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Developing Flow Photo-Thiol-Ene Functionalizations of Cinchona Alkaloids with an Autonomous Self-Optimizing Flow Reactor

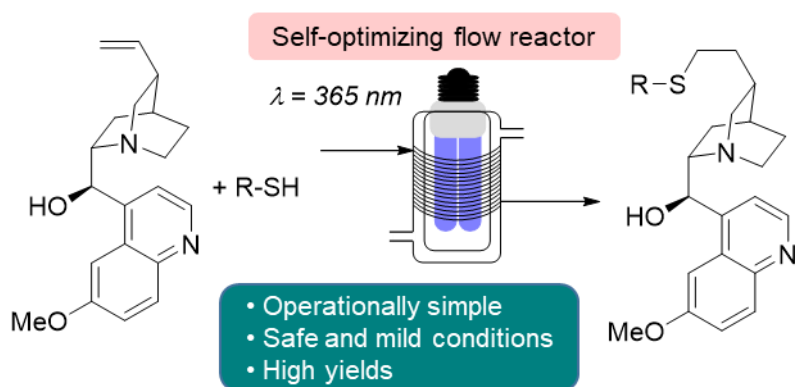
Kouakou Eric Konan,^{a,b} Abollé Abollé,^b Elvina Barré,^a Ehu Camille Aka,^{a,b} Vincent Coeffard,^a and François-Xavier Felpin^{a,*}

^a Université de Nantes, CNRS, CEISAM UMR 6230, 2 rue de la Houssinière, 44322 Nantes, France.

^b Université Nangui Abrogoua, Laboratoire de Thermodynamique et de Physico-Chimie du Milieu, 02 BP 801 Abidjan 02, Côte d'Ivoire

* Corresponding author. Tel.: +33-025-112-5422; e-mail: fx.felpin@univ-nantes.fr; ORCID: [0000-0002-8851-246X](https://orcid.org/0000-0002-8851-246X); Website: <http://felpin.univ-nantes.fr/>

Abstract Graphic



Continuous flow photo-thiol-ene reactions on cinchona alkaloids with a variety of organic thiols have been developed using enabling technologies such as a self-optimizing flow photochemical reactor.

Abstract

Continuous flow photo-thiol-ene reactions on cinchona alkaloids with a variety of organic thiols have been developed to deliver a series of unprecedented architectures. A self-optimizing flow

photochemical reactor was deployed to identify optimal experimental conditions. The flow thiol-ene reaction proceeds under mild conditions upon irradiation of the reaction mixture at 365 nm for 30 minutes in a custom built flow photochemical reactor. The short path length offered by the tubular photochemical reactor maximizes the absorption of photons emitted by the light source and increases both rates and reaction yields compared to a traditional batch reactor.

Introduction

In the 17th century, when the natives of South America were fighting the symptoms of malaria by chewing the bark of cinchona plants, they had no idea that 400 years later, natural products contained in the cinchona trees, foremost among them quinine **1a**, would become iconic alkaloids (Figure 1). Quinine **1a** became the first drug to fight against malaria and synthetic derivatives are very widely used in synthetic chemistry as chiral organocatalysts¹⁻³ and ligands for organometallic reactions, notably for the asymmetric Sharpless dihydroxylation of olefins.^{4, 5}

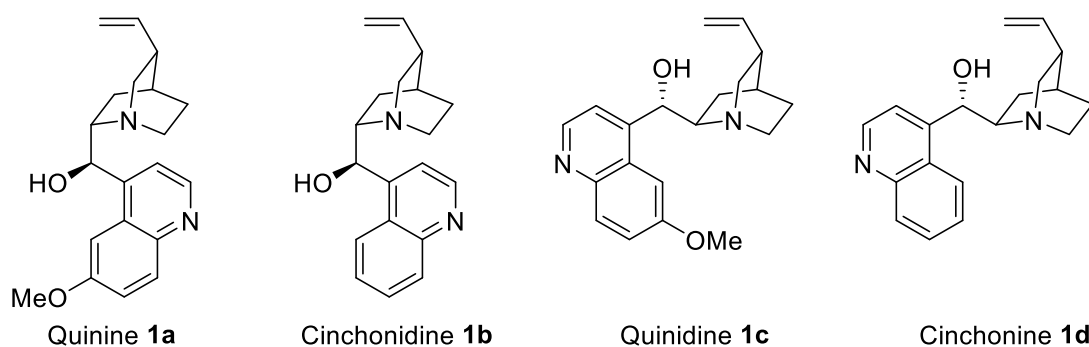


Figure 1. Alkaloid isolated from cinchona plants

Apart from these well-known applications, we recently exploited the coordination properties of quinine **1a** through the fabrication of a fully biosourced depolluting membrane with the aim of developing an affordable technology to address the dramatic pollution of drinking water resources by heavy metals in developing countries including Côte d'Ivoire (formerly Ivory Coast).⁶ Indeed, the rapid demographic growth in developing countries combined with the increase of industrial activities resulted in a severe pollution of ground water as domestic and industrial sewage water are often discharged without treatment. The first prototypes of depolluting membranes, fabricated by copper-catalyzed 1,3-dipolar cycloaddition of quinine-alkyne with cellulose-azide paper, showed good efficiency to remove several heavy metals at

pH compatible with the pH of drinking water. However, with the objective of developing a technology that could be industrialized, we looked for metal-free functionalization strategies of cinchona alkaloids that could be easily scaled-up under continuous process.

Special care should be taken with the modification of quinine **1a** because certain functional groups such as the hydroxyl function and the nitrogen atoms are essential for the coordination properties. In contrast, the vinyl group constitutes a platform of choice for providing structural diversity. The vinyl group of quinine **1a** can be functionalized by transition-metal catalyzed coupling reactions.⁷⁻⁹ While these approaches are particularly straightforward and efficient, the isolation of metal-free quinine-based compounds is often tricky due to the strong coordinating properties of quinine **1a**;⁶ this issue is particularly acute for the fabrication of depolluting technologies. The functionalization of quinine **1a** by carbon-centered radical species is also a standard process, but mostly limited to the introduction of fluorinated alkane chains.¹⁰⁻¹³ The thiol-ene reaction is a chemical transformation involving the addition of an organic thiol to a double bond either through an ionic pathway if the double bond is a Michael acceptor, or through a free-radical approach. The thiol-ene reaction is a powerful transformation compatible with a large number of chemical functions and allowing the introduction of a wide structural diversity.¹⁴⁻¹⁶ The thermally-induced free-radical thiol-ene reaction which involves the fragmentation of a radical initiator at temperatures above 80 °C has been used on several occasions on cinchona alkaloids.¹⁷⁻²⁵ On the other hand, the photochemical version of the thiol-ene reaction which allows milder reaction conditions because the radical initiator is fragmented by light irradiation at temperatures close to ambient, has been very little studied on cinchona alkaloids and only some sporadic examples can be found in the literature.²⁶⁻²⁹ Interestingly, we also showed that thiol-X ligations are compatible with cellulose paper.³⁰⁻³²

Continuous flow processing is particularly well suited for photochemical transformations as it offers the distinct advantages of allowing an intense and uniform light irradiation over a short path length.³³⁻³⁵ In addition the heat generated by the light source can be more efficiently controlled by a precise control of the flow rate and quickly dissipated thanks to the high surface area to volume ratio of capillary flow reactors. Therefore, it is now widely accepted that photochemical transformations are, in general, much more reproducible, cleaner and faster when carried out in a continuous flow reactor³⁶⁻⁴³ even on large scales.⁴⁴⁻⁴⁷

In this contribution we describe our effort toward the development of a general strategy for the functionalization of cinchona alkaloids through photochemical thiol-ene reactions conducted in a custom built flow photochemical reactor. A self-optimizing flow photochemical

reactor was deployed to expedite the optimization stage and the reaction scope was established on four cinchona alkaloids with a variety of organic thiols.

Results and discussion

We initiated our studies on the continuous flow photochemical thiol-ene functionalization of cinchona alkaloids by capitalizing on the recent report from Egan et al. who described a single example of photochemical thiol-ene reaction on quinine **1a** using 6 equivalents of an organic thiol following a standard batch approach.²⁸ With the aim of minimizing the number of thiol equivalents while maintaining a short residence time, we embarked in a careful optimization study using a custom built self-optimizing flow photochemical reactor. Optimization of chemical reactions, carried out either in batch or in flow, conventionally follows the easily set up one-variable-at-a-time methodology. However, this simple approach neglects interactions between variables and is poorly time-efficient and often fails for identifying a satisfactory optimum in multi-dimensional optimizations.

