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# Tetrahydroisoquinoline-based non-peptidomimetic plasmepsin inhibitors

**Linda Kinena[1]*, Vita Ozola[1]**

[1] *Latvian Institute of Organic Synthesis,*
*21 Aizkraukles St., Riga LV-1006, Latvia; e-mail: linda@osi.lv*

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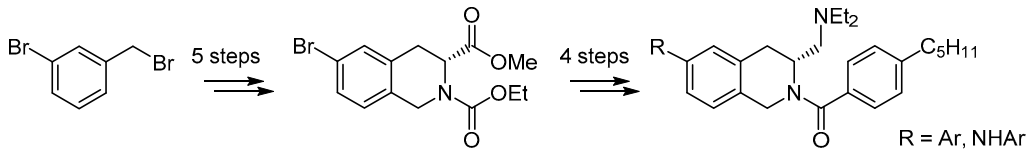



A series of tetrahydroisoquinoline derivatives containing different aryl substituents were designed and synthesized using Pictet–Spengler reaction as the key step. The synthesized tetrahydroisoquinoline derivatives displayed micromolar inhibitory activity against plasmepsins I and II.

**Keywords**: plasmepsins, tetrahydroisoquinoline, malaria, Pictet–Spengler reaction, X-ray analysis.

Malaria is a potentially life-threatening disease caused by *Plasmodium falciparum* parasite. It is transmitted through the bite of an infected mosquito. The increasing resistance of the malaria parasite to currently available drugs requires urgent development of new antimalarial agents.[1–3] Malarial aspartic proteases – plasmepsins (Plm I, Plm II, Plm IV) are involved in hemoglobin degradation and are potential drug targets.[4,5] There are two kinds of plasmepsin inhibitors: peptidomimetic and non-peptidomimetic inhibitors. Peptidomimetic plasmepsin inhibitors usually show high inhibitory activity, but low selectivity against human aspartic proteases.[6] Several studies have been performed to discover new non-peptidomimetic plasmepsin inhibitors in order to overcome selectivity issues.[7–9] Scientists from Actelion have published first non-peptidomimetic Plm II inhibitor **A** based on the aminopiperidine scaffold (Fig. 1). Aminopiperidine-based inhibitors have several drawbacks – they display adverse physicochemical properties such as high ClogP and low solubility.[10,11] Therefore, we decided to design a new series of inhibitors by rescaffolding Actelion aminopiperidine-type inhibitor **A** (Fig. 1).

A series of tetrahydroisoquinoline derivatives **B** were designed by introducing bond between C-3 carbon atom of aromatic ring and C-3 carbon atom of piperidine and opening piperidine cycle. According to the docking studies, the newly designed tetrahydroisoquinoline inhibitor **B** binds to the enzyme similarly to aminopiperidine derivative **A**. Our design retains the key pharmacophoric elements needed for inhibitory activity: amino moiety (makes ionic interaction with Asp 214 residue and water-bridged H-bonding interaction with the catalytic Asp 34), biphenyl substituent (occupies S1 subpocket), and *n*-pentyl chain (placed in the flap pocket) (Fig. 2).[12]

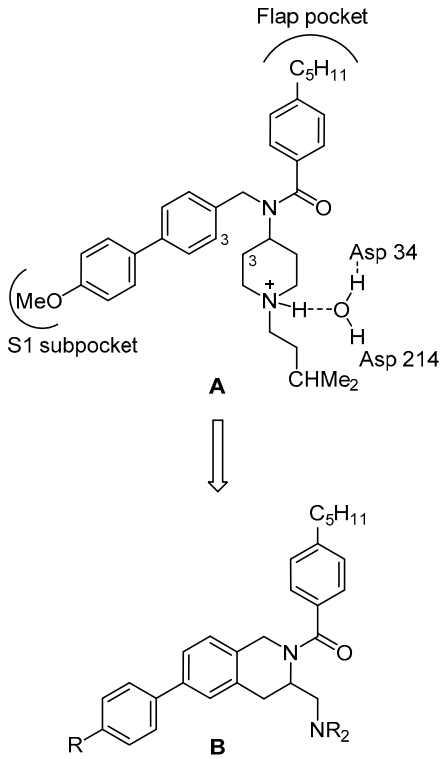



**Figure 1**. Design strategy of tetrahydroisoquinoline-based inhibitors **B** by rescaffolding Actelion aminopiperidine-type inhibitors **A**.

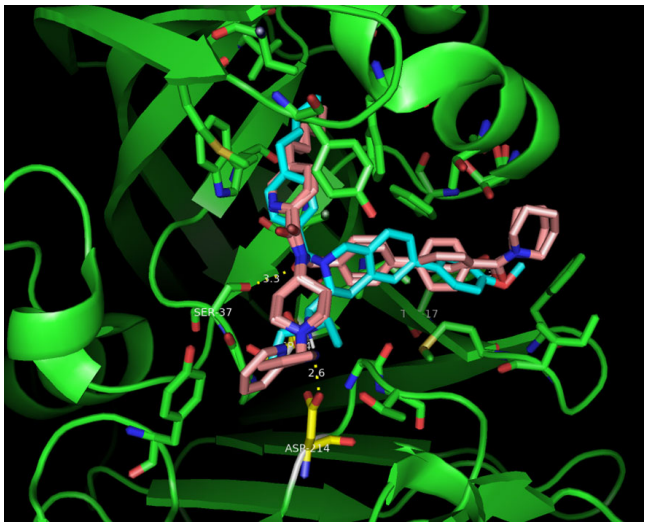



**Figure 2**. Binding mode of tetrahydroisoquinoline-based inhibitor **B** to the active site of Plm II. Docking was performed using the AutoDock Vina software package[18] on the crystal structure of Plm II solved in complex with an aminopiperidine-based Plm II inhibitor (Protein Data Bank ID 2IGX[11]).

A small series of tetrahydroisoquinoline derivatives (*R*)-**9a**–**c**, (*R*)-**10** with different aryl substituents was prepared to evaluate the inhibitory activity against Plm I, Plm II, and Plm IV isoforms. Tetrahydroisoquinoline-based inhibitors (*R*)-**9a**–**c**, (*R*)-**10** were synthesized from ester **4** and paraformaldehyde using Pictet–Spengler reaction as the key step. The synthesis was started by C-alkylation of diethyl 2-acetamidomalonate with *meta*-bromobenzyl bromide (**1**) in presence of NaOEt.[13] Subsequent hydrolysis of ester and deprotection of the amino group in compound **2** was followed by decarboxylation to afford amino acid **3**.[13] The Pictet–Spengler reaction involving protected amino acid **4** and paraformaldehyde[14] resulted in the formation of tetrahydroisoquinoline derivative as a mixture of regioisomers **5a** and **5b**. Enantiomerically pure tetrahydroisoquinoline (*R*)-**5a** was obtained by initial separation of regioisomers by preparative column chromatography, followed by separation of enantiomers on a chiral stationary phase (Scheme 1).

