Synthesis of Chiral Thiourea-Thioxanthone Hybrids

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Abstract

Four different 1-aminocyclohexanes bearing a tethered thioxanthone group in the 2-position were prepared. The synthesis commenced with the respective N-protected β-amino acids, the carboxyl group of which was employed for the introduction of the thioxanthone moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety. After construction of the thioxanthone and protecting group removal, the conversion of the amino group into the respective moiety.

Key words

Thioxanthone (9H-thioxanthen-9-one) exhibits its longest wavelength absorption maximum at \( \lambda = 376 \text{ nm} \) (\( \varepsilon = 6200 \text{ M}^{-1} \text{ cm}^{-1} \)) and its triplet energy has been determined as 265 kJ mol\(^{-1}\). The triplet state is populated by direct irradiation with a quantum yield of 0.85 in benzene and thioxanthone has consequently been employed as a triplet sensitizer for several applications. Recent interest in visible-light-induced enantioselective transformations has led to the development of thioxanthone derivatives in which the chromophore is linked to a chiral backbone. In our group, the linkage was achieved via oxazole annulation to a chiral 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one scaffold. Overall yields varied between 20–35%.

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The choice of compounds depicted in Figure 1 was inspired by the idea to make a set of chiral 1,2-disubstituted cyclohexanes available in which the thiourea and the thioxanthone unit would be oriented in varying spatial arrangements. Compound 1 bears both units in equatorial positions of a cyclohexane chair while a boat conformation of the cyclohexane is enforced in compound 2 with the thioxanthone and thiourea both located in a pseudoequatorial (exo) position. In compound 3, either thiourea or thioxanthone could be axially positioned with the other substituent being equatorial. Since there was evidence (vide infra) that the thioxanthone was equatorial in compound 3, a fourth cyclohexane derivative 4 was designed in which the thioxanthone unit would definitely be axial but the thiourea equatorial. In all catalysts 1–4, the aryl substituent was selected to be the privileged 3,5-bis(trifluoromethyl)phenyl group.

Taking compound 1 as an example, a few retrosynthetic considerations are illustrated in Scheme 1. Primary amine 5 was chosen as an immediate precursor for the thiourea since it was expected that treatment with 3,5-bis(trifluoro-
methyl)phenyl isothiocyanate\textsuperscript{15} would not interfere with the thioxanthone functionality. In previous work on chiral templates and catalysts for enantioselective reactions, the oxazole group was identified as a reliable linker to be annulated to a given arene.\textsuperscript{16} Formation of the oxazole requires a carboxylic acid precursor and it was expected that the amine group had to be protected prior to the annulation. The arene is normally introduced as its \textit{ortho}-nitro-substituted aryl ester that upon reduction rearranges to the respective \textit{ortho}-hydroxy-substituted amide (Scheme 2). For the desired thioxanthone annulation the starting material was thus 3-hydroxy-2-nitrothioxanthone,\textsuperscript{5a} which was to be linked to an appropriately N-protected carboxylic acid derived from enantiopure compound \textit{6}. Initial attempts to employ a benzyloxycarbonyl or tert-butyloxycarbonyl amine protecting group revealed that they were incompatible with the formation of the aryl ester bond or the subsequent reduction step. Likewise the immediate formation of the thiourea prior to the oxazole annulation was not viable. In most instances, not even the required ester A (Scheme 2) could be formed in useful yields. The phthaloyl protecting group (Phth) was thus selected as a putatively more robust protecting group with compound \textit{7} being the desired starting material.

In previous work, the introduction of the thioxanthone had been achieved by reduction of the nitro group with tin(II) chloride in refluxing THF.\textsuperscript{5a} The cyclization of amide B to the desired oxazole C was performed with thionyl chloride/pyridine (py) in refluxing benzene. When attempting to apply these conditions to the synthesis of N-substituted ester derivatives of acid \textit{6}, there was either no reaction or the formation of decomposition products was observed. The most promising route was the immediate use of the respective thiourea with which a moderate yield of the respective ester A was achieved. The reduction could, however, not be performed.

Similar issues were initially encountered with the N-phthaloyl derivative \textit{7}, which was readily accessible from acid \textit{6} by treatment with phthalic anhydride (8) and triethylamine in benzene (Scheme 3).\textsuperscript{17} Ester formation proceeded smoothly after activation via the acid chloride and reaction with thioxanthone \textit{9}.\textsuperscript{5a} Attempted reduction of compound \textit{10} with tin(II) chloride or by Pd-catalyzed transfer hydrogenation\textsuperscript{18} remained unsuccessful. Gratifyingly, it
was found that the nitro group could be reduced smoothly with indium in an acidic THF/water mixture. In the event, the acyl group underwent the expected O–N migration and amide 11 was isolated in 81% yield. The cyclization to the oxazole ring was achieved under Mitsunobu conditions while the use of SOCl₂ and POCl₃ as dehydrating agents failed. Oxazole 12 was obtained in 83% yield and the removal of the phthaloyl protecting group was accomplished by hydrazinolysis. Eventually, the desired thiourea was prepared by treatment of amine 5 with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (13). The relatively low overall yield is likely due to material loss in the hydrazinolysis reaction (vide infra).

For the synthesis of compound 2, access to enantiopure β-amino acid 14 was required (Scheme 4). This goal was accomplished by applying a known enantiotopos-differentiating methanolation reaction to the respective succinimide anhydride. Curtius rearrangement, reduction, and ester hydrolysis (100 °C in 1,4-dioxane/water) led to the desired compound, which was converted into the phthaloyl derivative 15 by treatment with phthalic anhydride. Hydrogenation of the endocyclic double bond furnished carboxylic acid 16, the enantiomeric excess (ee) of which was determined by chiral HPLC analysis to be 98%. The remaining sequence followed the route developed for compound 1. After formation of ester 17, the reduction of the nitro arene with indium and the concomitant rearrangement led to amide 18, which was further transformed under Mitsunobu conditions into thioxanthone 19. In this instance, the attempted removal of the phthaloyl group by hydrazinolysis was not successful but led only to decomposition. Methylamine led to the cleavage of one imide N–C bond but the reaction remained stalled at the stage of the amide. The best result was achieved by treating phthalimide 19 with ethylenediamine (EDA) at 50 °C. The protecting group was completely removed and the resulting primary amine was immediately converted into the desired thiourea 2.