The recent introduction of autonomous self-optimizing flow reactors marked a groundbreaking advance in the field of constraint optimization.⁴⁸⁻⁶⁵ The development of automation associated to the use of feedback algorithms integrated in closed-loop flow systems increased reproducibility and greatly speeded-up optimization campaigns with minimal user intervention.⁶⁶⁻⁷⁰ This still emerging technology requires process control instrumentations for automation, in-situ monitoring by process analytical technology (PAT) and feedback algorithms to assist chemists in the complex decision-making process.⁷¹⁻⁷⁵ Our lab contributed to this field of research with the development of a reconfigurable self-optimizing flow platform which was deployed for natural product synthesis,^{76, 77} ligand preparation⁷⁸ and palladium-catalyzed direct C-H arylation.⁷⁹

Capitalizing on our experience in this field and with the aim of demonstrating the capability of our platform to accommodate to photo-mediated thiol-ene reactions, we designed a self-optimizing flow device combining an automatic sample handler, a custom built photochemical reactor and an online HPLC unit (Figure 2). Self-optimizing photochemical flow reactors are complex platforms with the potential to optimize wavelength and light intensity, requiring future development.^{60, 80, 81} The thiol-ene functionalization of quinine **1a** with 2-(boc-amino)ethanethiol **2**, in the presence of 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photo-initiator was selected as the benchmark transformation to be optimized for the

development of a continuous flow strategy. To start the optimization campaign, the automatic sampler handler was populated with stock solutions of quinine **1a** (0.5 M), thiol **2** (2 M) and DMPA (1 M). Following instructions from the optimization algorithm, the sampler handler automatically determined the volume of suction in each vial to prepare 200 μL of the reacting mixture which was injected in the flow photochemical reactor. The flow stream was irradiated with a compact fluorescent lamp emitting at 365 nm with a measured irradiance of 5.5 W/m^2 in a custom built flow photochemical reactor. The heat generated by the lamp was dissipated using an air cooling system. The air flow rate was adjusted so that the temperature was stabilized at $32 \text{ }^\circ\text{C} \pm 1 \text{ }^\circ\text{C}$. The reactor outlet was connected to an automatic 2-way 6-port switch valve which sampled 1 μL of the crude mixture for the online HPLC system. Automated data acquisition and processing allowed for calculation of the reaction yield which was automatically sent to the algorithm. A new set of experimental conditions was proposed by the algorithm and the process control software modified it accordingly. This closed-loop process was repeated until the algorithm reached an optimum or another stopping criteria.

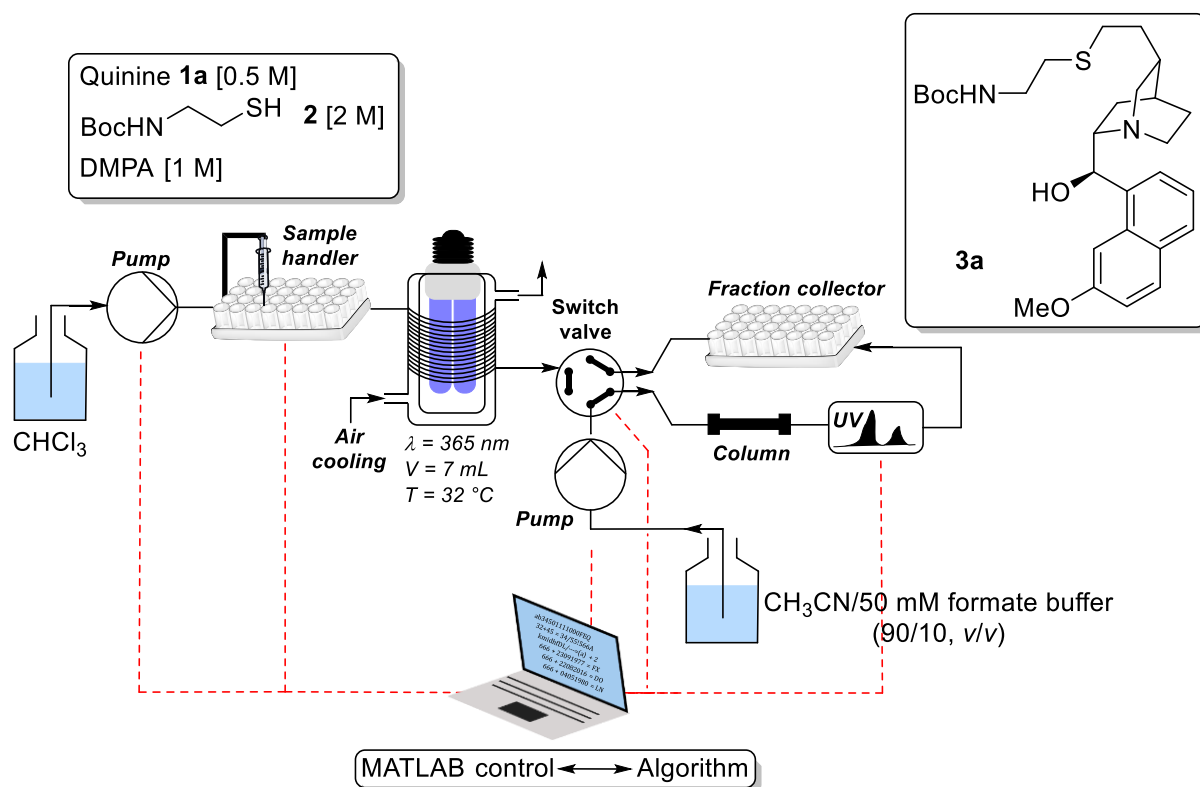


Figure 2. Autonomous self-optimizing flow photochemical reactor for the optimization of **9a**. The red dashed lines indicate the units controlled by the computer via MATLAB.

The reaction was optimized in a 3-dimension space using a profoundly modified version of the Nelder-Mead method that we recently described in detail elsewhere.⁸² While the Nelder-Mead method is generally modestly efficient to tackle complex problems in chemical synthesis, our improved algorithm includes several additional mechanisms : (i) multiple optional stopping criteria to minimize the number of experiments, (ii) various mechanisms of intensification or diversification to escape from a local optimum not reaching the initial objectives, (iii) a mechanism of modulation of the dimensionality of the search to faster explore a subspace, (iv) an optional mechanism to reduce the size of the search space where experimental conditions are considered as unsound (lack of reactivity, hazardous behavior of unstable reagents/products, etc.) using additional linear constraints, and (iv) the Golden search method for 1D optimizations which cannot be handled by the Nelder-Mead method. For details discussions on optimization algorithms available for chemical transformations, readers can refer to previous publications.^{56,}

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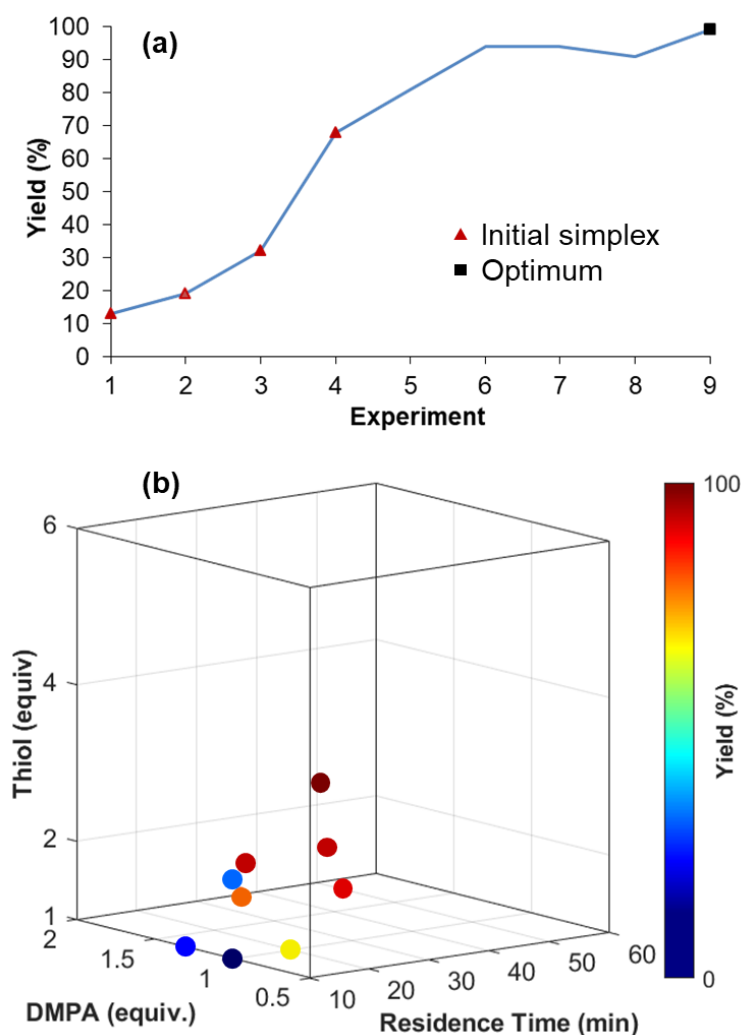


Figure 3. (a) Maximization of the yield of quinine derivative **3a**. (b) Representation of the three-dimensional experimental conditions for the maximization of the yield for **3a**