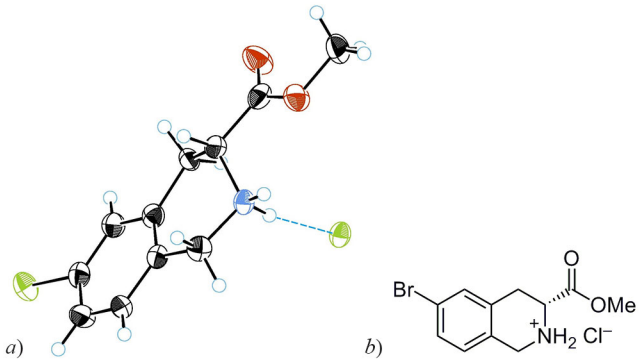
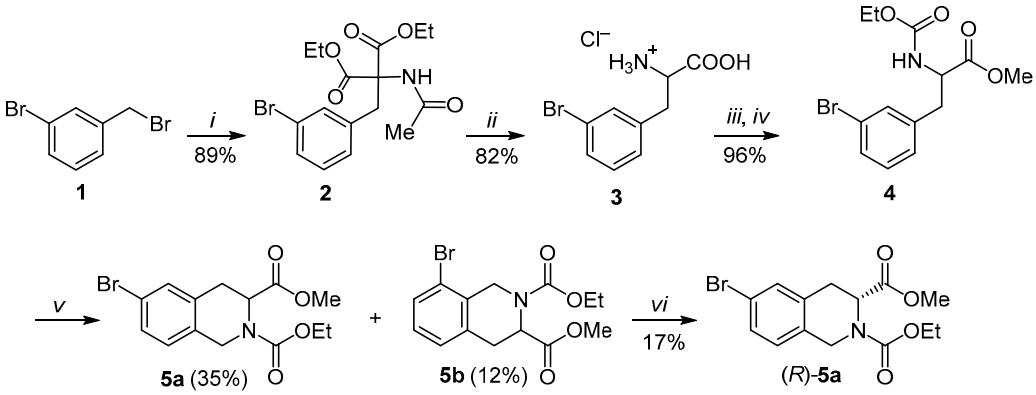



**Figure 3**. The molecular (*a*) and chemical (*b*) structure of methyl ester (*R*)-**6a** with atoms represented by thermal vibration ellipsoids of 50% probability.

After hydrolysis and deprotection of amino function in compound **5a**, acid **6** was obtained (Scheme 2). To determine the absolute configuration of carboxylic acid (*R*)-**6** it was converted to methyl ester (*R*)-**6a**. Single crystal X-ray analysis of methyl ester (*R*)-**6a** confirmed (*R*) absolute configuration of stereogenic center (Fig. 3).

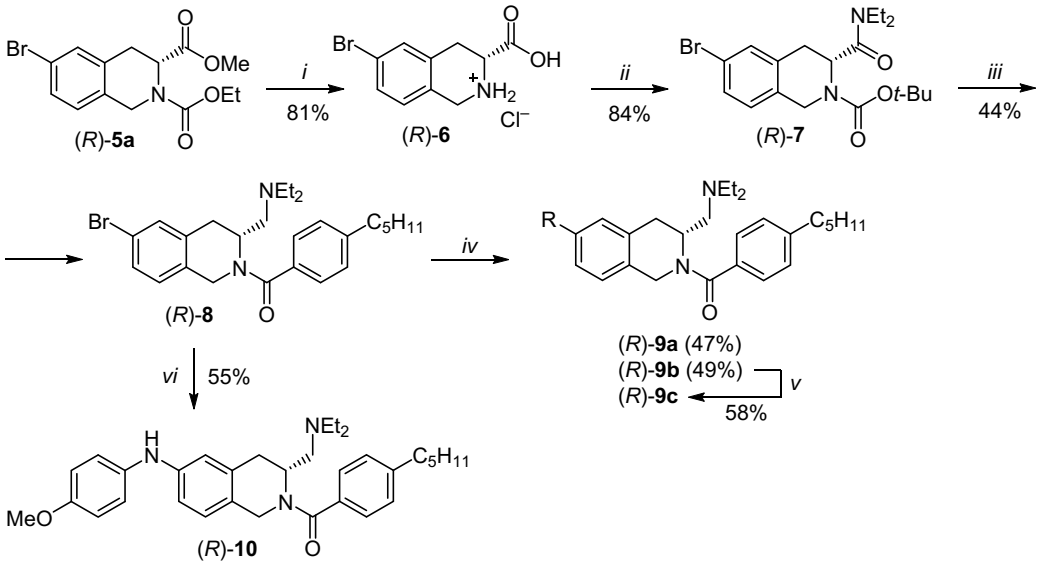
For further modifications, only acid (*R*)-**6** was used. Next, amino function was protected with Boc moiety,[15] yielding tetrahydroisoquinoline which was reacted with diethylamine in the presence of HOBt leading to tetrahydroisoquinoline derivative (*R*)-**7** (Scheme 2). After cleavage of the *N*-Boc protecting group, the amide moiety was reduced with $LiAlH_4$ to give amine. The latter was acylated with 4-pentylbenzoyl chloride in the presence of DIPEA yielding tetrahydroisoquinoline (*R*)-**8**. This was used as the key building block. Suzuki–Miyaura cross-coupling reaction between bromide (*R*)-**8** and boronic acids in the presence of $Pd(PPh_3)_4$ was used for the synthesis of diaryl derivatives (*R*)-**9a**,**b**. Demethylation of tetrahydroisoquinoline derivative (*R*)-**9b** was accomplished with NaH/1-dodecanethiol in DMF[16] to yield hydroxy group-containing derivative (*R*)-**9c**. Buchwald–Hartwig amination reaction[17] was used for the introduction of 4-methoxyphenylamino substituent yielding tetrahydroisoquinoline derivative (*R*)-**10** (Scheme 2).