While the thiourea and the thioxanthone are locked by the rigid norbornane ring in 2, a conformationally more flexible cis-substitution at the cyclohexane ring was expected for thiourea 3. The synthesis (Scheme 5) commenced with commercially available N-benzoyl (Bz)-protected amino acid 20, which was converted via free acid hydrochloride into the N-phthaloyl-protected amino acid 22. The subsequent sequence of esterification, reduction/rearrangement, and oxazole ring closure proved its reliability and efficiency by providing the respective intermediates 23, 24, and 25 in excellent yields (89–97%). Treatment with EDA turned out to be also in this case the preferred method for phthaloyl removal and delivered the primary amine for immediate conversion into thiourea 3. The overall yield for the six-step synthesis was 35%.

The conformational preference of compound 3 was studied by 1H NMR spectroscopy at ambient temperature. The proton at carbon atom C1 (Scheme 6) is expected to exhibit in conformation 3 one large coupling constant due to the axial-axial coupling (J₁,₃) and two small coupling constants due the axial-equatorial coupling (J₁,₃). Indeed, its precursor 25 showed exactly this pattern with J₁,₃ = 13.2 Hz and J₁,₃ = 5.2 Hz and J₁,₃ = 3.6 Hz. The proton at C2 appeared as a virtual quartet with an average coupling constant of J = 5.2 Hz. Related 1H NMR data were recorded for compounds 23 and 24. However, the situation was different for compound 3. The 1H NMR spectrum revealed for H1 a signal that appeared as virtual tt with two coupling constants of J
Applying there is no clear preference for either conformer $3'$ or $3''$ and neither proton H1 nor H2 has a clear preference for the axial position. Rather it seems as if an equilibrium was established at ambient temperature most likely due to the fact that the two substituents at C1 and C2 are similar in size. In order to establish a less ambiguous conformational situation within the cis-substituted cyclohexane ring, a thiourea-thioxanthone hybrid 4 was devised in which the thioxanthone was linked to the cyclohexane ring by the linear, sterically unencumbered ethynyl group. The synthesis of this compound started from hydrochloride 21, which was reduced with LiAlH4 in THF to furnish amino alcohol 26 in 93% yield (Scheme 7). Upon tert-butylcarbonyl (Boc) protection of the amino group, alcohol 27 was subjected to a Swern oxidation.31 The resulting aldehyde 28 was converted into the terminal alkyne 29 by Seyferth–Gilbert homologization.32 Sonogashira cross-coupling33 with the known 2-bromothioxanthone (30)34 gave the 2-substituted thioxanthone 31, which could be readily deprotected with trifluoroacetic acid (TFA) to give the desired amine 32. As in the previous syntheses, the desired thiourea was generated by treatment of the amine with 3,5-bis(trifluoromethyl)phenyl isothiocyanate (13).

As expected, compound 4 displays preferred conformation $4'$ in which the tethered thioxanthone is axially positioned. The $^1H$ NMR coupling pattern of proton H1 is a virtual ddt with coupling constants of $J' = 12.4$ Hz, $J' = 8.5$ Hz, and $J'' = 3.9$ Hz. Since the coupling constant of $J' = 8.5$ Hz could be clearly assigned to the vicinal CH–NH coupling the other coupling constants are due to vicinal CH–CH coupling. With $J_{	ext{ax}} = 12.4$ Hz and $J_{	ext{eq}} = 3.9$ Hz. Likewise, the equatorial proton H2 shows a virtual quartet with $J_{	ext{eq}} = 3.6$ Hz.

The UV/Vis spectra of the new thioxanthones are all similar (see the Supporting Information) and the spectrum of compound 4 is representatively shown in Figure 2. The long-wavelength absorption between 370 and 420 nm with a $\lambda_{\text{max}} = 392$ nm ($\varepsilon = 3340$ M$^{-1}$ cm$^{-1}$) is likely due to the thioxanthone chromophore while the strong absorptions setting in below 320 nm are attributed to allowed transitions of the thiourea and the thioxanthone. In line with their UV/Vis spectra, the compounds are yellow-colored solids. Phosphorescence data have not yet been obtained but it was expected that the compounds will act as triplet sensitizers in the same fashion as does the parent thioxanthone.

In preliminary and non-optimized experiments, it was probed whether the thiourea-thioxanthone hybrids would act as catalysts of visible-light-induced reactions. Along these lines, catalyst 4 was employed in the photocyclization of 2-aryloxy cyclohex-2-enones,35 which has recently
received increasing attention.\textsuperscript{3h,36} Gratifyingly, we found that the reaction of compound 33, which does not proceed at $\lambda = 419$ nm in the absence of a sensitizer could be successfully promoted by catalyst 4 (Scheme 8). Although the yield and enantioselectivity of product 34 was low, the experiment demonstrates that the thiourea-thioxanthone hybrids are catalytically active and that an asymmetric binding event at the NH-hydrogen atoms of the thiourea is likely to occur.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme8.png}
\end{center}

\textbf{Scheme 8} Sensitized photocyclization of 2-(4-bromophenoxy)-3,5,5-trimethylcyclohex-2-enone (33)

In summary, we have successfully synthesized four thiourea-thioxanthone hybrid compounds from the respective $\beta$-amino acids. For the attachment of the thioxanthone by oxazole annulation we have devised a generally applicable and mild reaction sequence. The compounds exhibit a two-point hydrogen bonding site at the thiourea and it is expected that the thiourea will act as a sensitizer to promote photochemical reactions of bound substrates in the respective 1:1 complexes. Work along these lines is currently underway in our laboratories and will be reported in due course.