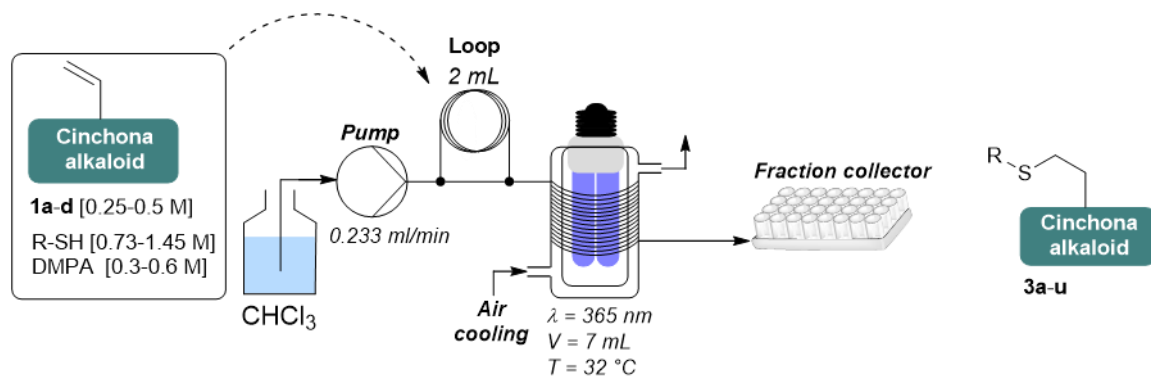
The reaction yield of **3a** was optimized with the residence time, equivalents of thiol **2** and loading of DMPA as variables in the range of 10-60 min, 1-6 equiv and 0.5-2 equiv, respectively. The initial experiment X_0 was fixed by the operator – but can be randomly generated by the algorithm as well - at 1 equivalent of thiol **2**, 1 equivalent of DMPA and 10 minutes of residence time with d values of 1 equiv, 0.3 equiv. and 10 min, respectively. The initial simplex, represented by the first four experiments, provided compound **3a** in yield ranging from 13 to 68%, the residence time having a strong impact on the yield. Impressively, the algorithm located an optimum (99% yield) in the 9th experiment at 30 minutes of residence time, 2.9 equivalents of thiol **2** and 1.2 equivalents of DMPA. The optimum reached in the 9th experiment corresponded to a stopping criterion (>95% yield) and therefore, the optimization stopped after only 9 experiments. Additional background reactions were conducted to characterize the impact of DMPA and light irradiation on the reaction conversion. For instance under the experimental conditions of experiment 9, when the light source was turned off, no conversion was observed while the omission of DMPA drastically reduced the conversion to only 11%.

With the optimized conditions in hand, the reaction scope was explored with the aim of determining the compatibility of the photochemical thiol-ene reaction on four cinchona alkaloids, *i.e.*, quinine **1a**, cinchonidine **1b**, quinidine **1c** and cinchonine **1d** using the continuous flow setup represented in Figure 4A. We initially examined the addition of a variety of organic thiols on quinine **1a** (compounds **3a-3m**). Within the thiol partner, various functionalities such as amide, alcohol and ester were accommodated at the β and γ position. When bifunctional 1,3-propanedithiol and 2-mercaptoethyl ether were used, only one thiol function reacted with quinine **1a** and the reaction selectively provided the expected compounds **3g-h**. Benzyl mercaptan was also tolerated (products **3i**) but in contrast, 2-mercaptobenzothiazole failed to give the expected addition product **3m** and the starting material **1a** was quantitatively recovered. Besides quinine **1a**, cinchonidine **1b** and quinidine **1c** displayed a similar reactivity providing addition products **3n-p** and **3q-s**, respectively, in good to excellent isolated yield (>75%). Surprisingly, cinchonine **1d** was significantly less reactive in our hands and only incomplete conversions were achieved even under prolonged residence time (compounds **3t-v**). This unexpected behavior is still unclear at this time, but we suspect

that it could be related to a peculiar conformation which interferes with the thiol substrates. In order to better understand the benefits provided by the use of a continuous flow photochemical reactor, compounds **3j**, **3k**, **3p**, **3q** and **3s** were also prepared in batch under otherwise similar experimental conditions, *i.e.*, 30 minutes reaction time, 32 °C and 2.9 equivalents of thiol.

At this point it must be stressed, that the use of an algorithm considerably speed-up the search of an optimum compared to the traditional one-variable-at-a-time optimization approach but does not confer a universal character on this optimum. We demonstrated that the optimal conditions found on the benchmark transformation were efficient for a wide variety of substrates but it can't be excluded that a different structure corresponds a different optimum.

A) Experimental setup used for the reaction scope



B) Photochemical thiol-ene reactions in flow on cinchona alkaloids

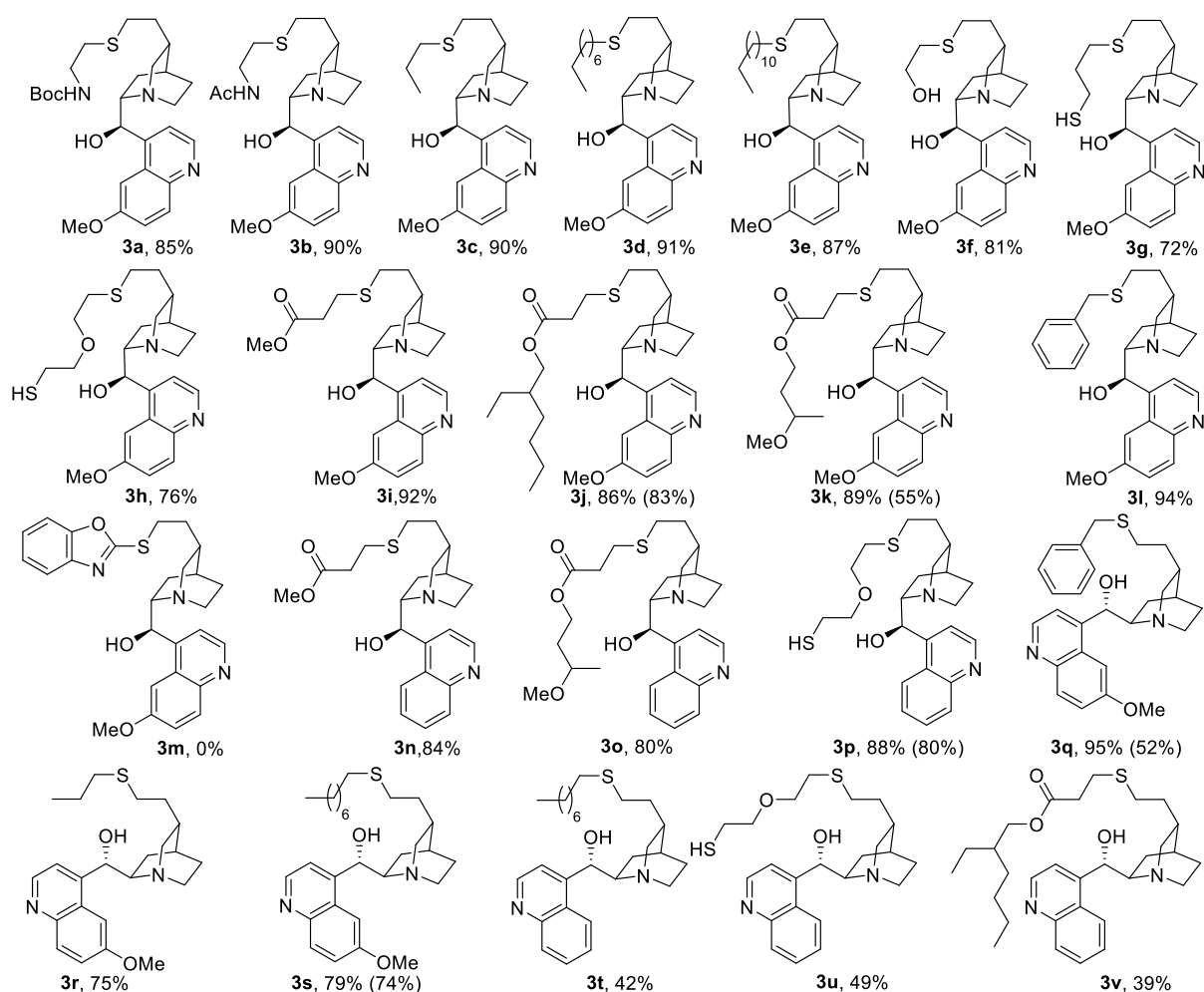


Figure 4. (A) Experimental setup used for the reaction scope study. (B) Cinchona alkaloids prepared through photo thiol-ene reactions. Isolated yields are reported. Yields in bracket refer to batch reactions.

A reduction of reactions yields (see values in bracket in Figure 4B) was systematically observed due to an incomplete conversion after 30 minutes of stirring. This result reveals the higher rate of conversion within the flow photochemical reactor mainly due to an intense and uniform light irradiation over the short path length of the tubing reactor (i.d. 0.75 mm) which maximize the absorption of photon emitted by the light source. Increasing the scale of a photochemical reaction carried out in batch often lead to reproducibility issues due to the change of the radiation path length. This issue can be partially mitigated by using a light source with a higher power density. However, increasing the light fluence comes at a price since it requires to significantly modify the experimental setup and energetic irradiations may favor the formation of unwanted side products. In flow, one way to increase the reaction scale consists in using the flow reactor on a longer period of time. In this frame we demonstrated the facile

scalability of our methodology by using the flow photochemical reactor over a period of 130 minutes, allowing to produce >3.2 g of compound **3k** with a reaction yield of 84%.

