). A fraction was collected and the two enantiomers of **58** were separated on chiral column (Chiralpak IA 10 x 250mm, 5 μ m) with Hexanes (0.1% Et₂NH)/iPrOH (0.1% Et₂NH) 80:20 to obtain **(+)-58** (0.177 g, ee = 100%) and **(-)-58** (0.171 g, ee = 100%) as colorless oils. MS (ESI⁺): m/z = 516 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.93 (d, 1H, J = 4.4 Hz), 8.22 (d, 1H, J = 9.2 Hz), 8.17 (d, 1H, J = 2.2 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.63 (d, 1H, J = 4.4 Hz), 7.60-7.55 (m, 3H), 7.44 (t, 1H, J = 7.8 Hz), 7.39-7.18 (m, 7H + CDCl₃), 4.14 (q, 2H, J = 7.2 Hz), 3.86 (t, 1H, J = 8.0 Hz), 2.70 (t, 2H, J = 7.6 Hz), 2.62 (t, 2H, J = 7.5 Hz), 2.62 (t, 2H, J = 8.0 Hz), 2.76 (quintuplet, 1H, J = 7.5 Hz), 2.22 (quintuplet, 1H, J = 7.5 Hz), 1.26 (t, 3H, J = 7.2 Hz). ¹³C NMR (CDCl₃) δ (ppm): 171.9, 151.2, 149.1, 143.3, 143.1, 141.1, 136.7, 135.7, 135.3, 129.2, 129.0, 128.6, 128.5, 128.4, 127.5, 126.7, 126.1, 126.1, 125.1, 122.6, 117.2, 60.7, 49.1, 37.9, 34.6, 33.6, 26.1, 14.2.

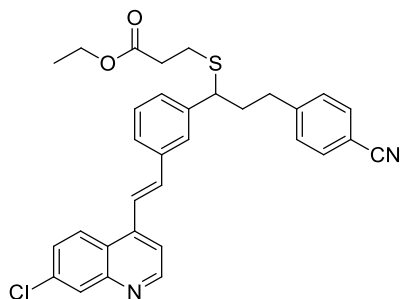


(E)-ethyl 3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-cyanophenyl)propyl)thio)propanoate (**59**)

Obtained according to general procedure F from **54**. Colorless oil (0.219 g, 48%). MS (ESI⁺): m/z = 541 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.93 (d, 1H, J = 4.6 Hz), 8.21 (d, 1H, J = 9.0 Hz), 8.17 (d, 1H, J = 2.1 Hz), 7.79 (d, 1H, J = 16.1 Hz), 7.63 (d, 1H, J = 4.6 Hz), 7.60-7.55 (m, 3H),

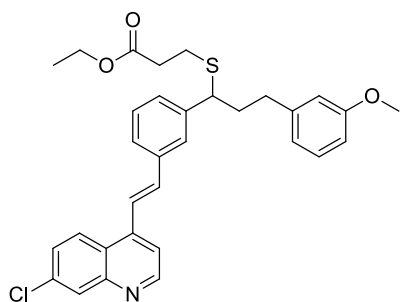
SUPPLEMENTAL INFORMATION

7.54-7.50 (m, 1H), 7.48-7.43 (m, 2H), 7.41 (m, 3H), 7.35-7.31 (m, 1H), 4.15 (q, 2H, $J = 7.1$ Hz), 3.84 (t, 1H, $J = 7.5$ Hz), 2.83-2.66 (m, 2H), 2.63 (t, 2H, $J = 6.8$ Hz), 2.49 (t, 2H, $J = 6.8$ Hz), 2.33-2.15 (m, 2H), 1.26 (t, 3H, $J = 7.1$ Hz).