All reactions involving moisture-sensitive chemicals were carried out in flame-dried glassware under positive pressure of argon with magnetic stirring. THF, CH$_2$Cl$_2$, and Et$_2$O were purified using a SPS-800 solvent purification system (M. Braun). TLC was performed on silica-coated glass plates (silica gel 60 F$254$) with detection by UV ($\lambda = 254$ nm), cerium ammonium molybdate (CAM) or KMnO$_4$ (0.5% in H$_2$O). All solvents were distilled prior to use. Solutions refer to sat. aq solutions, unless otherwise stated. IR spectra were recorded on a JASCO IR-4100 (ATR). MS/HRMS measurements were performed on a Finnigan MAT 8200 or thermo Fisher DFS (EI)/Finnigan LSQ classic or Thermo Fisher LTY Orbitrap XL (ESI). $^1$H and $^{13}$C NMR spectra were recorded in CDC$_3$ or DMSO-d$_6$ at 300 K on a Bruker AV-360, Bruker AVHD-400, Bruker AV-500, or a Bruker AVHD-500 instrument. Chemical shifts are reported relative to CHCl$_3$ ($\delta = 7.26$) or DMSO-d$_6$ ($\delta = 2.50$). Apparent multiplets that occur as a result of the accidental equality of coupling constants to those of magnetically nonequivalent protons are marked as virtual (vrt.). The multiplicities of the $^{13}$C NMR signals were determined by DEPT-edited phase sensitive HSQC experiments. Assignments are based on COSY, HMBC, HSQC, and NOESY experiments. Signals that could not be assigned unambiguously are marked with an asterisk (*). UV/Vis Spectroscopy was performed on a PerkinElmer Lambda 35 UV/Vis spectrometer. Unless otherwise mentioned, UV spectra were recorded using a Hellma precision cell made of quartz with a pathway of 1 mm. Solvents and concentrations are given for each spectrum. Rotation value measurements were performed on a Bellingham & Stanley ADP400+ with a 0.05 dm cuvette at $\lambda = 589$ nm (Na d-line) at room temperature. The specific rotation is given in $^{10}$° cm$^{-1}$ g$^{-1}$, the concentration is given in g/100 mL. Analytical HPLC was performed using a chiral stationary phase (flow rate: 1.0 mL/min, column type and eluent are given for the corresponding compounds) and UV detection ($\lambda = 210$ nm or 254 nm) at 20 °C.

(1R,2R)-2-(1′,3′-Dioxoisindolin-2′-yl)cyclohexane-1-carboxylate (7)

The protected amino acid 7 (666 mg, 2.34 mmol, 1.10 equiv) was dissolved in anhyd toluene (20 mL). Subsequently, phthalic anhydride (218 mg, 1.47 mmol, 1.05 equiv) and NEt$_3$ (283 mg, 0.38 mL, 2.80 mmol, 2.00 equiv) were added. The mixture was stirred at 100 °C. After 18 h, the solution was cooled to rt and washed with aq 3 M HCl (100 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 100 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered and the solvent was removed under reduced pressure. The desired product was obtained as a colorless solid (363 mg, 1.33 mmol, 95%) and was used in the next step without purification; mp 138–140 °C; $\alpha$$_D$$^{20}$ –10 (c = 1.00, CH$_2$Cl$_2$).

IR (ATR): 3514 (m, OH), 3369 (w, OH), 2936 (m, CH sp3), 2861 (m, CH sp3), 1766 (s, C=O), 1708 (s, C=O), 1635 (s), 1605 (s), 1519 (m, C=Csp2), 1379 (m), 1341 (s), 1293 (m), 1108 (m), 1077 (m), 718 cm$^{-1}$ (m).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.28–1.60 (m, 3 H, H-5, H-6), 1.69–1.90 (m, 3 H, H-3, H-4), 1.99–2.20 (m, 2 H, H-2, H-3, H-6), 2.43 (vrt. td, $J$ = $J_2$ = 12.1 Hz, $J_1$ = 3.7 Hz, 1 H, H-1), 4.28 (dd, $J$ = 12.1, 11.3, 4.0 Hz, 1 H, H-2), 7.67 (dd, $J$ = 5.5 Hz, $J_2$ = 3.0 Hz, 2 H, H-5’, H-6’), 7.78 (dd, $J$ = 5.5 Hz, $J$ = 3.0 Hz, 2 H, H-4’, H-7’), 10.40 (br s, 1 H, OH).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 24.7 (t, C-5), 25.3 (t, C-4), 29.7 (t, C-6), 29.8 (t, C-3), 44.7 (d, C-1), 51.0 (d, C-2), 123.4 (d, 2 C, C-4’, C-7’), 131.9 (s, 2 C, C-3a’, C-7a’), 140.4 (d, 2 C, C-5’, C-6’), 168.2 (s, 2 C, C-1’, C-3’), 179.2 (s, COOH).

MS (EI, 70 eV): m/z (%) = 273 (8 [M$^+$], 227 (12, [M – CH$_3$]), 186 (15), 160 (63), 148 (20, [C$_9$H$_8$NO$_4$]$^+$), 91 (100, [C$_5$H$_7$N]$^+$).


2′-Nitro-9′-oxo-9′H-thioxanthen-3′-yl (1R,2R)-2-(1′,3′-Dioxoisindolin-2′-yl)cyclohexane-1-carboxylate (10)

The protected amino acid 7 (666 mg, 2.34 mmol, 1.10 equiv) was dissolved in anhyd CH$_2$Cl$_2$ (33 mL). Oxalyl chloride (297 mg, 0.20 mL, 2.34 mmol, 1.10 equiv) and a catalytic amount of DMF (7 drops) were added at rt. The mixture was stirred at rt for 3 h. In parallel, thioxanthone 9 (581 mg, 2.13 mmol, 1.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (10 crystals) was dissolved in anhyd CH$_2$Cl$_2$ (33 mL) and cooled to 0 °C. At this temperature, NEt$_3$ (647 mg, 0.89 mL, 6.39 mmol, 3.00 equiv) was added. The mixture was warmed to rt and stirred overnight. After 18 h, aq NH$_4$Cl (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 150 mL) and the combined organic layers were washed with aq 2 M NaOH (200 mL) dried (Na$_2$SO$_4$) and filtered. The solvent was evaporated and the desired product was obtained without further purification as a yellowish solid (1.11 g, 2.11 mmol, 98%); mp 202–205 °C; $R$$_f$ = 0.89 (CH$_2$Cl$_2$/MeOH 98:2) [UV, KmnO$_4$]; $\alpha$$_D$$^{20}$ –92 (c = 1.00, CH$_2$Cl$_2$).