Conclusion

In summary, we have designed an experimental flow setup using a custom built photochemical reactor for the functionalization of cinchona alkaloids with organic thiols through a photo-thiol-ene strategy. The development of this methodology was enabled by the use of one of the rare example of a self-optimizing flow photochemical reactor which expedited the search for optimal experimental conditions. Experimental simplicity, mild conditions and high reaction yields are the main features of the developed flow thiol-ene process. We also demonstrated the sharp superiority of the continuous flow process for obtaining unprecedented functionalized cinchona alkaloids in high yields compared to a traditional batch approach. We interpreted the higher kinetics observed in the flow mode by the greater absorption of photons emitted by the light source thanks to the short path length offered by the tubular photochemical reactor. We are currently deploying this technology to the continuous functionalization of cellulose paper.

Experimental Section

General Information. All reagents, starting materials and solvents were obtained from commercial suppliers and used as such without further purification, unless otherwise noted. High-field ^1H and ^{13}C NMR spectra were recorded at 300 or 400 and 75 or 100 MHz, respectively. ^1H and ^{13}C NMR spectra were referenced to the internal deuterated solvent (CDCl_3) at 7.26 and 77.16 ppm, respectively and Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. FT-IR spectra were recorded in the ATR mode. Wavelengths of maximum absorbance (ν_{max}) are shown in wave numbers (cm^{-1}). High resolution mass spectrometry (HRMS) was recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). Melting points were determined on a Stuart melting point SMP3 apparatus. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254), and visualization was accomplished with UV light at 254 nm. Flash column chromatography was performed using silica gel 60 (40–63 μm).

Details of the experimental setup. HPLC pumps (JASCO PU2080) equipped with a RS-232 port were employed to flow the solution through the system. A sampler handler (JASCO AS 2055) equipped with a RS-232 port was used to inject reagent in the line. The reactor coil was heated with a heating plate (Heidolph, MR Hei-Connect) equipped with a RS-232 port. A 2-way 6-port valve (VICI, Cheminert C2-3006D) equipped with a RS-232 port was used to inject an aliquot of the crude mixture within the on-line HPLC unit. The HPLC column outlet was connected to a UV detector (JASCO, UV 2075) equipped with a RS-232 port. The flow outlet was connected to a programmable fraction collector (Advantec, CHF 1225C). All units equipped with a RS-232 port were autonomously controlled with MATLAB[®] through the use of communication protocols provided by the manufacturers.

***tert*-Butyl (2-mercaptoethyl) carbamate (**2**).**²⁸ To a solution of cysteamine (674 mg, 5.9 mmol) in CH₂Cl₂ (9 ml) was added dropwise Et₃N (0.9 ml, 5.9 mmol). After 20 minutes of stirring at room temperature, a solution of di-*tert*-butyl dicarbonate (1.77 g, 8.1 mmol) in CH₂Cl₂ (3 ml) was slowly added and the resulting mixture was stirred overnight. The solution was diluted with Et₂O (20 mL) and successively washed with 1M HCl (2 × 20 mL), water (2 × 20 mL) and brine (2 × 20 mL). The aqueous phase was dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (20% AcOEt-cyclohexane) gave **2** as a colorless oil (814 mg, 77%). IR (ATR) ν 3338, 2975, 2931, 1690, 1513, 1170 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 4.89 (br s, 1H), 3.25-3.33 (m, 2H), 2.60-2.68 (dt, 2H, *J* = 6.5, 8.4 Hz), 1.44 (s, 9H), 1.34 (t, 1H, *J* = 8.5 Hz). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ 155.8, 79.5, 43.8, 28.4, 25.0. HRMS (ESI) *m/z* [M + Na]⁺ Calcd for C₇H₁₅NO₂NaS 200.0721; Found 200.0724.

Procedure for the optimization. An automatic sample handler prepared 200 μ L of the reaction mixture from stock solutions of quinine **1a** (0.5 M in CHCl₃ plus compounds **3f** as the internal standard at 0.5 M in CHCl₃), DMPA (1 M in CHCl₃) and *tert*-butyl (2-mercaptoethyl) carbamate **2** (2 M in CHCl₃). The reaction mixture was injected in a stream of CHCl₃ pumped at the required flow rate. The thiol-ene reaction occurred in the flow photochemical reactor consisting of FEP tubing (7 mL, i.d. 0.75 mm) wrapped around a double wall glassware. A compact fluorescent lamp emitting at 365 nm was inserted in the photochemical reactor and an air cooling system stabilized the temperature in the range of 31-33 °C. The reactor outlet was connected to an automatic 2-way 6-port switch valve which injected 0.2 μ L of the crude mixture in the HPLC unit while the remaining stream was collected in a fraction collector. A mixture

of CH₃CN/50 mM ammonium formate buffer (90/10, v/v) was used as mobile phase for the HPLC analysis at a flowrate of 0.6 mL/min. A UV detector was connected to the outlet of the HPLC column (InChem Surf Silica C18, 3 mm × 150 mm, 5 μm) to follow the absorbance at a wavelength of 332 nm. Peak integration and yield calculation were under full MATLAB automation. The calculated yield was automatically sent to the algorithm which set new experimental conditions to the units via RS-232 ports. A 3-D optimization of the reaction yield was conducted using the stoichiometry of DMPA, stoichiometry of thiol **2** and residence time as the input variables. The initial experiment of the simplex was: 1 equivalent of DMPA, 1 equivalent of thiol **2** and 10 min of residence time with *d* values of 0.3 equivalent, 1 equivalent and 10 minutes, respectively. The lower and upper boundaries of the research space were the following: 0.5-2 equivalents, 1-6 equivalents and 10-60 min for the equivalents of DMPA, equivalents of thiol **2** and residence time, respectively. An optimum giving 99% HPLC yield was found in experiment 9 at 30 min of residence time and with 1.2 equivalent of DMPA and 2.9 equivalents of thiol **2** (see Table S1 for details).

General procedure for the library cinchona alkaloids. The experimental setup consisted of a single stream equipped with a stainless steel injection loop (2 mL, 0.76 mm id) as depicted in Figure 4A. The loop was loaded with a solution of cinchona alkaloids **1a-b** (0.25-0.5 M in CHCl₃), thiol compounds (0.73-1.45 M in CHCl₃) and 2,2-dimethoxy-2-phenylacetophenone (DMPA) as photo-initiator (0.3-0.6 M in CHCl₃). The mixture was flowed at 0.233 mL/min for alkaloids **1a-c** and 0.116 mL/min for **1d**. The thiol-ene reaction occurred in the flow photochemical reactor consisting of FEP tubing (7 mL, i.d. 0.75 mm) wrapped around a double wall glassware. A compact fluorescent lamp emitting at 365 nm was inserted in the photochemical reactor and an air cooling system stabilized the temperature in the range of 31-33 °C. The resulting functionalized cinchona alkaloids **3a-v** were collected in vials. Volatiles were removed under reduced pressure and the crude residues were purified by flash chromatography.

tert-butyl (2-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidine-3-yl)ethyl)thio)ethyl)carbamate [3a]. Compound **3a** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and *tert*-butyl (2-mercaptoethyl) carbamate **2** (1.45 M). Purification by flash chromatography on silica gel (10%

MeOH-CH₂Cl₂ with 1% ammonia) gave **3a** as a white solid (425 mg, 85%). mp 65.5 °C [Lit.²⁸ 69-71 °C]. IR (ATR) ν 3212, 2924, 2865, 1691, 1620, 1507, 1239, 1164, 1028 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 8.61 (d, 1H, *J* = 4.6 Hz), 7.93 (d, 1H, *J* = 9.2 Hz), 7.49 (d, 1H, *J* = 4.6 Hz), 7.28 (dd, 1H, *J* = 2.6 Hz, 9.2 Hz), 7.21 (d, 1H, *J* = 2.6 Hz), 5.59 (br s, 1H), 4.87 (br s, 1H), 3.86 (s, 3H), 3.46-3.57 (m, 1H), 3.17-3.28 (m, 2H), 3.03-3.15 (m, 2H), 2.60-2.70 (m, 1H), 2.35 (t, 2H, *J* = 6.6 Hz), 2.42 (t, 2H, *J* = 7.5 Hz), 2.35-2.42 (m, 1H), 1.64-1.84 (m, 4H), 1.37-1.56 (m, 4H), 1.40 (s, 9H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ 157.9, 155.9, 147.7, 147.4, 144.1, 131.4, 126.6, 121.6, 118.6, 101.4, 79.5, 71.1, 59.9, 58.1, 55.9, 43.3, 39.8, 34.5, 32.4, 29.7, 28.5, 27.8, 25.6, 21.1. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₇H₄₀N₃O₄S 502.2740; Found 502.2736.

