New 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ols with antituberculosis activity*

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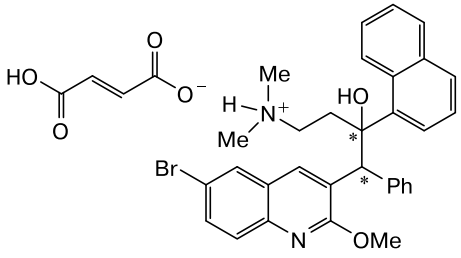
New 4-dimethylamino-2-(naphthalen-1-yl)-1-phenyl-1-(quinolin-3-yl)butan-2-ols with antituberculosis activity were synthesized. (1*R**,2*S**)-1-(6-Bromo-2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrocitrate exhibiting high antituberculosis activity is in the final stage of clinical trials and is prepared for use in clinical practice.

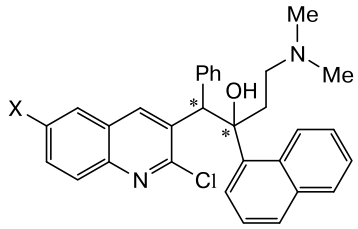
Key words: lithium diethylamide, diarylquinolines, 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ols, 3-benzyl-2-chloroquinolines, 3-dimethylamino-1-(naphthalen-1-yl)propan-1-one, tuberculosis.

A number of 3-benzyl-6-bromo-2-methoxyquinoline derivatives were found to have high activity against the mycobacterium *M. tuberculosis* (Mtb) and its drug-resistant strains. In 2013, the Janssen-Cilag International NV announced the development of the innovative antituberculosis drug TMC-207, Bedaquiline® containing (1*R**,2*S**)-1-(6-bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (**1**) as the active substance. This compound, in the form of hydrofumarate, was approved for medical use in 2014 under the brand name Sirturo®.[1] We investigated other derivatives of this class and synthesized a series of new compounds, which exhibited different activities against different *M. tuberculosis* strains.[2,3]



1 · HOOCCH=CHCOOH

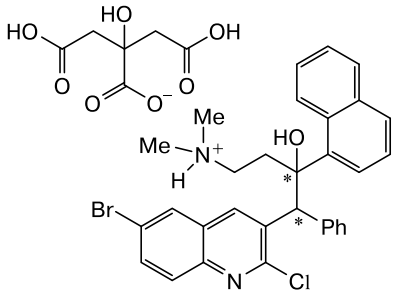
Due to a fundamentally new mechanism of action of diarylquinolines on *M. tuberculosis* based on their interaction with the C subunit of mycobacterial ATP synthase, these compounds are of great interest as potential antituberculosis agents.[4—6] It is assumed that the tertiary amine Bedaquiline is an arginine mimetic and blocks the proton pump for ATP synthase of mycobacteria. Investigations performed in the Pharm-Sintez resulted in the preparation of new patentable compounds of this class.[2,3]



2—4

X = Br (**2**), OMe (**3**), F (**4**)

Compounds **2** and **3** have passed microbiological testing. Compound **4** is planned to be tested for biological activity. Compound **2** is currently in clinical trials and is ready for the pilot production as hydrocitrate.



2 · $C_6H_8O_7$

* Based on the materials of the IV Interdisciplinary Symposium and Youth Forum on Medicinal, Organic, and Biological Chemistry and Pharmaceutics (MOBI-ChemPharma, 2018, Novy Svet, Crimea).