**Scheme 1**




*i*: $AcNHCH(CO_2Et)_2$, NaOEt, EtOH, 85°C, 16 h; *ii*: HCl, AcOH, 100°C, 18 h
*iii*: $SOCl_2$, MeOH, 60°C, 3 h; *iv*: $ClCO_2Et$, Py, $CH_2Cl_2$, rt, 18 h
*v*: paraformaldehyde, AcOH, $H_2SO_4$, rt, 20 h; *vi*: preparative HPLC on chiral stationary phase (Chiralpak-IC)

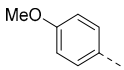
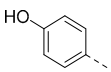
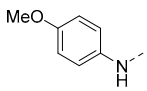
**Scheme 2**




*i*: 33% HBr in AcOH, rt, 84 h, then aq 6 M HCl, 70°C, 18 h
*ii*: $(Boc)_2O$, NaOH, *t*-BuOH–$H_2O$, 1:1, rt, 18 h, then $Et_2NH$, DCC, $HOBt·H_2O$, DMF, rt, 16 h
*iii*: 4 M HCl in dioxane, rt, 16 h, then $LiAlH_4$, THF, rt, 2 h, then 4-pentylbenzoyl chloride, DIPEA, $CH_2Cl_2$, rt, 16 h
*iv*: $RB(OH)_2$, $Pd(PPh_3)_4$ (3 mol %), aq 2 M $Na_2CO_3$, 1,4-dioxane, 105°C, 16 h
*v*: 1-dodecanethiol, NaH, DMF, 0°C, then 130°C, 2 h
*vi*: 4-methoxyaniline, $Pd_2(dba)_3$ (2 mol %), X-Phos (8 mol %), NaO*t*-Bu, PhMe, 90°C, 16 h

The synthesized tetrahydroisoquinoline derivatives (*R*)-**9a**–**c**, (*R*)-**10** were tested for their Plm I, Plm II, and Plm IV inhibiting properties (Table 1). Tetrahydroisoquinoline **9a** displayed micromolar inhibitory activity against Plm I, but hardly any activity against Plm II and Plm IV was observed. Inhibitor **9b** with *p*-OMe substituent at the phenyl ring showed the highest activity against Plm I, Plm II, and Plm IV. In contrast, *p*-OH-substituted and amino-linker-containing inhibitors **9c** and **10** showed 2–3 times lower inhibitory activity against Plm I, Plm II, Plm IV (Table 1).

**Table 1**. Plm I, Plm II, and Plm IV inhibitory activity of compounds **9a**–**c**, **10**, **A**

| Compound | R | $IC_{50}$*, μM | | |
|---|---|---|---|---|
| | | Plm I | Plm II | Plm IV |
| **9a** |  | 22 | –** | ~100 |
| **9b** |  | 1.9 ± 0.09 | 16.2 ± 0.8 | 46.6 ± 2 |
| **9c** |  | 7.3 ± 0.3 | 40 ± 2 | ~100 |
| **10** |  | 7 ± 0.3 | 45.5 ± 2 | 73.6 ± 3 |
| **A**** | | 0.4 | 0.42 | 0.92 |

* Plm I, Plm II, and Plm IV inhibitory activity was determined by enzymatic FRET assay in triplicate experiments.
** The assay was performed at five concentrations of the inhibitor (0.01–100 μM). At this range of concentrations inhibitor **9a** did not show any effect.
*** Reference compound, see Figure 1.

In summary, we have developed a new series of tetrahydroisoquinoline-based non-peptidomimetic Plm inhibitors. Synthesis of the inhibitors was performed using Pictet–Spengler reaction as the key step. Plm I, Plm II, and Plm IV inhibiting properties of the synthesized tetrahydroisoquinoline derivatives were tested. The best tetrahydroisoquinoline derivatives show inhibitory activity toward plasmepsins I and II at micromolar level. However, inhibition potency of tetrahydroisoquinoline derivatives is lower than Actelion aminopiperidine-type inhibitor. Hence, the performed rescaffolding does not allow the molecule to adopt the bioactive conformation in the active site of enzyme.

## Experimental

$^1H$ and $^{13}C$ NMR spectra (400 and 100 MHz, respectively) were recorded on a Bruker 400 spectrometer in $CDCl_3$, DMSO-$d_6$, or $CD_3OD$; TMS was used as internal standard. HRMS (ESI) spectra were recorded on a Waters Acquity UPLC H-Class apparatus with a time-of-flight (TOF) mass analyzer Waters Synapt G2 Si TOF MS. Analytical thin-layer chromatography (TLC) was performed on precoated Merck silica gel F-254 plates.

Unless otherwise noted, all chemicals were used as obtained from commercial sources and all reactions were performed under nitrogen or argon atmosphere in glassware dried in an oven (120°C) and cooled under a stream of argon. Dry PhMe, THF, $CH_2Cl_2$, and $Et_2O$ were obtained by passing commercially available anhydrous solvents through activated alumina columns.

**Diethyl (acetylamino)(3-bromobenzyl)propanedioate (2)**. A pressure tube was charged with diethyl 2-acetamidomalonate (1.74 g, 8.00 mmol) and NaOEt (2.59 g, 8.00 mmol), then anhydrous EtOH (10 ml) was added and light-yellow suspension formed. A solution of *m*-bromo-

benzyl bromide (**1**) (2.00 g, 8.00 mmol) in anhydrous EtOH (10 ml) was added, and the resulting orange solution was heated at 85°C for 16 h. After cooling to room temperature, orange suspension was concentrated under reduced pressure and the residue was partitioned between EtOAc (50 ml) and $H_2O$ (50 ml). Water phase was extracted with EtOAc (3×50 ml), combined extracts were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g), eluent hexane–EtOAc, gradient from 10 to 100% EtOAc. Yield 2.76 g (89%), light-yellow solid. Analytical data of the compound were identical to the literature data.[13]

**2-Amino-3-(3-bromophenyl)propanoic acid hydrochloride (3)**. Diethyl (acetylamino)(3-bromobenzyl)propanedioate (**2**) (2.95 g, 7.66 mmol) was dissolved in a mixture of concentrated AcOH (7.6 ml) and concentrated aqueous HCl (23 ml). The light-yellow solution was heated at 100°C for 18 h. The light-brown suspension was concentrated under reduced pressure, the precipitate was filtered off and washed with petroleum ether, dried over $P_2O_5$ at 60°C for 18 h. The product was used in a subsequent step without purification. Yield 1.75 g (82%), light-brown solid. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 14.22–13.52 (1H, br. s, COOH); 8.78–8.32 (3H, m, $NH_3^+$); 7.56–7.51 (1H, m, H Ar); 7.51–7.45 (1H, m, H Ar); 7.35–7.27 (2H, m, H Ar); 4.25–4.13 (1H, m, $CH_2C\underline{H}$); 3.16 (2H, d, $J$ = 6.3, $C\underline{H}_2CH$). $^{13}$C NMR spectrum (DMSO-$d_6$), δ, ppm: 170.1; 137.9; 132.3; 130.6; 130.1; 128.7; 121.8; 52.9; 35.1. Found, *m*/*z*: 243.9971 $[M+H]^+$. $C_9H_{11}BrNO_2$. Calculated, *m*/*z*: 243.9973.