N-(2-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)ethyl)thio)ethyl)acetamide [3b]. Compound **3b** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and N-acetylcysteamine (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-CH₂Cl₂ with 1% ammonia) gave **3b** as a yellow solid (401 mg, 90%). mp 76.5 °C. IR (ATR) ν 3260, 2920, 2863, 1650, 1621, 1508, 1431, 1236, 1029 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz) δ 8.61 (d, 1H, *J* = 4.4 Hz), 7.95 (d, 1H, *J* = 9.2 Hz), 7.46 (d, 1H, *J* = 4.5 Hz), 7.27 (dd, 1H, *J* = 2.7, 9.2 Hz), 7.25 (d, 1H, *J* = 2.7 Hz), 5.92 (br s, 1H), 5.46 (d, 1H, *J* = 4.5 Hz), 4.03 (br s, 1H), 3.88 (s, 3H), 3.30-3.43 (m, 1H), 3.35 (q, 2H, *J* = 6.5 Hz), 3.05-3.14 (m, 1H), 3.01 (dd, 1H, *J* = 9.7, 13.4 Hz), 2.51-2.65 (m, 3H), 2.37-2.46 (m, 2H), 2.27-2.37 (m, 2H), 1.92 (s, 3H), 1.67-1.79 (m, 3H), 1.35-1.66 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 100 MHz) δ 170.3, 157.9, 148.0, 147.7, 144.4, 131.7, 126.9, 121.5, 118.6, 101.7, 72.1, 60.0, 58.3, 55.8, 43.2, 38.6, 35.0, 34.8, 31.9, 29.8, 28.2, 25.8, 23.3, 22.1. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₄H₃₄N₃O₃S 444.2321; Found 444.2316.

(1R)-(6-methoxyquinolin-4-yl)((1S,4S,5R)-5-(2-(propylthio)ethyl)quinuclidin-2-yl)methanol [3c]. Compound **3c** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and 1-propanethiol (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-CH₂Cl₂ with 1% ammonia) gave **3c** as a yellow solid (363 mg, 90%). mp 66.5-67 °C. IR (ATR) ν 3074, 2922, 2865, 1619, 1507, 1234, 1029, 825 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.55 (d, 1H, *J* = 4.5 Hz), 7.92 (d, 1H, *J* = 9.2 Hz), 7.46 (d, 1H, *J* = 4.5 Hz), 7.28 (dd, 1H, *J* = 2.6, 9.2 Hz), 7.19 (d, 1H, *J* = 2.6 Hz), 5.50 (d, 1H, *J* = 3.8 Hz), 4.26 (br s, 1H), 3.86 (s, 3H), 3.37-3.51 (m, 1H), 2.98-3.11 (m, 2H), 2.54-2.68 (m, 1H), 2.29-2.45 (m,

5H), 1.60-1.81 (m, 4H), 1.34-1.59 (m, 6H), 0.92 (t, 3H, $J = 7.3$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz) δ 157.8, 147.9, 147.6, 144.2, 131.6, 126.7, 121.6, 118.5, 101.4, 72.0, 59.9, 58.4, 55.8, 43.3, 34.8, 34.8, 34.4, 30.1, 28.2, 25.8, 23.0, 21.5, 13.6. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_2\text{S}$ 401.2263; Found 401.2259.

(1R)-(6-methoxyquinolin-4-yl)((1S,4S,5R)-5-(2-(octylthio)ethyl)quinuclidin-2-yl)methanol [3d]. Compound **3d** was prepared following the general procedure using quinine **1a** (0.25 M), DMPA (0.3 M) and 1-octanethiol (0.73 M). Purification by flash chromatography on silica gel (10% MeOH- CH_2Cl_2 with 1% ammonia) gave **3d** as a yellow solid (214 mg, 91%). mp 76.5-77 °C. IR (ATR) ν 2920, 2853, 1620, 1589, 1507, 1459, 1432, 1233, 1029, 824 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 8.60 (d, 1H, $J = 4.5$ Hz), 7.94 (d, 1H, $J = 9.2$ Hz), 7.48 (d, 1H, $J = 4.5$ Hz), 7.28 (dd, 1H, $J = 2.6, 9.2$ Hz), 7.19 (d, 1H, $J = 2.6$ Hz), 5.57 (br s, 1H), 3.85 (s, 3H), 3.42-3.56 (m, 1H), 3.02-3.14 (m, 2H), 2.59-2.72 (m, 1H), 2.31-2.46 (m, 5H), 1.63-1.83 (m, 4H), 1.38-1.56 (m, 6H), 1.14-1.35 (m, 11H), 0.86 (t, 3H, $J = 6.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 157.9, 147.6, 147.5, 144.3, 131.7, 126.7, 121.6, 118.5, 101.3, 71.8, 59.9, 58.4, 55.9, 43.4, 34.7, 32.4, 31.9, 30.2, 29.7, 29.3, 29.3, 29.0, 28.1, 25.8, 22.8, 21.5, 14.2. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{28}\text{H}_{43}\text{N}_2\text{O}_2\text{S}$ 471.3045; Found 471.3040.

(1R)-((1S,4S,5R)-5-(2-(dodecylthio)ethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol [3e]. Compound **3e** was prepared following the general procedure using quinine **1a** (0.25 M), DMPA (0.3 M) and 1-dodecantethiol (0.73 M). Purification by flash chromatography on silica gel (8% MeOH- CH_2Cl_2 with 1% ammonia) gave **3e** as a yellow solid (230 mg, 87%). mp 76.5 °C [Lit.⁸⁴ 80-81°C]. IR (ATR) ν 2919, 2851, 1620, 1507, 1464, 1431, 1235, 1030 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 8.63 (d, 1H, $J = 4.5$ Hz), 7.93 (d, 1H, $J = 9.2$ Hz), 7.50 (d, 1H, $J = 4.5$ Hz), 7.26 (dd, 1H, $J = 2.6, 9.2$ Hz), 7.18 (d, 1H, $J = 2.6$ Hz), 5.64 (br s, 1H), 3.83 (s, 3H), 3.50-3.64 (m, 1H), 3.11 (dd, 2H, $J = 10.0, 13.2$ Hz), 2.63-2.74 (m, 1H), 2.32-2.48 (app q, 5H, $J = 7.5\text{Hz}$), 1.66-1.87 (m, 4H), 1.39- 1.56 (m, 6H), 1.16-1.35 (m, 19H), 0.87 (t, 3H, $J = 6.7$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 158.0, 147.6, 147.2, 144.4, 131.7, 126.6, 121.7, 118.6, 101.3, 71.4, 60.0, 58.3, 56.0, 43.5, 43.4, 34.7, 34.6, 32.5, 32.0, 30.2, 29.8, 29.7, 29.7, 29.6, 29.5, 29.4, 29.0, 27.8, 25.8, 22.8, 21.3, 14.2. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{32}\text{H}_{51}\text{N}_2\text{O}_2\text{S}$ 527.3671; Found 527.3671.

2-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)ethyl)thio)ethan-1-ol [3f]. Compound **3f** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and 2-mercaptoethanol (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-CH₂Cl₂ with 1% ammonia) gave **3f** as a yellow solid (326 mg, 81%). mp 64-65 °C [Lit.⁸⁴ 78-90°C]. IR (ATR) ν 3077, 2915, 2863, 1619, 1507, 1234, 1028, 824 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.52 (d, 1H, *J* = 4.5 Hz), 7.90 (d, 1H, *J* = 9.2 Hz), 7.44 (d, 1H, *J* = 4.5 Hz), 7.27 (dd, 1H, *J* = 2.6, 9.2 Hz), 7.19 (d, 1H, *J* = 2.6 Hz), 5.48 (d, 1H, *J* = 3.5 Hz), 4.51 (br s, 1H), 3.85 (s, 3H), 3.64 (t, 2H, *J* = 6.1 Hz), 3.36-3.52 (m, 1H), 3.29 (br s, 1H), 2.90-3.07 (m, 2H), 2.62 (t, 2H, *J* = 6.1 Hz), 2.49-2.58 (m, 1H), 2.39 (t, 2H, *J* = 7.5 Hz), 2.22-2.33 (m, 1H), 1.65-1.81 (m, 3H), 1.61 (br s, 1H), 1.30-1.54 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 157.8, 148.0, 147.4, 144.1, 131.4, 126.7, 121.5, 118.5, 101.5, 71.8, 60.5, 59.8, 58.3, 55.8, 43.2, 35.3, 34.7, 34.7, 29.9, 28.1, 25.7, 21.4. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₂H₃₁N₂O₃S 403.2055; Found 403.2044.

(1R)-((1S,4S,5R)-5-(2-((3-mercaptopropyl)thio)ethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol [3g]. Compound **3g** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and 1,3-propanedithiol (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-CH₂Cl₂ with 1% ammonia) gave **3g** as a yellow solid (310 mg, 72%). mp 51-52 °C. IR (ATR) ν 3073, 2918, 2861, 1619, 1507, 1226, 1028, 825 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.52 (d, 1H, *J* = 4.5 Hz), 7.90 (d, 1H, *J* = 9.2 Hz), 7.45 (d, 1H, *J* = 4.6 Hz), 7.26 (dd, 1H, *J* = 2.6, 9.2 Hz), 7.18 (d, 1H, *J* = 2.6 Hz), 5.52 (d, 1H, *J* = 3.5 Hz), 4.54 (br s, 1H), 3.86 (s, 3H), 3.39-3.54 (m, 1H), 3.05 (dd, 2H, *J* = 9.9, 13.2 Hz), 2.50-2.68 (m, 5H), 2.38 (t, 2H, *J* = 7.4 Hz), 2.29-2.35 (m, 1H), 1.69-1.86 (m, 5H), 1.64 (br s, 1H), 1.35-1.56 (m, 4H), 1.30 (br s, 1H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 157.8, 147.9, 147.5, 144.2, 131.5, 126.6, 121.5, 118.5, 101.4, 71.8, 59.9, 58.3, 55.9, 43.4, 34.8, 34.7, 33.3, 30.5, 30.1, 28.1, 25.7, 23.5, 21.4. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₃H₃₃N₂O₂S₂ 433.1983; Found 433.1977.

