Synthesis and structures of (*S*)- and (*R*)-2-[3-cyano-4-(2-thienyl)-5,6,7,8-tetrahydroquinolin-2-ylsulfanyl]-3-methyl-*N*-phenylbutyramide

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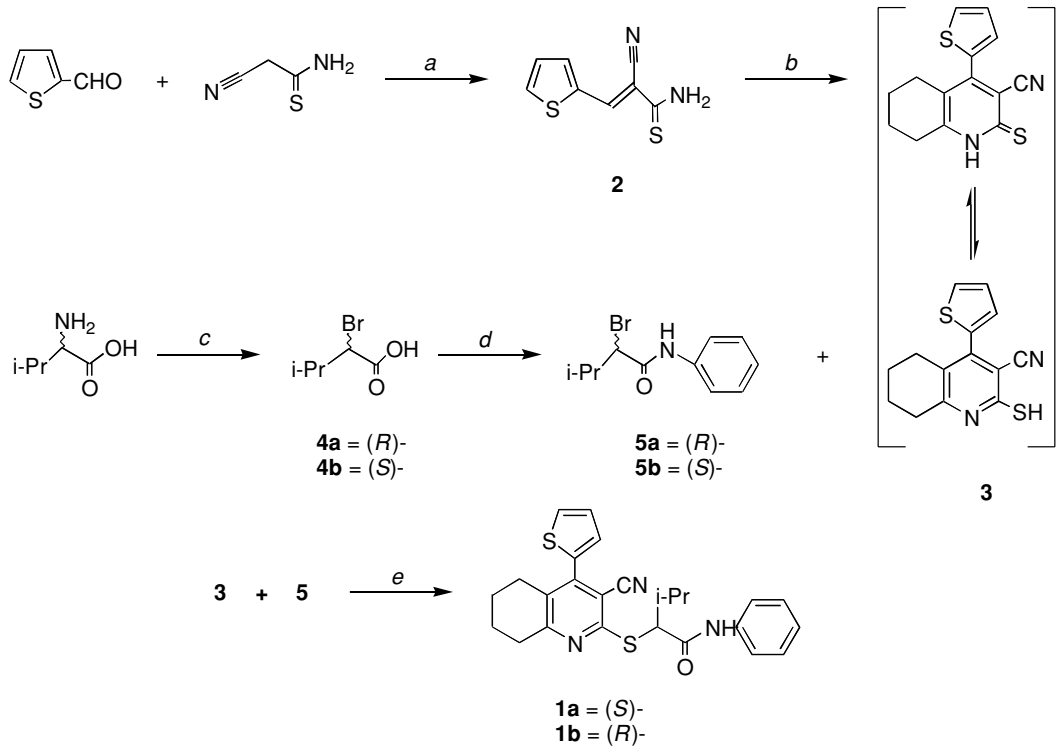
(*S*)- and (*R*)-2-[3-cyano-4-(2-thienyl)-5,6,7,8-tetrahydroquinolin-2-ylsulfanyl]-*N*-phenyl-3-methylbutyramide (**1a** and **1b**) were prepared from 2-thiophenaldehyde and D- and L-valines, respectively, and their crystal structures were elucidated by X-ray crystallography.

Keywords: quinolines, thiophenes, aminoacids

Some 5,6,7,8-tetrahydroquinolines and their derivatives are useful materials in the chemical industry or exhibit a broad range of biological activities.[1-3] During an exploration of novel biologically active compounds, we synthesised the enantiomeric (*S*)- and (*R*)-2-[3-cyano-4-(2-thienyl)-5,6,7,8-tetrahydroquinolin-2-ylsulfanyl]-*N*-phenyl-3-methylbutyramide (**1a** and **1b**). For a fuller insight into compounds **1a** and **1b**, their absolute configurations were determined by X-ray diffraction methods. (Fig. 1) The compounds **1a** and **1b** respectively were prepared from 2-thiophenaldehyde and D- and L-valines as the starting materials, and the total yields were 43% and 42% respectively. Scheme 1 depicts the sequence of reactions that led to the preparation of the target molecules. The intermediate 2-cyano-3-(2-thienyl)-2-propenethioamide (**2**) was synthesised by condensing commercially available 2-thiophenaldehyde with cyanothioacetamide in absolute ethanol. Then compound **2** reacted with cyclohexanone in hot ethanol in the presence of piperidine, affording 4-(2-thienyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**3**).[4] Another key intermediate, (*R*)-2-bromo-3-methyl-*N*-phenylbutyramide (**5a**), was synthesised from (*R*)-2-bromo-3-methylbutyric acid (**4a**),[5,6] which was prepared by diazotisation of D-valine in the presence of potassium bromide in aqueous sulfuric acid, as described by Izumiya and Nagamatsu.[6] The procedure for the preparation of (*S*)-2-bromo-3-methyl-*N*-phenylbutyramide (**5b**) is as described for **5a** but from L-valine.