**Methyl 3-(3-bromophenyl)-2-[(ethoxycarbonyl)amino]-propanoate (4)**. $SOCl_2$ (1.13 ml, 15.66 mmol) was added to cooled (0°C) anhydrous MeOH (20 ml), and the resulting solution was stirred for 10 min. Hydrochloride **3** (1.75 g, 6.27 mmol) was then added in portions, and the light-brown solution was stirred at 60°C for 3 h. The volatiles were removed under reduced pressure, and anhydrous PhMe (2×20 ml) was added and evaporated under reduced pressure. The precipitate was dried over $P_2O_5$ at 40°C and used in subsequent step without purification. Yield 1.82 g (98%), light-brown powder. Pyridine (1.50 ml, 18.54 mmol) was added dropwise to a solution of methyl 2-amino-3-(3-bromophenyl)propanoate hydrochloride from the previous step (1.82 g, 6.18 mmol) in anhydrous $CH_2Cl_2$ (20 ml). The light-brown solution was cooled to 0°C, and ethyl chloroformate (737 mg, 649 μl, 6.80 mmol) was added dropwise. After stirring at room temperature for 18 h, the light-brown suspension was concentrated under reduced pressure. The residue was dissolved in EtOAc (50 ml), washed with aqueous 1 M HCl solution (30 ml), saturated aqueous $NaHCO_3$ solution (50 ml), and brine (30 ml). The organic layer was evaporated under reduced pressure, and product **4** was used in a subsequent step without purification. Yield 1.98 g (96%), light-brown oil. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 7.38 (1H, ddd, $J$ = 7.9, $J$ = 2.0, $J$ = 1.1, H Ar); 7.30–7.26 (1H, m, H Ar); 7.16 (1H, dd, $J$ = 7.9, $J$ = 7.9, H Ar); 7.08–7.04 (1H, m, H Ar); 5.15 (1H, d, $J$ = 8.2, NH); 4.68–4.56 (1H, m, $CH_2C\underline{H}$); 4.11 (2H, q, $J$ = 7.1, $C\underline{H}_2CH_3$); 3.72 (3H, s, $CH_3$); 3.15–2.98 (2H, m, $C\underline{H}_2CH$); 1.23 (3H, t, $J$ = 7.1, $CH_2C\underline{H}_3$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 171.9; 155.9; 138.4; 132.5; 130.4; 130.2; 128.0; 122.7; 61.4; 54.7; 52.5; 38.1; 14.7. Found, *m*/*z*: 330.0331 $[M+H]^+$. $C_{13}H_{17}BrNO_4$. Calculated, *m*/*z*: 330.0341.

**2-Ethyl 3-methyl (*R*)-6-bromo-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (5a) and 2-ethyl 3-methyl 8-bromo-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (5b)**. AcOH (7.4 ml), $H_2SO_4$ (2.5 ml), and paraformaldehyde (198 mg, 6.60 mmol) were added to methyl 3-(3-bromophenyl)-2-[(ethoxycarbonyl)amino]propanoate (**4**) (1.98 g, 6.00 mmol), and the resulting light-brown suspension was stirred at room temperature for 20 h, then the second portion of paraformaldehyde (198 mg, 6.60 mmol) was added and stirring was continued for 20 h more. The light-brown solution was poured into ice water (25 ml). After 20 min, the suspension was extracted with EtOAc (3×50 ml). The combined extracts were washed with saturated $NaHCO_3$ solution (2×50 ml), brine (50 ml), dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (100 g), eluent hexane–EtOAc, gradient from 25 to 100% EtOAc. The crude product was obtained as a mixture of regioisomers **5a**:**5b** in ratio 2.9:1. The regioisomers **5a** and **5b** were separated by preparative chromatography (Sunfire™ Prep Silica OBD™ 5μm, 30 × 100 column), eluent hexane–EtOAc, 9:1, flow rate 40 ml/min, detector UV 230 nm, 260 nm. Yield of compound **5a** 717 mg (35%), yield of compound **5b** 247 mg (12%). Enantiomerically pure material (*R*)-**5a** was obtained by preparative HPLC on chiral stationary phase (DAICEL, Chiralpak-IC), eluent hexane–EtOAc, 5:1, flow rate 36 ml/min, detector UV 230 nm, 260 nm. Yield of compound (*R*)-**5a** 351 mg (17%), light-yellow oil, mixture of rotamers, $[\alpha]_D^{20}$ –45.7 (*c* 1.03, $CHCl_3$).

**Compound 5a**. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 7.36–7.28 (2H, m, H Ar); 7.02 (0.45H, d, $J$ = 8.0, H Ar); 6.98 (0.55H, d, $J$ = 8.0, H Ar); 5.18 (0.55H, dd, $J$ = 6.1, $J$ = 2.9, CH); 4.96 (0.45H, dd, $J$ = 6.1, $J$ = 4.2, CH); 4.77–4.67 (1H, m, $CH_2N$); 4.56–4.42 (1H, m, $CH_2N$); 4.32–4.13 (2H, m, $C\underline{H}_2CH_3$); 3.63 (3H, s, $OCH_3$); 3.33–3.06 (2H, m, $C\underline{H}_2CH$); 1.33 (1.65H, t, $J$ = 7.1, $CH_2C\underline{H}_3$); 1.26 (1.35H, t, $J$ = 7.1, $CH_2C\underline{H}_3$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 171.7; 171.5; 156.3; 155.7; 134.0; 132.2; 131.6; 131.5; 131.1; 130.2; 130.1; 128.2; 128.0; 120.5; 62.2; 62.1; 53.3; 52.6; 44.1; 44.0; 31.3; 31.0; 14.8; 14.7. Found, *m*/*z*: 342.0327 $[M+H]^+$. $C_{14}H_{17}BrNO_4$. Calculated, *m*/*z*: 342.0341.