(1R)-((1S,4S,5R)-5-(2-((2-(2-mercaptoethoxy)ethyl)thio)ethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol [3h]. Compound **3h** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and bis-(2-mercaptoethyl)ether (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-CH₂Cl₂ with 1% ammonia) gave

3h as a yellow solid (351 mg, 76%). mp 40-41 °C. IR (ATR) ν 3073, 2921, 2860, 1619, 1589, 1507, 1235, 1097, 1028, 825 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.59 (d, 1H, $J = 4.5$ Hz), 7.94 (d, 1H, $J = 9.2$ Hz), 7.47 (d, 1H, $J = 4.5$ Hz), 7.29 (dd, 1H, $J = 2.7, 9.2$ Hz), 7.19 (d, 1H, $J = 2.7$ Hz), 5.53 (d, 1H, $J = 3.7$ Hz), 3.95 (br s, 1H), 3.87 (s, 3H), 3.56 (t, 2H, $J = 6.6$ Hz), 3.53 (t, 2H, $J = 6.3$ Hz), 3.39-3.48 (m, 1H), 3.00-3.13 (m, 2H), 2.63 (app t, 5H, $J = 6.6$ Hz), 2.46 (t, 2H, $J = 7.6$ Hz), 2.30-2.41 (m, 1H), 1.70-1.81 (m, 3H), 1.65 (br s, 1H), 1.37-1.58 (m, 5H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 157.9, 147.9, 147.6, 144.3, 131.6, 126.8, 121.5, 118.5, 101.6, 72.6, 72.2, 70.7, 69.3, 60.0, 58.5, 55.8, 43.3, 38.7, 34.9, 30.8, 28.3, 25.8, 24.4, 21.8. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{35}\text{N}_2\text{O}_3\text{S}_2$ 463.2089; Found 463.2081.

methyl 3-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)quinuclidin-3-yl)ethyl)thio)propanoate [3i]. Compound **3i** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and methyl 3-mercaptopropionate (1.45 M). Purification by flash chromatography on silica gel (8% MeOH-DCM with 1% ammonia) gave **3i** as a yellow solid (409.5 mg, 92%). mp 42-43 °C. IR (ATR) ν 3074, 2923, 2862, 1733, 1620, 1590, 1508, 1432, 1237, 1028, 824 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.51 (d, 1H, $J = 4.5$ Hz), 7.90 (d, 1H, $J = 9.2$ Hz), 7.44 (d, 1H, $J = 4.5$ Hz), 7.27 (dd, 1H, $J = 2.6, 9.2$ Hz), 7.19 (d, 1H, $J = 2.6$ Hz), 5.48 (d, 1H, $J = 3.6$ Hz), 4.48 (br s, 1H), 3.86 (s, 3H), 3.64 (s, 3H), 3.36-3.50 (m, 1H), 2.95-3.10 (m, 2H), 2.66-2.74 (m, 2H), 2.57-2.65 (m, 1H), 2.49-2.57 (m, 2H), 2.41 (t, 2H, $J = 7.6$ Hz), 2.27-2.37 (m, 1H), 1.67-1.80 (m, 3H), 1.61 (br s, 1H), 1.33-1.56 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz) δ 172.4, 157.8, 148.0, 147.5, 144.1, 131.5, 126.7, 121.5, 118.5, 101.4, 72.0, 59.8, 58.3, 55.8, 51.9, 43.3, 34.7, 34.6, 34.5, 30.2, 28.2, 27.1, 25.7, 21.5. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{24}\text{H}_{33}\text{N}_2\text{O}_4\text{S}$ 445.2161; Found 445.2151.

2-ethylhexyl3-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)

quinuclidin-3-yl)ethyl)thio)propanoate [3j]. Compound **3j** was prepared following the general procedure using quinine **1a** (0.25 M), DMPA (0.3 M) and 2-ethylhexylmercaptopropionate (0.73 M). Purification by flash chromatography on silica gel (8% MeOH- CH_2Cl_2 with 1% ammonia) gave **3j** as a brown gel (235 mg, 86%). IR (ATR) ν 3074, 2925, 2861, 1731, 1620, 1508, 1457, 1236, 1030, 826 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 8.57 (d, 1H, $J = 4.5$ Hz), 7.94 (d, 1H, $J = 9.2$ Hz), 7.45 (d, 1H, $J = 4.5$ Hz), 7.29 (dd, 1H, $J = 2.6, 9.2$ Hz), 7.22 (d, 1H, $J = 2.6$ Hz), 5.47 (d, 1H, $J = 3.8$ Hz), 3.92-4.04 (m, 2H), 3.88 (s, 3H),

3.33-3.46 (m, 1H), 2.99-3.10 (m, 2H), 2.71 (t, 2H, $J = 7.2$ Hz), 2.57-2.66 (m, 1H), 2.54 (t, 2H, $J = 7.3$ Hz), 2.43 (t, 2H, $J = 7.4$ Hz), 2.29-2.38 (m, 1H), 1.59-1.79 (m, 4H), 1.37-1.58 (m, 5H), 1.17-1.36 (m, 8H), 0.80-0.92 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 172.2, 157.9, 147.9, 147.6, 144.4, 131.7, 126.8, 121.5, 118.5, 101.6, 72.2, 67.3, 60.0, 58.5, 55.8, 43.3, 38.8, 35.0, 34.9, 34.6, 30.5, 30.3, 29.0, 28.3, 27.3, 25.8, 23.9, 23.1, 21.8, 14.1, 11.1. HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{31}\text{H}_{47}\text{N}_2\text{O}_4\text{S}$ 543.3257; Found 543.3255.

3-methoxybutyl3-((2-((1S,3R,4S)-6-((R)-hydroxy(6-methoxyquinolin-4-yl)methyl)

quinuclidin-3-yl)ethyl)thio)propanoate [3k]. Compound **3k** was prepared following the general procedure using quinine **1a** (0.25 M), DMPA (0.3 M) and 3-methoxybutyl-3-mercaptopropionate (0.73 M). Purification by flash chromatography on silica gel (8% MeOH- CH_2Cl_2 with 1% ammonia) gave **3k** as a brown oil (231 mg, 89%). IR (ATR) ν 3074, 2924, 2864, 1730, 1620, 1590, 1508, 1237, 1082, 1029, 825 cm^{-1} . ^1H NMR (CDCl_3 , 400 MHz) δ 8.55 (d, 1H, $J = 4.5$ Hz), 7.92 (d, 1H, $J = 9.2$ Hz), 7.44 (d, 1H, $J = 4.5$ Hz), 7.28 (dd, 1H, $J = 2.6, 9.2$ Hz), 7.22 (d, 1H, $J = 2.6$ Hz), 5.46 (d, 1H, $J = 3.9$ Hz), 4.14 (t, 3H, $J = 6.6$ Hz), 3.88 (s, 3H), 3.32-3.45 (m, 2H), 3.27 (s, 3H), 2.98-3.10 (m, 2H), 2.70 (t, 2H, $J = 7.2$ Hz), 2.56-2.64 (m, 1H), 2.52 (t, 2H, $J = 7.2$ Hz), 2.42 (t, 2H, $J = 7.5$ Hz), 2.28-2.37 (m, 1H), 1.65-1.82 (m, 5H), 1.62 (br s, 1H), 1.34-1.57 (m, 4H), 1.13 (d, 3H, $J = 6.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 172.0, 157.8, 148.0, 147.6, 144.3, 131.6, 126.8, 121.5, 118.5, 101.6, 73.8, 72.2, 61.9, 60.0, 58.4, 56.2, 55.8, 43.3, 35.6, 35.0, 34.9, 34.6, 30.3, 28.3, 27.2, 25.8, 21.8, 19.2. HRMS (ESI) m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{28}\text{H}_{41}\text{N}_2\text{O}_5\text{S}$ 517.2736; Found 517.2736.

(1R)-((1S,4S,5R)-5-(2-(benzylthio)ethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-

yl)methanol [3l]. Compound **3l** was prepared following the general procedure using quinine **1a** (0.5 M), DMPA (0.6 M) and benzyl mercaptan (1.45 M). Purification by flash chromatography on silica gel (10% MeOH- CH_2Cl_2 with 1% ammonia) gave **3l** as a yellow solid (423 mg, 94%). mp 75-76 $^\circ\text{C}$ [Lit.⁸⁴ 50-55 $^\circ\text{C}$]. IR (ATR) ν 2919, 2862, 1619, 1589, 1507, 1451, 1430, 1234, 1027, 699 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.60 (d, 1H, $J = 4.5$ Hz), 7.90 (d, 1H, $J = 9.2$ Hz), 7.50 (d, 1H, $J = 4.5$ Hz), 7.15-7.24 (m, 5H), 7.08-7.14 (m, 2H), 5.70 (br s, 1H), 4.57 (br s, 1H), 3.80 (s, 3H), 3.65 (br s, 1H), 3.61 (s, 2H), 3.00-3.12 (m, 2H), 2.62-2.74 (m, 1H), 2.31-2.39 (m, 1H), 2.28 (t, 2H, $J = 7.48$ Hz), 1.74-1.90 (m, 2H), 1.62-1.74 (m, 2H), 1.24-1.51 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 100 MHz) δ 158.0, 147.5, 147.0, 144.2, 138.4,

131.6, 128.8, 128.6, 127.1, 126.4, 121.7, 118.6, 101.2, 70.7, 60.0, 58.0, 56.1, 43.5, 36.6, 34.4, 34.3, 29.3, 27.4, 25.6, 20.7. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{27}H_{33}N_2O_2S$ 449.2263; Found 449.2261.