The constitutions and relative configurations of the products **1a** and **1b** were determined by IR, ^{1}H NMR and HRMS. However, ^{1}H NMR could not differentiate the chirality of the carbon atoms C-14. Therefore the absolute configurations of **1a** and **1b** were confirmed by X-ray diffraction (Fig.1). As seen in Table 1, the torsion angles of the chiral carbon atoms C-14 for **1a** and **1b** respectively have almost the same value but are of opposite sign. All of these confirmed that **1a** and **1b** were enantiomers.



Scheme 1 *Reagents and conditions:* (a) Et_3N, absolute EtOH, reflux, (b) cyclohexanone, piperidine, absolute EtOH, reflux, (c) NaBr, H_2SO_4, $NaNO_2$, (d) (i) $(COCl)_2$, CH_2Cl_2, 0-5°C, (ii) $ArNH_2$, CH_2Cl_2, (e) K_2CO_3,THF, reflux.

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Table 1 Torsion angles (deg) for the chiral carbon atoms C(14) of compound **1a** and **1b**

Torsion angles	1a	1b
C(1)–S(1)–C(14)–C(18)	–83.7(2)	83.6(2)
C(1)–S(1)–C(14)–C(15)	155.2(2)	–155.5(2)
C(18)–C(14)–C(15)–C(17)	54.1(4)	–54.4(4)
S(1)– C(14)–C(15)–C(17)	173.6(3)	–173.6(3)
C(18)–C(14)–C(15)–C(16)	176.7(3)	–176.3(3)
S(1)– C(14)–C(15)–C(16)	–63.8(3)	64.5(3)

As Fig. 1 shows, the absolute configurations of **1a** and **1b** were respectively (*S*) and (*R*) at C-14. The Flack parameters for the two compounds are close to zero: 0.08(11) for **1a** and –0.02(9) for **1b**, which indicated that the absolute configurations that we had deduced were reliable.[7-9] There are also an obvious difference in the orientation of the refined amido hydrogen atom, H-3. In compound **1a**, H-3 is pointing towards N-1 and the N1···H3 distance is 2.47Å, implying a weak intramolecular hydrogen bond. However, in compound **1b** H-3 forms a weak intermolecular hydrogen bond with N-2' (in a neighbouring molecule) at a distance of 2.54Å. In addition, the sulfur atoms of the thienyl group were found to occur at the positions of S2 or S2'. For compounds **1a** and **1b**, the probabilities of the two sulfur atoms occupying S2 and S2' positions were estimated as 71.2% and 69.6%, respectively. This suggested that the sulfur atoms of the thienyl groups had an almost equal chance to occur at S2 and S2' positions due to free rotation about the C3–C10 bond (Fig. 1).

Experimental

Reagents were purchased from Shanghai Chemical Reagent Company and were used without further purification. Yields were not optimised. Melting points were measured in capillary tubes. IR spectra were determined of KBr discs using a Bruker IFS-48 FT-IR IR spectrometer. NMR spectra were determined using a Bruker AMX-400 spectrometer; shifts were referenced to Me_4Si. Chemical shifts are reported in parts per million (ppm,δ) downfield from TMS. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained with electron impact or chemical ionisation (ESI) produced by a MAT-95 spectrometer.

4-(2-Thienyl)-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**3**): A mixture of 2-thiophenaldehyde (5.6g, 50mmol), cyanothioacetamide (5.0g, 50mmol) and 2 drops of triethylamine in absolute ethanol (60ml) was heated at reflux for 25 min with constant stirring. After cooling, the resulting solid product was filtered off and crystallised from ethanol. Compound **2** was formed as yellow crystals (8.1g, 83.5%), m.p. 258–260 °C (dec.). (lit.[10] m.p. 260–262 °C).

A mixture of **2** (3.88g, 20mmol), cyclohexanone (1.96g, 22mmol) and six drops piperidine in absolute ethanol (50ml) was refluxed for 3 hours and evaporated until half of solvent left, then the precipitate was filtered off. The solid crude product was purified by flash chromatography with dichloromethane-methanol (20:1, v/v), and the compound **3** was formed as yellow crystals (4.2g, 77%), m.p.269–271 °C (dec.) (lit.[4] m.p. 270–272 °C).