**Compound 5b**. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 7.46–7.40 (1H, m, H Ar); 7.14–7.08 (1H, m, H Ar); 7.08–7.02 (1H, m, H Ar); 5.25 (0.6H, dd, $J$ = 6.3, $J$ = 2.5, CH); 5.06 (0.4H, dd, $J$ = 6.3, $J$ = 3.2, CH); 4.86 (0.4H, d, $J$ = 17.6, $CH_2N$); 4.79 (0.6H, d, $J$ = 17.6, $CH_2N$); 4.45 (0.6H, d, $J$ = 17.6, $CH_2N$); 4.43 (0.4H, d, $J$ = 17.6, $CH_2N$); 4.31–4.16 (2H, m, $C\underline{H}_2CH_3$); 3.64 (3H, s, $OCH_3$); 3.33–3.13 (2H, m, $C\underline{H}_2CH$); 1.35 (1.8H, t, $J$ = 7.1, $CH_2C\underline{H}_3$); 1.28 (1.2H, t, $J$ = 7.1, $CH_2C\underline{H}_3$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 171.5; 171.4; 156.4; 134.1; 133.9; 132.3; 131.8; 131.2; 131.1; 128.1; 128.0; 127.6; 122.6; 122.5; 62.3; 62.1; 53.1; 52.6; 52.4; 45.2; 31.6; 31.2; 14.8; 14.7.

**(*R*)-6-Bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride (6)**. 2-Ethyl 3-methyl (*R*)-6-bromo-3,4-dihydroisoquinoline-2,3(1*H*)-dicarboxylate (**5a**) (351 mg, 1.03 mmol) was dissolved in 33% HBr in AcOH (4.1 ml, 24.6 mmol) and the orange solution was stirred at room temperature for 84 h. Volatiles were removed under reduced pressure, and the residue was treated with aqueous 6 M HCl solution (10 ml). The light-brown suspension was stirred at 70°C for 18 h. The formed precipitate was filtered off, dried over $P_2O_5$ at 50°C. Yield 244 mg (81%), light-brown solid, $[\alpha]_D^{20}$ 66.5 (*c* 1.05, MeOH). $^1$H NMR spectrum ($CD_3OD$), δ, ppm: 7.55–7.50 (1H, m, H Ar); 7.46 (1H, dd, *J* = 8.3, *J* = 2.1, H Ar); 7.20 (1H, d, *J* = 8.3, H Ar); 4.50–4.34 (3H, m, $CH_2N$, $CH_2C\underline{H}$); 3.48 (1H, dd, *J* = 17.4, *J* = 5.3, $C\underline{H}_2CH$); 3.23 (1H, dd, *J* = 17.4, *J* = 11.6, $C\underline{H}_2CH$). $^{13}$C NMR spectrum ($CD_3OD$), δ, ppm: 170.7; 134.2; 132.9; 131.7; 129.6; 128.1; 122.9; 55.0; 45.2; 29.3. Found, *m*/*z*: 255.9970 $[M+H]^+$. $C_{10}H_{11}BrNO_2$. Calculated, *m*/*z*: 255.9973.

**Methyl (*R*)-6-bromo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride (6a)**. $SOCl_2$ (12 ml, 0.17 mmol) was added to the cooled (0°C) anhydrous MeOH (1 ml), and resulting solution was stirred for 10 min. Hydrochloride **6** (20 mg, 0.068 mmol) was then added, and the light-brown solution was stirred at 60°C for 3 h. The volatiles were removed under reduced pressure, and anhydrous PhMe (2×1 ml) was added and evaporated under reduced pressure. The precipitate was dried over $P_2O_5$ at 40°C. Yield 20 mg (95%), light-brown powder, $[\alpha]_D^{20}$ 55.2 (*c* 0.55, MeOH). $^1$H NMR spectrum ($CD_3OD$), δ, ppm: 7.55–7.49 (1H, m, H Ar); 7.47 (1H, dd, *J* = 8.3, *J* = 2.0, H Ar); 7.20 (1H, d, *J* = 8.3, H Ar); 4.56–4.34 (3H, m, $CH_2N$, $CH_2C\underline{H}$); 3.91 (3H, s, $OCH_3$); 3.47 (1H, dd, *J* = 17.4, *J* = 5.2, $C\underline{H}_2CH$); 3.28–3.17 (1H, m, $C\underline{H}_2CH$). $^{13}$C NMR spectrum ($CD_3OD$), δ, ppm: 169.9; 133.8; 132.9; 131.7; 129.6; 128.0; 122.9; 55.1; 54.0; 45.3; 29.1. Found, *m*/*z*: 270.0141 $[M+H]^+$. $C_{11}H_{13}BrNO_2$. Calculated, *m*/*z*: 270.0130.

***tert*-Butyl (*R*)-6-bromo-3-(diethylcarbamoyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7)**. NaOH (70 mg, 1.76 mmol) was added to a suspension of hydrochloride **6** (215 mg, 0.84 mmol) in *t*-BuOH–$H_2O$, 1:1 (6 ml). The reaction mixture was stirred till clear solution was formed, then $Boc_2O$ (183 mg, 0.84 mmol) was added. The light-yellow solution was stirred at room temperature for 16 h. The solution was evaporated under reduced pressure to 1/3 of volume, then acidified with aqueous 5% $KHSO_4$ solution to pH 3 and extracted with EtOAc (3×15 ml). The combined extracts were washed with brine (20 ml), dried over $Na_2SO_4$, and evaporated under reduced pressure. The crude product (258 mg, 0.72 mmol) was dissolved in anhydrous DMF (4 ml) and HOBt·$H_2O$ (144 mg, 0.94 mmol) was added, followed by DCC (194 mg, 0.94 mmol). The resulting light-yellow solution was stirred at 0°C for 1 h, then diethylamine (79 mg, 112 µl, 1.09 mmol) was added and stirring was continued at room temperature for 16 h. The light-yellow solution was diluted with $H_2O$ (10 ml) and extracted with EtOAc (3 × 10 ml). The combined extracts were washed with $H_2O$ (15 ml), brine (15 ml), dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (25 g), eluent hexane–EtOAc, gradient from 15 to 85% EtOAc. Yield 250 mg (84%), light-yellow oil, mixture of rotamers, $[\alpha]_D^{20}$ 27.9 (*c* 0.86, $CHCl_3$). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 7.33–7.26 (2H, m, H Ar); 7.04–6.91 (1H, m, H Ar); 5.33–5.24 (0.6H, m, $CH_2C\underline{H}$); 5.00–4.84 (0.8H, m, $CH_2N$, $CH_2C\underline{H}$); 4.78 (0.6H, d, *J* = 16.6, $CH_2N$); 4.35 (0.6H, d, *J* = 16.6, $CH_2N$); 4.25 (0.4H, d, *J* = 16.2, $CH_2$); 3.56–3.16 (4H, m, $(C\underline{H}_2CH_3)_2$); 3.14–2.92 (2H, m, $C\underline{H}_2CH$); 1.47 (9H, s, $C(CH_3)_3$); 1.31–1.19 (3H, m, $CH_2C\underline{H}_3$); 1.14–1.01 (3H, m, $CH_2C\underline{H}_3$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 170.3; 154.7; 135.5; 135.3; 132.6; 131.2; 130.6; 129.6, 129.3; 127.7; 127.4; 120.4; 120.2; 80.9; 51.5; 49.5; 44.3; 43.7; 42.0; 40.6; 31.4; 30.8; 28.6; 14.6; 13.0. Found, *m*/*z*: 433.1086 $[M+Na]^+$. $C_{19}H_{27}BrNaN_2O_3$. Calculated, *m*/*z*: 433.1103.