Methyl 3-((2-((3R,4S,6S)-6-((R)-hydroxy(quinolin-4-yl)methyl)quinuclidin-3-yl)ethylthio)propanoate [3n].

Compound **3n** was prepared following the general procedure using cinchonidine **1b** (0.25 M), DMPA (0.3 M) and methylmercaptopropionate (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3n** as a yellow solid (174 mg, 84%). mp 146.5 °C [Lit.⁸⁵ 142 °C]. IR (ATR) ν 2925, 2858, 1721, 1590, 1433, 1223, 824, 750 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.76 (d, 1H, J = 4.5 Hz), 8.04 (dd, 1H, J = 0.9, 8.5 Hz), 7.92 (d, 1H, J = 8.1 Hz), 7.57-7.64 (m, 1H), 7.54 (d, 1H, J = 4.5 Hz), 7.29-7.36 (m, 1H), 5.64 (d, 1H, J = 3.6 Hz), 4.72 (br s, 1H), 3.64 (s, 3H), 3.41-3.56 (m, 1H), 2.94-3.09 (m, 2H), 2.64-2.75 (m, 2H), 2.48-2.63 (m, 3H), 2.53 (t, 2 H, J = 7.0 Hz), 2.26-2.36 (m, 1H), 1.68-1.85 (m, 3H), 1.62 (br s, 1H), 1.32-1.55 (m, 4H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 172.5, 150.2, 149.5, 148.2, 130.3, 129.2, 126.8, 125.7, 123.0, 118.3, 71.7, 60.3, 58.3, 51.9, 43.3, 34.7, 34.6, 34.5, 30.2, 28.0, 27.1, 25.8, 21.2. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{23}H_{31}N_2O_3S$ 415.2055; Found 415.2047.

3-methoxybutyl 3-((2-((3R,4S,6S)-6-((R)-hydroxy(quinolin-4-yl)methyl)quinuclidin-3-yl)ethylthio)propanoate [3o].

Compound **3o** was prepared following the general procedure using cinchonidine **1b** (0.25 M), DMPA (0.3 M) and 3-methoxybutyl-3-mercaptopropionate (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3o** as a yellow solid (194 mg, 80%). mp 105.5 °C. IR (ATR) ν 2926, 1729, 1162, 1098, 754 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.77 (d, 1H, J = 4.5 Hz), 8.05 (d, 1H, J = 8.4 Hz), 7.93 (d, 1H, J = 8.3 Hz), 7.62 (d t, 1H, J = 1.1, 6.9 Hz), 7.55 (d, 1H, J = 4.5 Hz), 7.35 (d t, 1H, J = 1.1, 7.7 Hz), 5.63 (d, 1H, J = 3.6 Hz), 4.49 (br s, 1H), 4.14 (t, 2H, J = 6.7 Hz), 3.41-3.55 (m, 1H), 3.31-3.41 (m, 1H), 3.27 (s, 3H), 2.95-3.10 (m, 2H), 2.69 (t, 2H, J = 7.0 Hz), 2.48-2.63 (m, 1H), 2.52 (t, 2H, J = 6.9 Hz), 2.40 (t, 2H, J = 7.5 Hz), 2.26-2.45 (m, 1H), 1.57-1.84 (m, 6H), 1.31-1.56 (m, 4H), 1.12 (d, 3H, J = 6.2 Hz). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 172.0, 150.2, 149.4, 148.2, 130.3, 129.2, 126.8, 125.7, 123.1, 118.3, 73.7, 71.8, 61.9, 60.3, 58.3, 56.2, 43.3, 35.6, 34.9, 34.7, 34.5, 30.2, 28.1, 27.2, 25.8, 21.3, 19.2. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{27}H_{39}N_2O_4S$ 487.2631; Found 487.2630.

(1R)-((2S,4S,5R)-5-(2-((2-(2-mercaptoethoxy)ethyl)thio)ethyl)quinuclidin-2-yl)(quinolin-4-yl)methanol [3p]. Compound **3p** was prepared following the general procedure using cinchonidine **1b** (0.25 M), DMPA (0.3 M) and bis-mercaptoethylether (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3p** as a yellow solid (190 mg, 88%). mp 122 °C. IR (ATR) ν 2917, 2859, 1589, 1570, 1508, 1450, 1095 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.82 (d, 1H, *J* = 4.5 Hz), 8.08 (dd, 1H, *J* = 0.9 Hz, 8.5 Hz), 7.96 (d, 1H, *J* = 8.2 Hz), 7.60-7.69 (m, 1H), 7.56 (d, 1H, *J* = 4.5 Hz), 7.35-7.43 (m, 1H), 5.66 (d, 1H, *J* = 3.7 Hz), 4.01 (br s, 1H), 3.56 (t, 2H, *J* = 6.7 Hz), 3.54 (t, 2H, *J* = 6.3 Hz), 3.41-3.51 (m, 1H), 2.97-3.13 (m, 2H), 2.53-2.70 (m, 5H), 2.45 (t, 2H, *J* = 7.5 Hz), 2.31-2.41 (m, 1H), 1.69-1.84 (m, 3H), 1.64 (br s, 1H), 1.36-1.59 (m, 5H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 150.2, 149.3, 148.2, 130.3, 129.2, 126.8, 125.6, 123.0, 118.3, 72.6, 71.6, 70.7, 60.3, 58.2, 43.4, 34.7, 34.6, 31.8, 30.7, 28.0, 25.8, 24.4, 21.2. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₃H₃₃N₂O₂S₂ 433.1983; Found 433.1978.

(1S)-((2R,4S,5R)-5-(2-(benzylthio)ethyl)quinuclidin-2-yl)(6-methoxyquinolin-4-yl)methanol [3q]. Compound **3q** was prepared following the general procedure using quinidine **1c** (0.25 M), DMPA (0.3 M) and benzyl mercaptan (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3q** as a yellow solid (214 mg, 95%). mp 55.5 °C. IR (ATR) ν 2924, 2858, 1721, 1590, 1568, 1448, 1206, 1105, 1090, 750 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.63 (d, 1H, *J* = 4.5 Hz), 7.95 (d, 1H, *J* = 9.2 Hz), 7.50 (d, 1H, *J* = 4.5 Hz), 7.20-7.33 (m, 6H), 7.13 (d, 1H, *J* = 2.7 Hz), 5.61 (d, 1H, *J* = 3.5 Hz), 4.00 (br s, 1H), 3.82 (s, 3H), 3.69 (s, 2H), 3.05-3.14 (m, 1H), 2.97-3.04 (m, 1H), 2.80-2.92 (m, 2H), 2.63-2.77 (m, 1H), 2.37 (t, 2H, *J* = 7.5 Hz), 1.89-1.98 (m, 1H), 1.64-1.74 (m, 2H), 1.53-1.63 (m, 2H), 1.39-1.49 (m, 2H), 1.00-1.11 (m, 1H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 157.8, 147.7, 147.6, 144.3, 138.6, 131.7, 128.9, 128.6, 127.1, 126.6, 121.7, 118.5, 101.2, 71.9, 59.7, 55.8, 50.9, 50.3, 36.5, 34.7, 31.9, 29.4, 26.9, 26.5, 20.6. HRMS (ESI) *m/z* [M + H]⁺ Calcd for C₂₇H₃₃N₂O₂S 449.2263; Found 449.2259.

(1S)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-(2-(propylthio)ethyl)quinuclidin-2-yl)methanol [3r]. Compound **3r** was prepared following the general procedure using quinidine **1c** (0.25 M), DMPA (0.3 M) and 1-propanethiol (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3r** as a yellow solid (152 mg, 75%).

mp 142-144 °C [Lit.¹⁸ 148-149 °C]. IR (ATR) ν 3125, 2929, 2867, 1620, 1590, 1507, 1227, 1027, 828 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.58 (d, 1H, J = 4.5 Hz), 7.92 (d, 1H, J = 9.2 Hz), 7.50 (d, 1H, J = 4.5 Hz), 7.27 (dd, 1H, J = 2.7, 9.2 Hz), 7.13 (d, 1H, J = 2.7 Hz), 5.60 (d, 1H, J = 3.5 Hz), 4.45 (br s, 1H), 3.82 (s, 3H), 3.08-3.23 (m, 1H), 2.94-3.06 (m, 1H), 2.63-2.94 (m, 3H), 2.38-2.51 (m, 4H), 1.91-2.03 (m, 1H), 1.51-1.78 (m, 6H), 1.36-1.51 (m, 2H), 1.01-1.11 (m, 1H), 0.98 (t, 3H, J = 7.3 Hz). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 157.8, 147.8, 147.6, 144.2, 131.6, 126.6, 121.6, 118.5, 101.2, 71.9, 59.7, 55.7, 51.0, 50.3, 34.7, 34.4, 32.4, 30.2, 27.0, 26.5, 23.1, 20.6, 13.7. HRMS (ASAP+) m/z [M + H]⁺ Calcd for C₂₃H₃₃N₂O₂S 401.2263; Found 401.2259.