IR (ATR): 3086 (w, CH$_2$), 3036 (w, CH$_2$), 2933 (m, CH sp3), 2864 (m, CH$_2$), 1766 (s, C=O), 1708 (s, C=O), 1635 (s), 1605 (s), 1519 (m, C=Csp2), 1379 (m), 1341 (s), 1293 (m), 1108 (m), 1077 (m), 1025 (m), 717 cm$^{-1}$ (m).
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1H NMR (400 MHz, CDCl₃): δ = 1.50–1.56 (m, 2 H, H-4′, H-5), 1.78 (vrt. td., J = 7.5 Hz, J = 7.8 Hz, 1 H, H-3), 1.85–1.92 (m, 4 H, H-2′, H-3′, H-4′, H-5′), 2.30–2.37 (m, 4 H, H-2′, H-3′, H-4′, H-5′), 3.19 (m, 2 H, H-6′, H-7′), 7.58 (s, 1 H, H-3′), 7.84 (d, J = 7.5 Hz, 1 H, H-4′), 7.91 (d, J = 8.0 Hz, 1 H, H-5′), 8.40 (s, 1 H, H-1′), 8.48 (d, J = 8.0 Hz, 1 H, H-2′)

IR (ATR): 3296 (w, NH), 3066 (w, OH), 2931 (m, CH sp3), 2857 (m, C-H sp3), 2813 (w, CH sp3).

**HRMS (EI): m/z [M + H]+ calc for C₂₀H₁₅N₂O₂S: 528.0991; found: 528.0995.

**(1R,2R)-2-(1′′-3′′-Dioxoisoinolin-2′-yl)N-(3′′-hydroxy-9′′-oxo-9′′H-thioxanthen-2′-yl)cyclohexane-1-carboxamide (11)**

Ester 10 (406 mg, 768 µmol, 1.00 equiv) was dissolved in THF (27 mL) and H₂O (27 mL) was added. To this solution in [441 mg, 3.84 mmol, 5.00 equiv] and concd HCl (0.75 mL) were added. The mixture was stirred at 80 °C for 18 h. After this time, the mixture was cooled to rt and CH₂Cl₂ (50 mL) was added. The mixture was filtered over Celite and washed withaq NaHCO₃ (100 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. Purification by flash chromatography (4 × 20 cm, CH₂Cl₂/MeOH 95:5) furnished the title compound as an orange-colored solid (310 mg, 622 µmol, 81%); mp 150–154 °C; Rf = 0.51 (CH₂Cl₂/MeOH 95:5) [UV, KMnO₄]; [α]D²⁰ = +91 (c = 1.00, CH₂Cl₂).

IR (ATR): 3296 (w, NH), 3066 (w, OH), 2931 (m, CH sp3), 2857 (m, C-H sp3), 2813 (w, CH sp3).

**HRMS (ESI): m/z [M + H]+ calc for C₂₀H₁₄N₂O₂S: 481.1217; found: 481.1217.

**1-[3′′,5′′- Bis(trifluoromethyl)phenyl]-3-(1R,2R)-2-(10′′-oxo-10′′H-thioxanthen-2′-yl)cyclohexylthioiurea (12)**

Oxazole 12 (70.0 mg, 146 µmol, 1.00 equiv) was dissolved in anhyd MeOH (13 mL). Hydrazine hydrate (364 mg, 3.68 mL, 20.00 equiv) was added, and the mixture was stirred at rt for 24 h. Upon removal of the solvent, the residue was dissolved in CH₂Cl₂ and filtered over SiO₂ (1 × 2 cm, CH₂Cl₂/MeOH 95:5). After evaporation of the solvent, the crude material was used in the next step without further purification. The crude material was dissolved in anhyd THF (10 mL) and 3.5-bis(trifluoromethyl)phenyl isothiocyanate (83.1 mg, 0.06 mL, 307 µmol, 2.10 equiv) was added. The reaction mixture was stirred at rt and after 18 h, the solvent was evaporated. Purification by flash chromatography (2 × 7 cm, CH₂Cl₂/MeOH 99:1) afforded the desired thioureia as a yellow solid (29.0 mg, 46.7 µmol, 32% over two steps); mp 124–126 °C; Rf = 0.20 (CH₂Cl₂/MeOH 99:1) [UV, KMnO₄]; [α]D²⁰ = +80 (c = 1.00, CH₂Cl₂).

IR (ATR): 3272 (w, NH), 2956 (w, CH₃), 2929 (w, CH₂), 2852 (w, CH₂), 1701 (m, C=O), 1625 (m, C=O), 1438 (m, CH₃), 1277 (m, CH₂), 1028 (m), 910 (m), 749 cm⁻¹ (m, CH₂).

1H NMR (400 MHz, CDCl₃): δ = 1.55–1.70 (m, 2 H, H-4′, H-5′), 1.93–2.00 (m, 2 H, H-3′, H-5′), 2.08–2.17 (m, 1 H, H-6′), 2.37–2.41 (m, 1 H, H-3′), 3.73 (br s, 1 H, H-1′), 4.96–5.16 (m, 1 H, H-1′), 7.41–7.68 (m, 5 H, H-4′, H-5′, H-6′, H-7′, H-8′), 7.95 (s, 2 H, H-2′, H-3′), 8.15 (br s, 1 H, NH), 8.50 (d, J = 8.1 Hz, 1 H, H-9′), 8.68 (s, 1 H, H-11′), 9.15 (br s, 1 H, NH).

1H NMR (400 MHz, CDCl₃): δ = 21.3 ± 0.2 (C-4′), 22.0 ± 0.3 (C-5′), 28.3 ± 0.3 (C-6′), 39.7 ± 0.3 (C-3), 54.0 ± 0.2 (C-2), 60.6 ± 0.1 (C-4), 108.8 ± 0.2 (C-4′), 117.8 (C-3′), 119.0 (C-1′′), 121.3 (C-1′′′), 122.5 (q, JCF = 165 Hz, 2 C, C-F₃).
Amino acid 14 (962 mg, 6.28 mmol, 1.00 equiv) was dissolved in anhyd toluene (150 mL). Subsequently, phthalic anhydride (978 mg, 6.60 mmol, 1.05 equiv) and NEt₃ (1.26 g, 1.74 mL, 12.6 mmol, 47.8 (t, C-7), 55.6 (d, C-3), 123.2 (d, 2 C, C-4*)', 123.4 (t, C-5), 134.3 (d, 2 C, C-5a'), 138.1 (d, 2 C, C-3a', C-7a'), 140.0 (s, C-3a'), 152.5 (s, C-11a'), 169.3 (s, C-2'), 180.0 (s, 180.3), 180.5 (s, NCS).