**(*R*)-{6-Bromo-3-[(diethylamino)methyl]-3,4-dihydroisoquinolin-2(1*H*)-yl}(4-pentylphenyl)methanone (8)**. 4 M HCl in 1,4-dioxane (1.52 ml, 6.10 mmol) was added dropwise to a solution of amide (*R*)-**7** (251 mg, 0.61 mmol) in anhydrous 1,4-dioxane (4 ml). The light-yellow solution was stirred at room temperature for 16 h, then solvent was evaporated under reduced pressure to give unprotected tetrahydroisoquinoline (207 mg, 98%) which was used in the next step without purification. $LiAlH_4$ (2.4 M solution in THF, 496 µl, 1.19 mmol) was added dropwise to a cooled solution (0°C) of crude product from previous step (207 mg, 0.59 mmol) in anhydrous THF (6 ml). After stirring at room temperature for 2 h, the light-yellow solution was cooled to 0°C and quenched by sequential (within intervals of 10 min) addition of $H_2O$ (45 µl), aqueous 4 M NaOH solution (90 µl), and more $H_2O$ (135 µl). Ten minutes after addition of the final amount of $H_2O$, the white suspension was filtered. The filter cake was washed with EtOAc (20 ml). The filtrate was evaporated to dryness to yield 162 mg (92%) of (*R*)-*N*-[(6-bromo-1,2,3,4-tetrahydroisoquinolin-3-yl)methyl]-*N*-ethylethanamine as a light-yellow oil, which was used in subsequent step without purification. DIPEA (283 µl, 211 mg, 1.64 mmol) was added to a cooled (0°C) solution of amine from previous step (162 mg, 0.54 mmol) in anhydrous $CH_2Cl_2$ (7 ml) followed by 4-pentylbenzoyl chloride (122 µl, 126 mg, 0.60 mmol). The light-yellow solution was stirred at room temperature for 16 h, then evaporated under reduced pressure. The residue was partitioned between EtOAc (10 ml) and $H_2O$ (10 ml) and extracted with EtOAc (3×10 ml). The combined extracts were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g), eluent hexane–EtOAc, gradient from 10 to 100% EtOAc. Yield 113 mg (44% in three steps), light-yellow oil, mixture of rotamers, $[\alpha]_D^{20}$ 10.2 (*c* 0.98, $CHCl_3$). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 7.38–7.28 (4H, m, H Ar); 7.24–7.17 (2H, m, H Ar); 7.11–7.03 (1H, m, H Ar); 5.23 (1H, d, *J* = 17.9, $CH_2N$); 4.57–4.12 (2H, m, $CH_2N$, $CH_2C\underline{H}$); 3.20–2.97 (1H, m, $C\underline{H}_2CH$); 2.89–2.75 (1H, m, $C\underline{H}_2CH$); 2.69–2.45 (4H, m, 1-$CH_2$, $C\underline{H}_2CH_3$); 2.44–2.10 (4H, m, $CHC\underline{H}_2NEt_2$, $C\underline{H}_2CH_3$); 1.62 (2H, quint, *J* = 7.3, 2-$CH_2$); 1.42–1.20 (4H, m, 3,4-$CH_2$); 1.01–0.93 (3H, m, $CH_2C\underline{H}_3$); 0.89 (3H, t, *J* = 6.9, 5-$CH_3$); 0.82–0.63 (3H,

m, $CH_2C\underline{H}_3$). $^{13}C$ NMR spectrum ($CDCl_3$), δ, ppm: 172.3; 144.9; 134.6; 133.9; 132.3; 131.4; 129.7; 128.6; 128.3; 126.9; 120.3; 54.3; 51.7; 47.3; 45.1; 41.7; 35.9; 31.5; 31.4; 31.1; 22.7; 14.2; 11.8. Found, *m*/*z*: 471.2007 $[M+H]^+$. $C_{26}H_{36}BrN_2O$. Calculated, *m*/*z*: 471.2011.