General procedures for preparations of **4** *are described as for* **4a**

(R)-2-Bromo-3-methylbutyric acid (**4a**): Acid **4a** was synthesized as described by Izumiya and Nagamatsu.[6] D-Valine (1.1g, 10mmol) and potassium bromide (1.84g, 20mmol) were dissolved in 2.5 ml 1N sulfuric acid, to which a solution of sodium nitrite was added slowly at 0–5 °C. The mixture was stirred at room temperature overnight, and then extracted with AcOEt. The final organic layer was dried under anhydrous Na_2SO_4 and the solvent was removed by evaporation under vacuum. After flash chromatography with dichloromethane-methanol (20:1, v/v), **4a** was obtained as a white semi-solid (1.32g, 73%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.11 (q, 6H), 2.25 (m, 1H), 4.09 (d, 1H), 10.35 (b, 1H).

(S)-2-Bromo-3-methylbutyric acid (**4b**): This compound was obtained as a white semi-solid (1.25g, 69%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.11 (q, 6H), 2.25 (m, 1H), 4.09 (d, 1H), 10.35 (b, 1H).

General procedures for preparations of **5** *are described as for* **5a**[5,6]

(R)-2-Bromo-3-methyl-N-phenylbutyramide (**5a**): To the cold solution (0–5 °C) of **4a** (0.2g, 1.1mmol) in dry dichloromethane (8ml) was added dropwise oxalyl chloride (0.31g, 2.4mmol) in dry dichloromethane (5ml). Reaction was continued for 1 hour with constant stirring. Thereafter, the mixture was stirred at room temperature for 48 hours, and then the solvent was removed by evaporation under vacuum to give (*R*)-2-bromo-3-methylbutyryl chloride (0.2g, 92%).

(*R*)-2-Bromo-3-methylbutyryl chloride (0.2g, 1mmol) in dry dichloromethane (10ml) was added dropwise to a stirred solution of aniline (93mg, 1mmol) in dry dichloromethane (10ml) and then cooled to 0 °C. The mixture was stirred at room temperature for 2 hours, and then washed with water (2 × 20ml). The organic layer was dried with anhydrous Na_2SO_4 and the solvent was removed by evaporation under vacuum. After flash chromatography with dichloromethane-petroleum (2:1; v/v), **5a** was obtained as a white semi-solid (1.7g, 66%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.15 (q, 6H), 2.54 (m, 1H), 4.12 (d, 1H), 7.10 (m, 1H), 7.18 (m, 2H), 7.54 (m, 2H), 8.98 (s, 1H).

(S)-2-Bromo-3-methyl-N-phenylbutyramide (**5b**): This compound was obtained as a white semi-solid (1.6g, 62%). ^{1}H NMR (400MHz, $CDCl_3$): δ 1.15 (q, 6H), 2.54 (m, 1H), 4.12 (d, 1H), 7.10 (m, 1H), 7.18 (m, 2H), 7.54 (m, 2H), 8.98 (s, 1H).

General procedures for preparations of ***1*** *are described as for* **1a**

(S)-2-[3-Cyano-4-(2-thienyl)-5,6,7,8-tetrahydroquinolin-2-ylsulfanyl]-N-phenyl-3-methylbutyramide (**1a**): A mixture of compound **3** (272mg, 1mmol), **5a** (271mg, 1mmol), K_2CO_3 (1.08g, 5mmol) and tetrabutylammonium bromide (32mg, 0.1mmol) in THF (30ml) was refluxed for 3 hours with constant stirring, then filtered and condensed. Flash chromatography was performed with dichloromethane-methanol