**Paper**

**Synthesis**

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123.8 (d, 2 C, C-2*'), 125.9 (d, C-6*'), 126.3 (d, C-7*'), 128.2 (s, C-4a*), 129.9 (d, C-8*'), 132.4 (q, J = 33.6 Hz, 2 C, C-3*'), 132.8 (d, C-9*'), 134.9 (s, C-9a*'), 137.4 (s, C-5a*), 139.9 (s, C-10a*), 140.0 (s, C-3a*), 152.5 (s, C-11a*), 169.3 (s, C-2'), 180.0 (s, 180.3), 180.5 (s, NCS).


**15,25,3R,3R)-3-(1',3'-Dioxoindolin-2'-yl)bicyclo[2.2.1]hept-5-en-2-carboxylic Acid (16)**

IR (ATR): 3089 (w, CH sp²), 2956 (w, CH sp³), 2880 (w, CH sp³), 1759 (s, C=O), 1640 (s, C=C sp²), 1338 (s, N=O), 1105 (s, C–O), 730 cm⁻¹ (m, C–S).


**15,25,3R,3R)-3-(1',3'-Dioxoindolin-2'-yl)bicyclo[2.2.1]heptane-2-carboxylate (17)**

The protected amino acid 16 (870 mg, 3.05 mmol, 1.10 equiv) was dissolved in anhyd CH₂Cl₂ (30 mL) and oxalyl chloride (387 mg, 0.26 mL, 3.05 mmol, 1.10 equiv) and a catalytic amount of DMF (5 drops) were added. The mixture was stirred at rt for 3 h. Meanwhile thionoxanthone 9 (757 mg, 2.77 mmol, 1.00 equiv) was dissolved in anhyd CH₂Cl₂ (65 mL) and cooled to 0 °C. At this temperature, NEt₃ (854 mg, 1.17 mL, 8.31 mmol, 3.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (5 crystals) was added. At 0 °C the freshly prepared solution of acid chloride was added slowly. After addition, the mixture was slowly warmed to rt and stirred overnight. After 18 h, the mixture was filtered over Celite. The combined filtrates were washed with aq 2 N NaOH (150 mL), then with CH₂Cl₂ (3 × 100 mL). The combined organic layers were washed with aq 2 N NaOH (150 mL), dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure. The desired product was obtained as a brown viscous oil (1.00 g, 5.65 mmol, 90%); [α]₂⁰⁻⁰⁴ (c = 1.00, CHCl₃).

IR (ATR): 3258 (m, OH), 2938 (w, CH₃), 2925 (w, CH₂), 1770 (m, C=O), 1703 (s, C=O), 1640 (s, C=C sp²), 1338 (s, N=O), 1105 (s, C–O), 730 cm⁻¹ (m, C–S).


**2'-Nitro-9'-oxo-9'H-thioxanthen-3'-yl(1R,2S,3R,4S)-3-(1',3'-Dioxoindolin-2'-yl)bicyclo[2.2.1]heptane-2-carboxylate (18)**

The ester 17 (400 mg, 741 mmol, 1.00 equiv) was dissolved in THF (26 mL) and H₂O (26 mL) was added. In (425 mg, 3.70 mmol, 5.00 equiv) and concd HCl (0.72 mL) were added. The mixture was heated to 80 °C and stirred for 20 h. After cooling to rt, CH₂Cl₂ (100 mL) was added and the mixture was filtered over Celite. The mixture was washed with aq NaHCO₃ (150 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (Na₂SO₄), filtered, and the solvent was removed under reduced pressure and the product was obtained as a yellow solid (1.48 g, 2.74 mmol, 99%); mp 202–206 °C; [α]₂⁰⁺⁰.4 (c = 1.00, CHCl₃).

IR (ATR): 3089 (w, CH₃), 2925 (w, CH₂), 1770 (m, C=O), 1703 (s, C=O), 1640 (s, C=C sp²), 1338 (s, N=O), 1105 (s, C–O), 730 cm⁻¹ (m, C–S).

1H NMR (75 MHz, CDCl₃): δ = 4.53 (d, 3 C, C-1), 45.6 (d, C-6, 45.9 (d, C-4, 47.8 (t, C-7), 55.6 (d, C-3), 123.2 (d, 2 C, C-4*, C-7*), 132.0 (s, 2 C, C-3a*, C-7a*), 134.0 (d, 2 C, C-5*, C-6*), 138.3 (d, C-5), 169.8 (s, C-2, C-1*, C-3*), 176.9 (s, COOH).

MS (EI): m/z (%): 92 (60, [C₆H₄⁺]), 91 (100, 65), 46 (12, [C₄H₄⁺]).

The oxazole 19 (70.0 mg, 142 μmol, 1.00 equiv) was suspended in anhyd EtOH (4.5 mL), and anhyd CH₂Cl₂ (4.5 mL) was added. To the solution ethylenediamine (85.0 mg, 0.10 mL, 1.40 mmol, 1.00 equiv) was added. The mixture was warmed to 50 °C and stirred for 20 h. After cooling, the solvent was evaporated and the crude material was filtered through a short flash column chromatography (1 × 2 cm, CH₂Cl₂/MeOH) under vacuum. The isolated product was used in the next step without further purification. The readily prepared amine was dissolved in anhyd THF (8 mL) and isothiocyanate 13 (80.8 mg, 54.0 μL, 2.10 equiv) was added. The mixture was stirred at rt. After 18 h, the solvent was evaporated and the crude material was purified by flash column chromatography (1 × 5 cm, CH₂Cl₂/MeOH 99:1). The product was isolated as a yellow solid (351.5 mg, 55.4 μmol, 39% over 2 steps); mp 202–204 °C; R₂f = 0.21 (CH₂Cl₂/MeOH 99:1) [UV, KMNq]: [α]20 D = −40 (c = 1.00, CH₂Cl₂).