**(*R*)-{3-[(Diethylamino)methyl]-6-(pyridin-3-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl}(4-pentylphenyl)methanone (9a)**. A vial was charged with bromide (*R*)-**8** (20 mg, 0.042 mmol), pyridin-3-ylboronic acid (7.8 mg, 0.064 mmol), and $Pd(PPh_3)_4$ (1.5 mg, 0.0013 mmol), then 1,4-dioxane (0.5 ml) was added, followed by aqueous 2 M $Na_2CO_3$ solution (42 μl, 0.084 mmol). After stirring at 105°C for 16 h, the orange suspension was cooled to room temperature and diluted with $H_2O$ (5 ml) and EtOAc (5 ml). The organic layer was decanted, and the aqueous layer was extracted with EtOAc (3×5 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g), eluent hexane–EtOAc, gradient from 50 to 100% EtOAc, then EtOAc–MeOH, 9:1. Yield 9 mg (47%), light-yellow oil, mixture of rotamers, $[\alpha]_D^{20}$ 7.0 (*c* 0.62, $CHCl_3$). $^1H$ NMR spectrum ($CD_3OD$), δ, ppm: 8.84–8.76 (1H, m, H Ar); 8.55–8.47 (1H, m, H Ar); 8.15–8.04 (1H, m, H Ar); 7.59–7.48 (3H, m, H Ar); 7.46–7.36 (3H, m, H Ar); 7.36–7.28 (2H, m, H Ar); 5.24 (1H, d, *J* = 18.5, $CH_2N$); 4.65–4.24 (2H, m, $CH_2N$, $CH_2C\underline{H}$); 3.30–3.17 (1H, m, $C\underline{H}_2CH$); 3.07–2.94 (1H, m, $C\underline{H}_2CH$); 2.76–2.53 (4H, m, 1-$CH_2$, $C\underline{H}_2CH_3$); 2.52–2.13 (4H, m, $CHC\underline{H}_2NEt_2$, $C\underline{H}_2CH_3$); 1.66 (2H, quintet, *J* = 7.5, 2-$CH_2$); 1.45–1.23 (4H, m, 3,4-$CH_2$); 1.03 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 0.96–0.84 (3H, m, 5-$CH_3$); 0.77 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). $^{13}C$ NMR spectrum ($CD_3OD$), δ, ppm: 174.4; 148.8; 148.3; 138.2; 137.2; 136.4; 134.8; 133.5; 133.1; 133.0; 130.0; 129.9; 129.8; 129.2; 128.5; 128.1; 126.4; 125.5; 55.2; 53.6; 49.3; 48.5; 43.1; 36.7; 32.4; 32.3; 23.6; 14.4; 12.1. Found, *m*/*z*: 470.3164 $[M+H]^+$. $C_{31}H_{40}N_3O$. Calculated, *m*/*z*: 470.3171.

**(*R*)-{3-[(Diethylamino)methyl]-6-(4-methoxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl}(4-pentylphenyl)-methanone (9b)**. A vial was charged with bromide (*R*)-**8** (50 mg, 0.106 mmol), (4-methoxyphenyl)boronic acid (24 mg, 0.159 mmol), and $Pd(PPh_3)_4$ (3.7 mg, 0.0032 mmol), then 1,4-dioxane (1 ml) was added, followed by aqueous 2 M $Na_2CO_3$ solution (106 μl, 0.212 mmol). After stirring at 105°C for 16 h, the orange suspension was cooled to room temperature and diluted with $H_2O$ (5 ml) and EtOAc (5 ml). The organic layer was decanted, and the aqueous layer was extracted with EtOAc (3×5 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g), eluent hexane–EtOAc, gradient from 10 to 100% EtOAc. Yield 26 mg (49%), light-yellow oil, $[\alpha]_D^{20}$ 13.3 (*c* 1.03, $CHCl_3$). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 7.54–7.46 (2H, m, H Ar); 7.44–7.28 (4H, m, H Ar); 7.25–7.19 (3H, m, H Ar); 7.01–6.93 (2H, m, H Ar); 5.31 (1H, d, *J* = 18.9, $CH_2N$); 4.61–4.16 (2H, m, $CH_2N$, $CH_2C\underline{H}$); 3.85 (3H, s, $OCH_3$); 3.29–3.07 (1H, m, $C\underline{H}_2CH$); 2.95–2.83 (1H, m, $C\underline{H}_2CH$); 2.72–2.49 (4H, m, 1-$CH_2$, $C\underline{H}_2CH_3$); 2.47–2.37 (1H, m, $CHC\underline{H}_2NEt_2$); 2.34–2.13 (3H, m, $CHC\underline{H}_2NEt_2$, $C\underline{H}_2CH_3$); 1.63 (2H, quint, *J* = 7.4, 2-$CH_2$); 1.41–1.23 (4H, m, 3,4-$CH_2$); 1.08–0.94 (3H, m, $CH_2C\underline{H}_3$); 0.90 (3H, t, *J* = 6.8, 5-$CH_3$); 0.76 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$). $^{13}C$ NMR spectrum ($CDCl_3$), δ, ppm: 172.3; 159.3; 144.7; 139.3; 134.2; 133.5; 132.6; 130.8; 128.6; 128.1; 127.7; 127.0; 126.2; 125.0; 114.3; 55.5; 54.5; 52.1; 47.4; 47.2; 41.9; 35.9; 31.5; 31.1; 22.7; 14.2; 11.8. Found, *m*/*z*: 499.3322 $[M+H]^+$. $C_{33}H_{43}N_2O_2$. Calculated, *m*/*z*: 499.3325.

**(*R*)-{3-[(Diethylamino)methyl]-6-(4-hydroxyphenyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)}(4-pentylphenyl)-methanone (9c)**. A vial was charged with NaH (60% suspension in mineral oil) (7.4 mg, 0.184 mmol) and washed with anhydrous $Et_2O$ (3×1 ml), then anhydrous DMF (1 ml) was added. The suspension was cooled to 0°C, and 1-dodecanethiol (44 μl, 0.184 mmol) was added dropwise (*Caution! Gas evolution!*). After stirring at room temperature for 10 min, solution of isoquinoline derivative (*R*)-(**9b**) (23 mg, 0.046 mmol) in anhydrous DMF (0.5 ml) was added to the white suspension. The yellow solution was stirred at 130°C for 2 h, then evaporated, and $H_2O$ (3 ml) was added to the residue and extracted with EtOAc (3 × 3 ml). The combined extracts were washed with $H_2O$ (7 ml), brine (7 ml), dried, and evaporated. The mixture was purified by column chromatography on silica gel (10 g), eluent $CH_2Cl_2$, gradient to $CH_2Cl_2$–MeOH, 96:4. Yield 13 mg (58%), light-yellow oil, $[\alpha]_D^{20}$ 9.8 (*c* 1.16, $CHCl_3$). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 7.46–7.34 (4H, m, H Ar); 7.34–7.17 (5H, m, H Ar); 7.00–6.82 (2H, m, H Ar); 5.32 (1H, d, *J* = 18.0, $CH_2N$); 4.66–4.17 (2H, m, $CH_2N$, $CH_2C\underline{H}$); 3.31–3.06 (1H, m, $C\underline{H}_2CH$); 2.96–2.84 (1H, m, $C\underline{H}_2CH$); 2.76–2.54 (4H, m, 1-$CH_2$, $C\underline{H}_2CH_3$); 2.50–2.37 (1H, m, $CHC\underline{H}_2NEt_2$); 2.35–2.15 (3H, m, $CHC\underline{H}_2NEt_2$, $C\underline{H}_2CH_3$); 1.71–1.54 (2H, m, 2-$CH_2$); 1.44–1.23 (4H, m, 3,4-$CH_2$); 1.12–0.96 (3H, m, $CH_2C\underline{H}_3$); 0.90 (3H, t, *J* = 6.7, 5-$CH_3$); 0.76 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$). $^{13}C$ NMR spectrum ($CDCl_3$), δ, ppm: 172.6; 156.0; 144.9; 139.5; 133.8; 133.0; 132.4; 130.5; 128.6; 128.2; 127.6; 127.3; 127.0; 126.2; 125.0; 116.0; 54.5; 52.2; 47.3; 42.0; 35.9; 31.5; 31.1; 22.7; 14.2; 11.7. Found, *m*/*z*: 514.3428 $[M+H]^+$. $C_{33}H_{44}N_3O_2$. Calculated, *m*/*z*: 514.3434.