(E)-ethyl-3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-cyanophenyl)propyl)thio)propanoate (**60**)

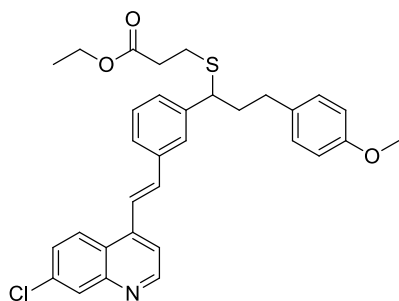
Obtained according to general procedure F from **55**. Colorless oil (0.227 g, 46%). MS (ESI⁺): $m/z = 541$ [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.93 (d, 1H, $J = 4.7$ Hz), 8.21 (m, 2H), 7.79 (d, 1H, $J = 16.1$ Hz), 7.64 (d, 1H, $J = 4.7$ Hz), 7.62-7.54 (m, 5H), 7.44 (t, 1H, $J = 7.6$ Hz), 7.38 (d, 1H, $J = 16.1$ Hz), 7.33 (d, 1H, $J = 7.7$ Hz), 7.29 (m, 2H+CDCl₃), 4.15 (q, 2H, $J = 7.2$ Hz), 3.84 (t, 1H, $J = 7.5$ Hz), 2.81-2.74 (m, 2H), 2.65-2.61 (m, 2H), 2.51-2.47 (m, 2H), 2.29 (m, 2H), 1.26 (t, 3H, $J = 7.2$ Hz).



(E)-ethyl 3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(3-methoxyphenyl)propyl)thio)propanoate (**61**)

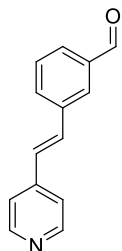
Obtained according to general procedure F from **56**. Colorless oil (0.249 g, 47%). MS (ESI⁺): $m/z = 546$ [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.93 (d, 1H, $J = 4.6$ Hz), 8.28-8.17 (m, 2H), 7.79 (d, 1H, $J = 16.1$ Hz), 7.65 (d, 1H, $J = 4.6$ Hz), 7.62-7.54 (m, 3H), 7.46-7.35 (m, 3H), 7.23 (t, 1H, $J = 7.9$ Hz), 6.80-6.71 (m, 3H), 4.14 (q, 2H, $J = 7.1$ Hz), 3.88-3.84 (m, 1H), 3.81 (s, 3H), 2.69-2.61 (m, 4H), 2.51-2.47 (m, 2H), 2.29-2.22 (m, 2H), 1.26 (t, 3H, $J = 7.1$ Hz).

SUPPLEMENTAL INFORMATION



(E)-ethyl 3-((1-(3-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)-3-(4-methoxyphenyl)propyl)thio)propanoate (**62**)

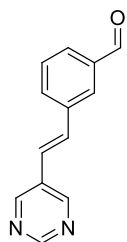
Obtained according to general procedure F from **57**. Colorless oil (0.207 g, 55%). MS (ESI⁺): m/z = 546 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 8.93 (d, 1H, J = 4.6 Hz), 8.22 (d, 1H, J = 16.0 Hz), 8.21 (d, 1H, J = 4.8 Hz), 7.79 (d, 1H, J = 16.0 Hz), 7.64 (d, 1H, J = 4.7 Hz), 7.59 (dd, 1H, J = 9.0 and 2.2 Hz), 7.57-7.55 (m, 2H), 7.48-7.31 (m, 3H), 7.10 (d, 2H, J = 8.6 Hz), 6.86 (d, 2H, J = 8.6 Hz), 4.14 (q, 2H, J = 7.2 Hz), 3.86-3.79 (m, 4H), 2.66-2.60 (m, 4H), 2.51-2.47 (m, 2H), 2.28-2.13 (m, 2H), 1.26 (t, 3H, J = 7.2 Hz).



(E)-3-(2-(pyridin-4-yl)vinyl)benzaldehyde (**63**)

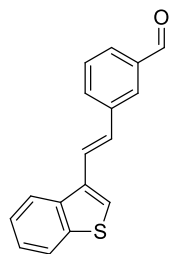
Obtained according to general procedure A from 3-vinylbenzaldehyde and 4-bromopyridine. White solid (0.032 g, 10%). MS (ESI⁺): m/z = 210 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.08 (s, 1H), 8.63 (d, 2H, J = 6.0 Hz), 8.08 (s, 1H), 7.85 (d, 1H, J = 7.5 Hz), 7.80 (d, 1H, J = 7.5 Hz), 7.59 (t, 1H, J = 7.5 Hz), 7.40 (d, 2H, J = 6.0 Hz), 7.35 (d, 1H, J = 16.5 Hz), 7.14 (d, 1H, J = 16.5 Hz). ¹³C NMR (CDCl₃) δ (ppm): 192.0, 150.3, 144.0, 137.2, 136.9, 132.7, 131.6, 130.0, 129.6, 127.9, 127.5, 121.0.