IR (ATR): 3281 (m, NH), 3063 (w, CH₂), 2960 (w, CH₂), 2876 (w, CH₂), 1766 (w, CH₂), 1719 (s, C=O), 1673 (s, C=O), 1345 (s), 1239 (s), 1110 (m), 715 cm–1 (m, C–S).

HR-MS (EI): m/z [M]+ calc for C₂₇H₂₃NO₅S: 524.1527; found: 524.1522.

(1R,2S,5R)-2-Aminocyclohexane-1-carboxylic Acid Hydrochloride (21)

Amino acid 20 (3.00 g, 12.1 mmol, 1.00 equiv) was dissolved inaq 6 N HCl (150 mL). The mixture was stirred at 120 °C for 48 h. After this time, the solvent was evaporated and the product was obtained as a colorless solid (2.15 g, 12.0 mmol, 99%); mp 198–220 °C.

IR (ATR): 3281 (m, NH), 3063 (w, CH₂), 2960 (w, CH₂), 2876 (w, CH₂), 1766 (w, CH₂), 1719 (s, C=O), 1673 (s, C=O), 1345 (s), 1239 (s), 1110 (m), 715 cm–1 (m, C–S).

HR-MS (EI): m/z [M]+ calc for C₃₀H₂₄N₂O₅HCl: 538.1662; found: 538.1671.
(1R,2S)-2-(1′,3′-Dioxoisoinolin-2′-yl)cyclohexane-1-carboxylic Acid (22)
Hydrochloride 21 (493 mg, 2.75 mmol, 1.00 equiv) was dissolved in anhyd toluene (50 mL). Subsequently phthalic anhydride (427 mg, 2.88 mmol, 1.05 equiv) and NEt₃ (556 mg, 0.76 mL, 5.49 mmol, 2.00 equiv) were added. The mixture was stirred at 100 °C. After 18 h, the solution was cooled and washed with aq 3 M HCl (150 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were dried (Na₂SO₄) and filtered. The solvent was removed under reduced pressure. The desired product was obtained as a colorless solid (743 mg, 2.72 mmol, 99%); mp 144–146 °C; [α]ᵢ^20
−52 (c = 1.00, CH₂Cl₂).

IR (ATR): 3285 (m, OH), 2960 (m, CH₃), 2925 (w, CH₃), 2868 (m, CH₂), 1719 (s, C=O), 1690 (s, C=O), 1405 (m), 1372 (s, C–N), 1331 (m), 1184 (m), 1082 (m), 1018 (m), 713 cm⁻¹ (m, CH₂).

1H NMR (400 MHz, CDCl₃): δ = 1.33–1.44 (m, 1 H, H-5), 1.55 (vrt. dt, J = 13.8 Hz, J₂ = 4.0 Hz, 1 H, H-6), 1.66 (vrt. ddt, J = 13.8 Hz, 12.4 Hz, J₃ = 4.6 Hz, 1 H, H-5), 1.77 (dd, J = 13.2 Hz, 3.6 Hz, 1 H, H-4), 1.9–2.01 (vrt. t, 2 H, H-6, H-3), 2.15 (vrt. s, J = 13.8 Hz, 1 H, H-4), 2.82 (vrt. ddt, J₂ = 2.8 Hz, 1 H, H-4), 2.88 (m, 3 H, Me), 3.00 (vrt. q, J = 2.8 Hz, 1 H, H-1), 4.33 (ddd, J = 12.7 Hz, 5.3 Hz, 3.5 Hz, 1 H-2), 7.66 (dd, J = 5.5 Hz, J = 3.0 Hz, 2 H, H-5, H-6), 7.77 (dd, J = 5.5 Hz, J = 3.0 Hz, 2 H, H-4, H-7), 8.42 (br s, 1 H, COOH).

13C NMR (101 MHz, CDCl₃): δ = 21.6 (t, C-5), 26.0 (t, C-6), 26.1 (t, C-4), 27.5 (t, C-3), 42.9 (d, C-1), 52.8 (d, C-2), 128.8 (d, C-4′, C-7′), 132.0 (s, C-2, C-3′, C-7′a), 134.0 (d, 2 C, C-5′, C-6′), 168.7 (s, 2 C, C-1′, C-3′), 178.0 (s, COOH).

MS (EI, 70 eV): m/z (%) = 273 (12, [M]+), 256 (25, [C₃H₇NO₄S]+), 227 (15), 186 (23), 148 (33, [C₆H₅NO₄S]+), 91 (100).


2′-Nitro-9′-oxo-9′H-thioxanthen-3′-yl(1R,2S)-2-(1′,3′-Dioxoisoinolin-2′-yl)cyclohexane-1-carboxylic Acid (23)
The protected amino acid 22 (450 mg, 1.65 mmol, 1.10 equiv) was dissolved in anhyd CH₂Cl₂ (20 mL) and oxalyl chloride (209 mg, 0.14 mL, 1.65 mmol, 1.10 equiv) and a catalytic amount of DMF (5 drops) was added at rt. The mixture was stirred at rt for 3 h. Me₂N- while thioxanthone 9 (388 mg, 1.50 mmol, 1.00 equiv) and a catalytic amount of 4-dimethylaminopyridine (5 crystals) was dissolved in anhyd CH₂Cl₂ (45 mL) and cooled to 0 °C. At this temperature, NEt₃ (456 mg, 0.63 mL, 4.50 mmol, 3.00 equiv) was added. At 0 °C the readily prepared solution of acid chloride was added slowly. The mixture was warmed to rt and stirred overnight. After 18 h, aq NH₄Cl (80 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL) and the combined organic layers were washed with aq 2 M NaOH (150 mL), dried (Na₂SO₄), and filtered. The solvent was evaporated and the desired product was obtained without further purification as a yellowish solid (768 mg, filtered. The solvent was evaporated and the desired product was obtained after 18 h, the solution was cooled and washed with aq 3 M HCl (150 mL). The aqueous layer was extracted with CH₂Cl₂ (3 × 150 mL). The combined organic layers were dried (Na₂SO₄) and filtered. The solvent was removed under reduced pressure. The desired product was obtained as a colorless solid (743 mg, 2.72 mmol, 99%); mp 144–146 °C; [α]ᵢ^20
−52 (c = 1.00, CH₂Cl₂).
The synthesized amide 24 (575 mg, 1.15 mmol, 1.00 equiv) was dissolved in anhyd THF (55 mL). At rt, PPh₃ (666 mg, 2.54 mmol, 2.20 equiv) and disopropyl azodicarboxylate (513 mg, 0.50 mL, 2.54 mmol, 2.20 equiv) were added. The mixture was stirred at rt for 4 h. After this time, the solvent was evaporated. The crude product was purified by flash chromatography (4 × 25 cm, CH₂Cl₂/MeOH 98:2). The desired product was obtained as a yellow solid (510 mg, 1.06 mmol, 89%). mp 95–98 °C; δ 8 = 6.44 (CH₂Cl₂/MeOH 98:2) [UV, KMnO₄]; [α]D = 270°–276° (c = 1.00, CH₂Cl₂).