(1S)-(6-methoxyquinolin-4-yl)((2R,4S,5R)-5-(2-(octylthio)ethyl)quinuclidin-2-yl)methanol [3s]. Compound **3s** was prepared following the general procedure using quinidine **1c** (0.25 M), DMPA (0.3 M) and 1-octanethiol (0.73 M). Purification by flash chromatography on silica gel (5% MeOH-CH₂Cl₂ with 1% ammonia) gave **3s** as a yellow solid (186 mg, 79%). mp 105.5 °C. IR (ATR) ν 3069, 2922, 2853, 1620, 1509, 1459, 1257, 1038, 821 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.62 (d, 1H, J = 4.5 Hz), 7.95 (d, 1H, J = 9.2 Hz), 7.51 (d, 1H, J = 4.5 Hz), 7.29 (dd, 1H, J = 2.7, 9.2 Hz), 7.15 (d, 1H, J = 2.7 Hz), 5.59 (d, 1H, J = 3.7 Hz), 4.08 (br s, 1H), 3.84 (s, 3H), 3.07-3.19 (m, 1H), 2.96-3.07 (m, 1H), 2.80-2.96 (m, 2H), 2.64-2.80 (m, 1H), 2.47 (q, 4H, J = 7.2 Hz), 1.90-2.02 (m, 1H), 1.64-1.77 (m, 3H), 1.42-1.64 (m, 5H), 1.17-1.42 (m, 10H), 1.00-1.14 (m, 1H), 0.79-0.93 (m, 3H). ¹³C{¹H} NMR (CDCl₃, 75 MHz) δ 157.8, 147.7, 147.7, 144.3, 131.7, 126.6, 121.6, 118.5, 101.2, 72.1, 59.8, 55.7, 51.0, 50.3, 34.7, 32.4, 32.0, 30.3, 29.8, 29.4, 29.3, 29.1, 27.1, 26.6, 26.3, 22.8, 20.8, 14.2. HRMS (ESI) m/z [M + H]⁺ Calcd for C₂₈H₄₃N₂O₂S 471.3045; Found 471.3054.

(1S)-((2R,4S,5R)-5-(2-(octylthio)ethyl)quinuclidin-2-yl)(quinolin-4-yl)methanol [3t]. Compound **3t** was prepared following the general procedure using cinchonine **1d** (0.25 M), DMPA (0.3 M) and 1-octanethiol (0.73 M). Purification by flash chromatography on silica gel (4% MeOH-CH₂Cl₂ with 1% ammonia) gave **3t** as a white solid (92 mg, 42%). mp 166 °C. IR (ATR) ν 3065, 3035, 2920, 2870, 2852, 2708, 2590, 1590, 1568, 1507, 1457, 1113 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) δ 8.85 (d, 1H, J = 4.5 Hz), 8.09 (dd, 1H, J = 0.84 Hz, 8.5 Hz), 7.90 (d, 1H, J = 8.2 Hz), 7.56-7.68 (m, 2H), 7.36 (app tm, 1H, J = 8.2 Hz), 5.75 (d, 1H, J = 3.6 Hz), 4.21 (br s, 1H), 3.11-3.23 (m, 1H), 2.95-3.07 (m, 1H), 2.78-2.94 (m, 2H), 2.63-2.78 (m, 1H),

2.38-2.52 (m, 4H), 1.98 (dd, 1H, $J = 9.4, 12.7$ Hz), 1.42-1.81 (m, 8H), 1.18-1.41 (m, 10H), 1.00-1.13 (m, 1H), 0.88 (t, 3H, $J = 6.5$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz) δ 150.3, 149.2, 148.3, 130.5, 129.1, 126.8, 125.7, 123.1, 118.4, 71.8, 60.1, 51.0, 50.3, 34.7, 32.4, 32.4, 32.0, 30.3, 29.8, 29.4, 29.4, 29.1, 27.0, 26.5, 22.8, 20.7, 14.3. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{27}\text{H}_{41}\text{N}_2\text{OS}$ 441.2940; Found 441.2936.

(1S)-((2R,4S,5R)-5-(2-((2-(2-mercaptoethoxy)ethyl)thio)ethyl)quinuclidin-2-yl)(quinolin-4-yl)methanol [3u]. Compound **3u** was prepared following the general procedure using quinuclidine **1d** (0.25 M), DMPA (0.3 M) and bis-mercaptoethylether (0.73 M). Purification by flash chromatography on silica gel (3% MeOH- CH_2Cl_2 with 1% ammonia) gave **3u** as a white solid (105 mg, 49%). mp 172 °C. IR (ATR) ν 3064, 3033, 2920, 2870, 2854, 2705, 2557, 1589, 1567, 1506, 1455, 1419, 1108 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.83 (d, 1H, $J = 4.5$ Hz), 8.08 (dd, 1H, $J = 0.9, 8.5$ Hz), 7.88 (d, 1H, $J = 8.2$ Hz), 7.57-7.70 (m, 2H), 7.28-7.40 (m, 1H), 6.90 (app tm, 1H, $J = 8.3$ Hz), 5.72 (d, 1H, $J = 3.6$ Hz), 4.48 (br s, 1H), 3.60 (q, 4H, $J = 6.9$ Hz), 3.11-3.23 (m, 1H), 2.96-3.05 (m, 1H), 2.74-2.96 (m, 2H), 2.57-2.74 (m, 5H), 2.40-2.57 (m, 2H), 1.90-2.09 (m, 1H), 1.69-1.87 (m, 2H), 1.52-1.69 (m, 2H), 1.34-1.52 (m, 2H), 0.96-1.12 (m, 1H). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz) δ 150.2, 149.4, 148.3, 130.4, 129.1, 126.8, 125.7, 123.1, 118.3, 72.7, 72.0, 70.7, 60.1, 50.9, 50.3, 34.8, 32.6, 31.7, 30.8, 27.1, 26.6, 24.5, 20.6. HRMS (ESI) m/z $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{23}\text{H}_{33}\text{N}_2\text{O}_2\text{S}_2$ 433.1983; Found 433.1982.

2-ethylhexyl 3-((2-((3R,4S,6R)-6-((S)-hydroxy(quinolin-4-yl)methyl)quinuclidin-3-yl)ethyl)thio)propanoate [3v]. Compound **3v** was prepared following the general procedure using quinuclidine **1d** (0.25 M), DMPA (0.3 M) and 2-ethylhexylmercaptopropanoate (0.73 M). Purification by flash chromatography on silica gel (3% MeOH- CH_2Cl_2 with 1% ammonia) gave **3v** as a white solid (100 mg, 39%). mp 129.5 °C. IR (ATR) ν 3065, 3046, 2954, 2923, 1731, 1590, 1567, 1505, 1458, 1335, 1234 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 8.82 (d, 1H, $J = 4.5$ Hz), 8.07 (d, 1H, $J = 8.5$ Hz), 7.88 (d, 1H, $J = 8.4$ Hz), 7.54-7.67 (m, 2H), 7.35 (t, 1H, $J = 7.2$ Hz), 5.74 (d, 1H, $J = 3.1$ Hz), 4.64 (br s, 1H), 3.90-4.05 (m, 2H), 3.11-3.25 (m, 1H), 2.91-3.05 (m, 1H), 2.63-2.90 (m, 5H), 2.58 (t, 2H, $J = 7.2$ Hz), 2.47 (t, 2H, $J = 6.8$ Hz), 1.89-2.08 (m, 1H), 1.68-1.87 (m, 2H), 1.49-1.67 (m, 3H), 1.38-1.49 (m, 2H), 1.16-1.39 (m, 8H), 0.94-1.14 (m, 1H), 0.87 (t, 6H, $J = 7.2$ Hz). $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz) δ 172.4, 150.3, 149.4, 148.2, 130.4, 129.1, 126.8, 125.6, 123.0, 118.3, 71.9, 67.3, 60.1, 50.8, 50.3, 38.8, 35.0, 34.7, 32.3,

30.5, 30.2, 29.0, 27.2, 27.0, 26.5, 23.9, 23.1, 20.4, 14.2, 11.1. HRMS (ESI) m/z $[M + H]^+$ Calcd for $C_{30}H_{45}N_2O_3S$ 513.3151; Found 513.3154.

Author contributions

FXF conceived the project, created the flow photochemical reactor and coordinated the efforts of the research team. EKK, EB and EA conducted chemical experiments in flow. ADA and VC supervised chemical experiments. FXF wrote the paper with input from all authors.

Conflicts of interest

There are no conflicts to declare.

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