SUPPLEMENTAL INFORMATION



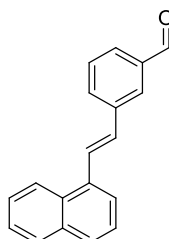
(E)-3-(2-(pyrimidin-5-yl)vinyl)benzaldehyde (**64**)

Obtained according to general procedure A from 3-vinylbenzaldehyde and 5-bromopyrimidine. White solid (0.061 g, 18%). MS (ESI⁺): m/z = 211 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.08 (s, 1H), 9.14 (s, 1H), 8.91 (s, 2H), 8.08 (s, 1H), 7.86 (td, 1H, J = 1.2 and 7.6 Hz), 7.80 (d, 1H, J = 7.6 Hz), 7.60 (t, 1H, J = 7.6 Hz), 7.31 (d, 1H, J = 16.8 Hz), 7.13 (d, 1H, J = 16.8 Hz). ¹³C NMR (CDCl₃) δ (ppm): 191.9, 157.6, 154.4, 137.0, 136.9, 132.6, 131.2, 130.5, 130.1, 129.6, 127.3, 123.1.



(E)-3-(2-(benzo[*b*]thiophen-3-yl)vinyl)benzaldehyde (**65**)

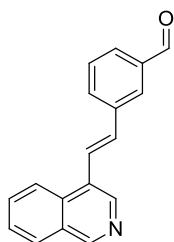
Obtained according to general procedure A from 3-vinylbenzaldehyde and 3-bromobenzo[*b*]thiophene. Colorless oil (0.128 g, 48%). Purity = 81%; tr = 3.40 min; MS (ESI⁺): m/z = 265 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.10 (s, 1H), 8.10 (s, 1H), 8.06 (d, 1H, J = 6.4 Hz), 7.93 (d, 1H, J = 8.0 Hz), 7.83-7.81 (m, 2H), 7.64 (s, 1H), 7.58 (t, 1H, J = 7.6 Hz), 7.53-7.48 (m, 2H), 7.44 (t, 1H, J = 7.4 Hz), 7.26 (d, 1H, J = 13.2 Hz). ¹³C NMR (CDCl₃) δ (ppm): 192.3, 140.5, 138.4, 137.6, 136.9, 133.6, 132.2, 129.4, 129.0, 128.6, 127.0, 124.7, 124.5, 123.0, 122.8, 122.5, 121.9.



SUPPLEMENTAL INFORMATION

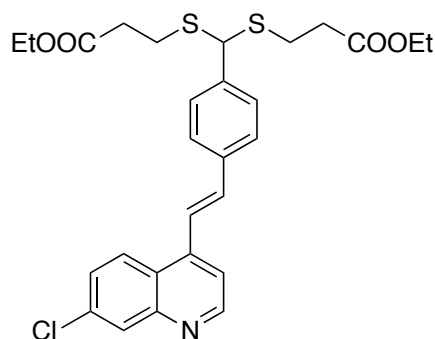
(E)-3-(2-(naphthalen-1-yl)vinyl)benzaldehyde (**66**)

Obtained according to general procedure A from 3-vinylbenzaldehyde and 1-bromonaphthalene. Colorless oil (0.192 g, 74%). MS (ESI⁺): m/z = 259 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.11 (s, 1H), 8.26 (d, 1H, J = 8.2 Hz), 8.13 (t, 1H, J = 1.7 Hz), 8.01 (d, 1H, J = 16.0 Hz), 7.95–7.77 (m, 5H), 7.64–7.50 (m, 4H), 7.21 (d, 1H, J = 16.0 Hz). ¹³C NMR (CDCl₃) δ (ppm): 192.3, 138.6, 136.9, 134.4, 133.8, 132.5, 131.4, 130.2, 129.4, 129.0, 128.7, 128.6, 127.6, 127.3, 126.3, 126.0, 125.7, 123.8, 123.7.