IR (ATR): 2936 (w, CH sp³), 1711 (s, C=O), 1607 (m, C=C sp²), 1589 (m, C≡C).

1H NMR (400 MHz, CDCl₃): δ = 1.51–1.89 (m, 6 H, H-3, H-4, H-5, H-6), 1.99–2.15 (m, 2 H, H-3, H-6), 3.79 (vitr. td, J = J = 7.4 Hz, J = 4.3 Hz, 1 H, H-2), 4.99 (vitr. tt, J = J = 8.3 Hz, 4.0 Hz, 1 H, H-1), 7.58 (dd, J = 8.2, 6.8 Hz, J = 1.5 Hz, 1 H, H-8), 7.62 (s, 3 H, H-4), 7.70–7.84 (m, 2 H, H-6, H-7), 8.07 (d, J = 8.6 Hz, 1 H, NH), 8.16 (s, 1 H, H-4′), 8.20 (s, 2 H, H-2′), 8.49 (dd, J = 8.2 Hz, J = 1.4 Hz, 1 H, H-9′), 8.73 (s, 1 H, H-11′), 9.97 (s, 1 H, NH).

13C NMR (101 MHz, DMSO-d₆): δ = 22.1 (t, C-4′), 22.4 (t, C-5′), 25.9 (t, C-3), 28.3 (t, C-6), 38.8 (d, C-2), 52.0 (d, C-1), 107.4 (d, C-1′), 116.1 (d, C-4′), 116.2 (s, C-1″), 120.0 (d, C-11″) 120.9 (q, J = 183 Hz, 2 C, CF₃), 121.8 (d, 2 C, C-2′, C-2″), 126.1 (q, J = 109 Hz, 2 C, C-3′, C-3″), 126.2 (d, C-7′), 126.7 (d, C-8″), 127.7 (s, C-4′a), 129.1 (d, C-9″), 132.9 (d, C-6″), 133.5 (s, C-9′a), 136.5 (s, C-5′a), 140.7 (s, C-10′a), 141.6 (s, C-3′a), 152.6 (s, C-11′a), 169.1 (s, C-2′′), 178.6 (s, NCNS), 179.9 (s, C-10″).


HRMS (ESI): m/z [M + H]+ calc for C₂₃H₂₀N₂O₄S₂: 482.1052; found: 482.1045.

**tert-Butyl [((15R,2)-2-[(Hydroxymethyl)cyclohexyl]carbamate (27)**

To a solution of [(15R,2)-2-amino cyclohexyl]methanol (26: 130 mg, 1.01 mmol, 1.00 equiv) in CH₂Cl₂ (2 mL) was added Et₂N (280 µL, 203 mg, 2.01 mmol, 2.00 equiv). The solution was cooled to 0 °C and added 200 mmol, 1.05 equiv) was added. The solution was stirred and allowed to warm to rt overnight. The reaction was quenched by the addition ofaq HCl. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 5 mL). The organic layers were combined and successively washed withaq NaHCO₃ (2 × 15 mL) and dried (Na₂SO₄). The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (3 × 10 cm, C₆H₆/CH₂Cl₂). Product 27 was obtained as a yellow oil (213 mg, 928 µmol, 92%); δ = 0.17 (CH₂Cl₂).

1H NMR (500 MHz, CDCl₃): δ = 0.86–0.98 (m, 1 H, H-5), 1.14–1.36 (m, 3 H, H-3, H-4, H-6), 1.45 [s, 9 H, (CH₃)₃], 1.52–1.63 (m, 5 H, H-2, H-3, H-5, H-6, OH), 3.21 (virt. t, 3 J = 4.7 Hz, 1 H, CH), 4.04–4.07 (m, 1 H, H-1), 4.77 (d, J = 9.0 Hz, 1 H, NH).

13C NMR (101 MHz, CDCl₃): δ = 8.2–8.8 (m, 1 H, H-5), 11.9 Hz, 1 H, CH(OH)), 13.44 (m, 1 H, H-9), 4.04–4.07 (m, 1 H, H-1), 4.77 (d, J = 9.0 Hz, 1 H, NH).

13C NMR (101 MHz, CDCl₃): δ = 210.0 (t, C-5), 231.3 (t, C-4), 249.4 (t, C-3), 28.2 (q, CH₃), 30.3 (t, C-6), 43.1 (d, C-2), 45.1 (d, C-1), 63.9 (t, CH₂OH), 80.0 [s, C(Ch₃)], 157.2 (s, NHCO).

The spectroscopic data match the literature values. 30a

**tert-Butyl [(15R,2)-2-Formylcyclohexyl]carbamate (28)**

A solution of oxalyl chloride (0.55 mL, 824 mg, 6.50 mmol, 1.00 equiv) in CH₂Cl₂ (16 mL) was cooled to –78 °C. A solution of DMSO (1.36 mL, 1.52 g, 19.5 mmol, 3.00 equiv) in CH₂Cl₂ (2 mL) was added dropwise. The solution was stirred for 1 h at –78 °C. Subsequently, a solution of carbamate 27 (1.49 g, 6.50 mmol, 1.00 equiv) in CH₂Cl₂ (7 mL) was added slowly over 10 min. After an additional 10 min, NH₃ (4.50 mL, 3.30 g, 32.5 mmol, 5.00 equiv) was added. The reaction mixture was stirred for an additional 15 min at –78 °C and then allowed to warm to rt. The reaction was quenched by the addition of H₂O (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL). The combined organic layers were washed successively withaq NaHCO₃ (1 × 60 mL) and brine (1 × 60 mL), dried (Na₂SO₄), and filtered. All volatiles were removed under reduced pressure and the product 28 was obtained as a brownish solid (1.39 g, 6.12 mmol, 94%) and used in the next step without further purification.