**(*R*)-{3-[(Diethylamino)methyl]-6-[(4-methoxyphenyl)-amino]-3,4-dihydroisoquinolin-2(1*H*)-yl}(4-pentylphenyl)-methanone (10)**. A vial was charged with $Pd_2(dba)_3$ (0.78 mg, 0.0009 mmol), X-Phos (0.81 mg, 0.0017 mmol), then anhydrous PhMe (1 ml) was added and the solution was heated to 60°C. After 10 min, bromide (*R*)-**8** (20 mg, 0.042 mmol), 4-methoxyaniline (6.3 mg, 0.051 mmol), and NaO*t*-Bu (5.7 mg, 0.059 mmol) were added. After stirring at 90°C for 16 h, the yellow suspension was cooled to room temperature and diluted with $H_2O$ (5 ml) and EtOAc (5 ml). The organic layer was decanted, and the aqueous layer was extracted with EtOAc (3×5 ml). The combined organic layers were washed with brine, dried over $Na_2SO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (15 g), eluent hexane–EtOAc, gradient from 50 to 100% EtOAc. Yield 12 mg (55%), light-yellow oil, $[\alpha]_D^{20}$ 11.5 (*c* 0.81, $CHCl_3$). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 7.40–7.33

(2H, m, H Ar); 7.25–7.18 (2H, m, H Ar); 7.10–6.98 (3H, m, H Ar); 6.90–6.83 (2H, m, H Ar); 6.82–6.66 (2H, m, Ar); 5.43 (1H, s, NH); 5.19 (1H, d, $J$ = 17.4, $CH_2N$); 4.47–4.06 (2H, m, $CH_2N$, $CH_2C\underline{H}$); 3.80 (3H, s, $OCH_3$); 3.17–2.96 (1H, m, $C\underline{H}_2CH$); 2.72 (1H, d, $J$ = 16.2, $C\underline{H}_2CH$); 2.67–2.49 (4H, m, 1-$CH_2$, $C\underline{H}_2CH_3$); 2.44–2.33 (1H, m, $CHC\underline{H}_2NEt_2$); 2.31–2.12 (3H, m, $CHC\underline{H}_2NEt_2$, $C\underline{H}_2CH_3$); 1.71–1.54 (2H, m, 2-$CH_2$); 1.44–1.19 (4H, m, 3,4-$CH_2$); 1.03–0.94 (3H, m, $CH_2C\underline{H}_3$); 0.93–0.86 (3H, m, 5-$CH_3$); 0.75 (3H, t, $J$ = 7.1, $CH_2C\underline{H}_3$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 172.2; 155.4; 144.6; 143.8; 136.1; 134.3; 133.2; 128.5; 127.6; 127.2; 127.0; 122.4; 122.1; 116.2; 114.8; 55.7; 54.6; 52.1; 47.4; 41.7; 35.9; 31.6; 31.2; 27.7; 22.7; 14.2; 11.9. Found, $m/z$: 514.3428 $[M+H]^+$. $C_{33}H_{44}N_3O_2$. Calculated, $m/z$: 514.3434.

**Inhibitory activity assays of compounds 9a–c, 10**. A fluorescence resonance energy transfer (FRET) assay was performed to evaluate the ability of compounds to inhibit Plm I, Plm II, and Plm IV. $K_m$ of the substrate was determined for each enzyme: Plm I – 2.7 ± 0.3 μM, Plm II – 2 ± 0.2 μM, Plm IV – 2.8 ± 0.2 μM. A solution of each compound for testing (concentration 0.01–100 μM) was added to the enzyme (Plm I, Plm II, or Plm IV) in buffer (0.1 M NaOAc, pH 4.5, 10% glycerol) on 96-well plate. The mixture was incubated for 30 min at 37°C. Substrate (DABCYL-Glu-Arg-Nle-Leu-Ser-Phe-Pro-EDANS, AnaSpec Inc.) was then added to reach the final concentration of 5 μM. Hydrolysis of the substrate was detected as an increase in fluorescence (Em 490 nm, Ex 336 nm) at 37°C. The data points were collected every 1 min within 8–15 min. For the rate calculation, only the linear interval was used, which was slightly different for each enzyme. Compounds were tested in triplicate experiments. $IC_{50}$ values were calculated using the software Graph Pad Prism 5.0. Pepstatin A ($IC_{50}$, nM: 0.42 ± 0.02 (Plm II), 0.9 ± 0.02 (Plm I), 0.3 ± 0.04 (Plm IV)) and compound **A** were used as positive control.

**X-ray structural analysis of compound (*R*)-6a**. Single crystals of $C_{11}H_{13}BrClNO_2$ were investigated on a Rigaku, XtaLAB Synergy, Dualflex, HyPix diffractometer. The crystal was kept at 150.0(1) K during data collection. Using Olex2,[19] the structure was solved with the ShelXT[20] structure solution program using Intrinsic Phasing and refined with the olex2.refine[21] refinement package using Levenberg–Marquardt minimization. Crystal data for $C_{11}H_{13}BrClNO_2$ ($M$ 306.59 g/mol): triclinic, space group $P\bar{1}$; $a$ 7.0731(4), $b$ 7.9997(4), $c$ 12.2609(4) Å; α 77.412(4), β 74.682(4), γ 68.708(5)°; $V$ 617.68(6) Å$^3$; $Z$ 1; μ(Cu$K\alpha$) 6.417 mm$^{-1}$; $d_{calc}$ 1.6483g/cm$^3$. 16651 reflections measured ($2\Theta \leq 155.0°$), 4805 unique ($R_{int}$ 0.0475, $R_{sigma}$ 0.0349) which were used in all calculations. The final $R_1$ was 0.0438 ($I > 2\sigma(I)$) and $wR_2$ was 0.1318 (all data). The complete crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1953912).

**Docking studies**. Docking studies were performed using the AutoDock Vina software package.[18]

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