(E)-3-(2-(isoquinolin-4-yl)vinyl)benzaldehyde (**67**)

Obtained according to general procedure A from 3-vinylbenzaldehyde and 4-bromoisoquinoline. Colorless oil (0.139 g, 74%). MS (ESI⁺): m/z = 260 [M+H]⁺; ¹H NMR (CDCl₃) δ (ppm): 10.11 (s, 1H), 9.23 (s, 1H), 8.80 (s, 1H), 8.20 (d, 1H, J = 8.5 Hz), 8.15 (s, 1H), 8.04 (d, 1H, J = 7.8 Hz), 7.88–7.77 (m, 4H), 7.68 (t, 1H, J = 7.8 Hz), 7.61 (t, 1H, J = 7.6 Hz), 7.31–7.24 (m, 1H + CDCl₃). ¹³C NMR (CDCl₃) δ (ppm): 192.2, 152.3, 140.5, 138.1, 136.9, 133.8, 132.8, 131.6, 130.7, 129.5, 129.5, 128.3, 128.2, 127.4, 127.3, 124.4, 122.8.



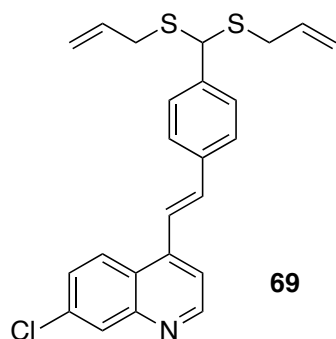
Diethyl 3,3'-(((4-(2-(7-chloroquinolin-4-yl)vinyl)phenyl)methylene)bis(sulfanediyl))-(*E*)-dipropionate (**68**)

Compound **38** (100 mg, 0.34 mmol) and TsOH·H₂O (126 mg, 0.68 mmol) were dissolved in toluene (15 mL) and 4Å molecular sieves were added. Allyl thiol (84 μ L, 1.02 mmol) and ethyl

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3-mercaptopropanoate (129 mg, 1.02 mmol) were added and the reaction mixture was stirred at reflux for 2.5 h under inert conditions. The mixture was diluted with EtOAc and the organic phase was washed with saturated NaHCO₃ and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column (EtOAc:hexanes; 98:2 to 40:60) to afford **68** as yellow solid (17%).

¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm): 8.93 (d, 1H, *J* = 4.7 Hz), 8.61 (d, 1H, *J* = 9.1 Hz), 8.10 (d, 1H, *J* = 16.1 Hz), 8.09 (d, 1H, *J* = 2.3 Hz), 7.91 (d, 1H, *J* = 4.7 Hz), 7.85 (d, 2H, *J* = 8.3 Hz), 7.70 (dd, 1H, *J* = 9.1, 2.3 Hz), 7.63 (d, 1H, *J* = 16.1 Hz), 7.51 (d, 2H, *J* = 8.3 Hz), 5.34 (s, 1H), 4.07 (q, 4H, *J* = 7.1 Hz), 2.84 – 2.80 (m, 2H), 2.75 – 2.56 (m, 6H), 1.18 (t, 6H, *J* = 7.1 Hz).



(E)-4-(4-(bis(allylthio)methyl)styryl)-7-chloroquinoline (**69**)

Further processing of chromatographic fractions from the reaction affording **11** yielded compound **69** (ca 80% pure) as a yellow solid (11%).

¹H NMR (500 MHz, DMSO-*d*₆) δ 9.17 (d, *J* = 5.6 Hz, 1H), 8.90 (d, *J* = 9.2 Hz, 1H), 8.36 (d, *J* = 2.2 Hz, 1H), 8.30 (d, *J* = 5.6 Hz, 1H), 8.25 (d, *J* = 16.0 Hz, 1H), 8.03 – 7.90 (m, 4H), 7.52 (d, *J* = 8.2 Hz, 2H), 5.81 (ddt, *J* = 17.0, 9.9, 7.0 Hz, 2H), 5.19 – 5.10 (m, 4H), 4.96 (s, 1H), 3.31 (dd, *J* = 13.6, 7.1 Hz, 2H), 3.14 (dd, *J* = 13.6, 7.0 Hz, 2H).

SUPPLEMENTAL INFORMATION

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