**References**


[30a] The spectroscopic data match the literature values.
tert-Butyl [1(15S)-2-Ethynylcyclohexyl]carbamate (29)

A solution of dimethyl(diazomethyl)phosphonate (1.90 g, 12.6 mmol, 2.10 equiv) in THF (15 mL) was cooled to –78 °C. KO

Bu (1.45 g, 12.9 mmol, 2.10 equiv) was added and the mixture was again degassed under reduced pressure. The crude product was purified by flash chromatography (4 × 20 cm, Chx/EtOAc 10:1) to afford 29 as a colorless solid (0.91 g, 4.07 mmol, 20%).

IR (ATR): 3360 (w, N–H), 3058 (w, ArH), 2929 (m, CH2), 2855 (w, C–H), 2221 (vs, C≡O), 1681 (m, C=O), 1642 (m, C=O), 1438 (m, CH=C), 1365 (m), 1326 (m), 1293 (w), 1269 (m), 1226 (m, C–O), 1179 (m), 1079 (w), 917 (w), 743 (m), 635 cm–1 (w).


2’-[(15S)-2-Aminocyclohexyl(ethyl)-9H-thioxanthen-9’-one (32)

Boc-protected amine 31 (75 mg, 173 mmol, 1.00 equiv) was dissolved in CH2Cl2 (2 mL) and cooled to 0 °C. TFA (132 μL, 175 mg, 1.73 mmol, 10.00 equiv) was slowly added and the solution was stirred at rt for 2 h. The reaction was quenched by the addition of aq NH4Cl (80 mL). The layer was separated and the aqueous layer was extracted with CH2Cl2 (2 × 3 mL) and brine (2 × 2 mL), dried (Na2SO4), and all the volatiles were removed under reduced pressure. The crude product was purified by flash chromatography (2 × 20 cm, CHx/CH2Cl2 5:1) to give the title compound as a slowly crystallizing yellow oil (43.3 mg, 130 μmol, 89, [C15H9OS]+), 139 (11, [C7H7OS]+).

IR (ATR): 3348–3350 (w, N–H), 3032 (w, CH), 2933 (s, CH3), 1790 (s, C=O).
1-[3',5'-Bis[(trifluoromethyl)phenyl]-3-(15(S)-2-[[9'-oxo-9'H-thioxanthen-2-yl]ethyl]cyclohexyl]thiourea (4)

To a solution of amine 32 (240 mg, 730 μmol, 1.00 equiv) in THF (11 mL) was added isothiocyanate 13 (145 μL, 214 mg, 791 μmol, 1.10 equiv) and the reaction mixture was stirred for 16 h at rt. Then, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (3 × 15 cm, CHx/EtOAc 9:1 → 4:1). The product 4 was isolated as a bright yellow solid (330 mg, 550 μmol, 74%). mp 201–202 °C; Rf = 0.43 (CHx/EtOAc 4:1) [UV, KMnO4]; [α]D20 = -104 (c = 1.00, CH2Cl2).

IR (ATR): 3327 (br w, N–H), 2934 (w, CH2), 2858 (w, C–H), 2223 (w, C=C), 1618 (m, C=O), 1585 (m, N–H), 1523 (m, N–H), 1276 (m, C–F), 1172 (s, C=S), 1128 (s), 986 (m), 884 (m), 744 (m), 681 cm⁻¹ (m).

13C NMR (101 MHz, CDCl₃); δ = 1.40–1.50 (m, 1, H–H–5), 1.59–1.67 (m, 2, H, H–4), 1.67–1.73 (m, 1, H, H–3), 1.77 (td, J = 12.4 Hz, 3.8 Hz, 1, H–H–6), 1.82–1.88 (m, 1, H–H–5), 1.95–2.01 (m, 1, H–H–3), 2.06–2.12 (m, 1, H–H–6), 2.48 (s, H, H–3), 2.65 (s, H, H–4), 3.12 (d, J = 7.7 Hz, 1, H–H–3), 3.17 (d, J = 8.3 Hz, 1, H–H–4), 7.38 (d, J = 8.7 Hz, 1, H1, cyclohexyl NHCl), 7.49–7.54 (m, 2, H, H–4, H–5), 7.58 (dd, J = 8.1 Hz, J = 0.7 Hz, 1, H–H–7), 7.66 (dd, J = 8.3 Hz, 7.0 Hz, 1, H–H–6), 7.99 (br s, 2, H, H–2–H–6), 8.32 (dd, J = 1.6 Hz, 1, H–H–1), 8.50 (dd, J = 8.2 Hz, J = 1.3 Hz, 1, H–H–8), 9.11 (s, 1, H–Ar–NHCl).


8-Bromo-2,2,9-btrimethyl-2,3,4a,9b-tetrahydro-1H-dibenzo-furan-4-one (34)

2-(4-Bromophenoxo)-3,5,5-trimethyl-2-cyclohexen-1-one (33: 30.6 mg, 100 μmol, 1.00 equiv) was irradiated with thiourea 4 (6.04 mg, 0.10 μmol, 0.10 equiv) in a solution of CH₂Cl₂ (c = 20 mM) at λ = 419 nm for 24 h at rt. The reaction was stopped, all volatiles were removed under reduced pressure, and the crude product was purified by flash chromatography (2 × 15 cm, Pe/EtOAc 4:1 → 2:1). The title compound was isolated as a yellowish oil (8.1 mg, 26.0 μmol, 12%). IR (UV, KMnO4): ν = 2946, 2845, 1618, 1585, 1523, 1495, 1370, 1331, 1276, 1172, 1128, 984, 884, 744, 681 cm⁻¹ (m).

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(6) For a list of the references, see: European Research Council Horizon 2020 (665951 – ELICOS) and the Alexander von Humboldt-Stiftung (postdoctoral fellowship to E. R.) is gratefully acknowledged.

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