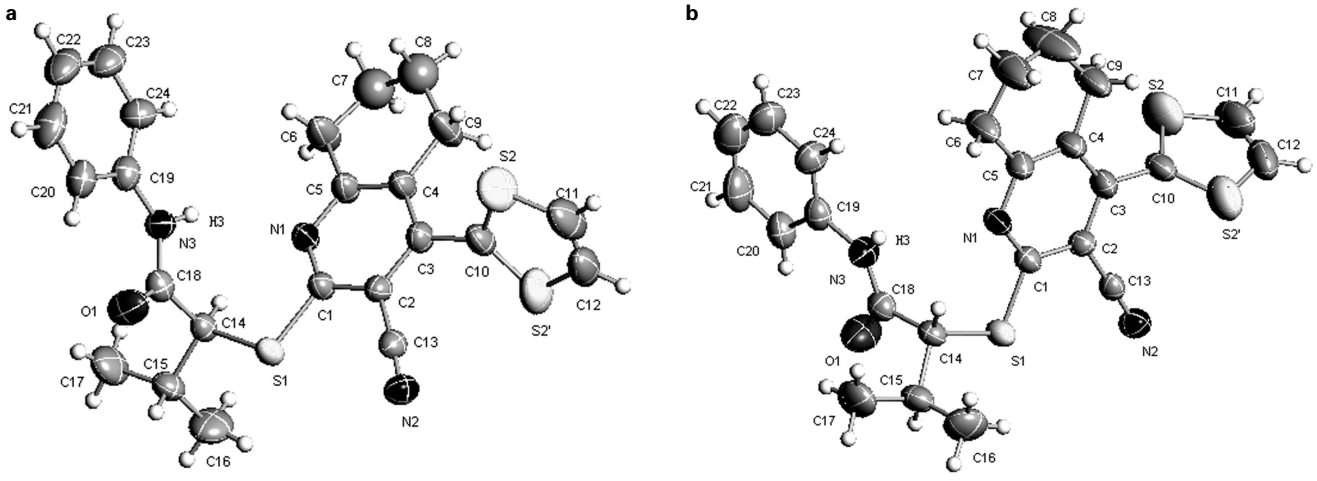

Fig. 1 a, X-ray crystal structure of **1a**; b, X-ray crystal structure of **1b**.

(10:1, v/v), and compound **1a** was formed as yellow crystals (355mg, 67%), m.p. 239–241 °C (dec.). IR (KBr): 3377, 1687, 1600, 1490 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 1.20 (q, 6H), 1.75 (m, 2H), 1.90 (m, 2H), 2.60 (m, 2H), 2.62 (m, 1H), 3.04 (m, 2H), 4.38 (d, 1H), 7.30 (m, 2H), 7.10 (m, 1H), 7.15 (m, 2H), 7.30 (m, 2H), 7.51 (m, 3H), 8.98 (s, 1H). HRMS (SCI) *m/z* calcd for M^+ 447.1439; found 447.1429.

(R)-2-[3-Cyano-4-(2-thienyl)-5,6,7,8-tetrahydroquinolin-2-ylsulfanyl]-N-phenyl-3-methylbutyramide (**1b**)**:** This compound was given as yellow crystals (355mg, 65%). M.p. 238–240 °C (dec.) IR (KBr): 3377, 1687, 1600, 1490 cm^{-1}. ^1H NMR (400MHz, $CDCl_3$): δ 1.20 (q, 6H), 1.75 (m, 2H), 1.90 (m, 2H), 2.60 (m, 2H), 2.62 (m, 1H), 3.04 (m, 2H), 4.38 (d, 1H), 7.10 (m, 1H), 7.15 (2H), 7.30 (m, 2H), 7.51 (m, 3H), 8.98 (s, 1H) HRMS (SCI) *m/z* calcd for M^+, 447.1439; found, 447.1444.

Crystallographic studies

Single crystals of **1a** and its enantiomer **1b** suitable for X-ray crystal structure analysis were respectively obtained by growth under slow evaporation at 5 °C from a dichloromethane/petroleum ether mixture (1:4 v/v). Crystal data and structure solutions at T = 293(2)°K: **1a** $C_{25}H_{25}N_3OS_2$, M_r = 447.60, orthorhombic, $P2_12_12_1$, a = 9.1731(7), b = 15.1163(11), c = 16.8961(13)Å, V = 2342.9(13)$Å^3$, Z = 4, D_x = 1.269Mg/m^3, F(000) = 944, λ(MoKα) = 0.71073Å, μ = 0.249mm^{-1} and **1b** $C_{25}H_{25}N_3OS_2$, M_r = 447.60, orthorhombic, $P2_12_12_1$, a = 9.166(3), b = 15.148(4), c = 16.896(5)Å, V = 2345.8(12)$Å^3$, Z = 4, D_x = 1.267Mg/m^3, F(000) = 944, λ(MoKα) = 0.71073Å, μ = 0.249mm^{-1}

The intensity data were collected on a Bruker Smart APEX CCD diffractometer with graphite monochromated MoKα radiation and phi and omega scan technique [5a: $2\theta_{max}$ = 54.00° and 5b: $2\theta_{max}$ = 54.00°]. The structures were solved by direct methods using SHELXS-97[11] and expanded using Fourier techniques.[12] The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement was based on 5112 (**1a**) and 5103 (**1b**) unique reflections and 276 (**1a**) and 286 (**1b**) variable parameters and converged with unweighted and weighted factors of **1a** (R_1 = 0.0735 and R_{w2} = 0.1584) and **1b** (R_1 = 0.0879 and R_{w2} = 0.1091).

Neutral atom scattering factors were taken from Cromer and Waber.[13] Anomalous dispersion effects were included in F_{calc},[13] the values for Δf´ and Δf'' were those of Creagh and McAuley,[14] the values for the mass attenuation coefficients were those of Creagh and Hubbell.[16] All calculations were performed using the SHELXL-97.[17]Their crystal structures have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers: CCDC 255058 for **1a** and CCDC 254890 for **1b**.

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