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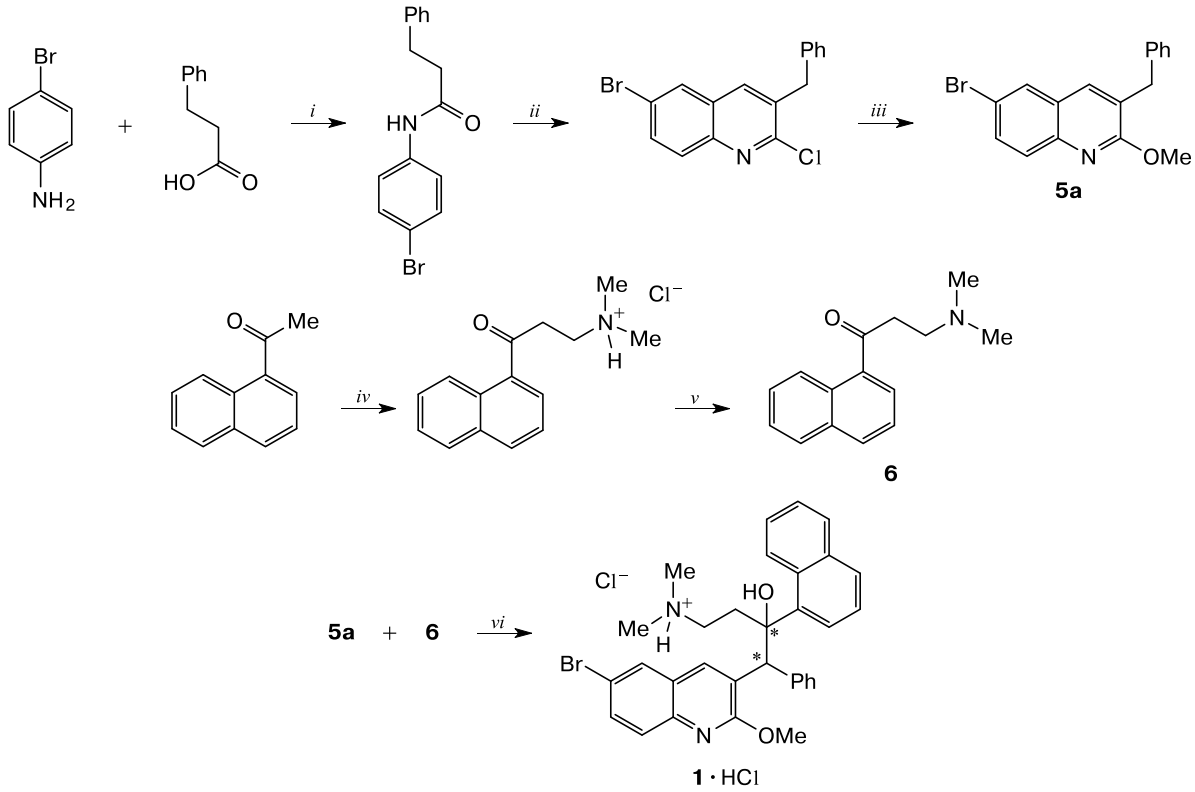
Scheme 1



Reagents and conditions: *i*. H_3BO_3, xylene, reflux; *ii*. Me_2NCHO, $POCl_3$, 80 °C; *iii*. MeONa/MeOH, reflux; *iv*. $(CH_2O)_x$, $Me_2NH \cdot HCl$, $CHCl_3$, reflux; *v*. NaOH, water, toluene; *vi*. Pr^i_2NLi, THF, −78 °C, then HCl.

Results and Discussion

Russia's demands for hydrocitrate of amine **2** are estimated at 1—1.2 tons per year. There is a need to optimize the synthesis conditions for such compounds in order to accomplish large-scale production taking into account high cost of the starting materials.

Two procedures for the synthesis of such compounds are described in the literature.[7,8] One procedure is shown in Scheme 1. The drawback of this method is the use of organolithium compounds, which require high-purity solvents and very low reaction temperatures necessary for the formation of tertiary alcohols.

Another route to such alcohols (Scheme 2) is covered by a patent.[8] The advantage of this method is that the reaction can be performed at −35 °C (rather than at −78 °C) due to lower acidity of compound **7** compared to compound **6**. Besides, this method affords product **8** in higher yield. The drawback of this approach is an additional double bond hydrogenation step.

The latter procedure seemed to us preferable for application at the industrial and pilot-plant levels because it requires less cooling in the step of adding an organolithium component at the C=O-bond .

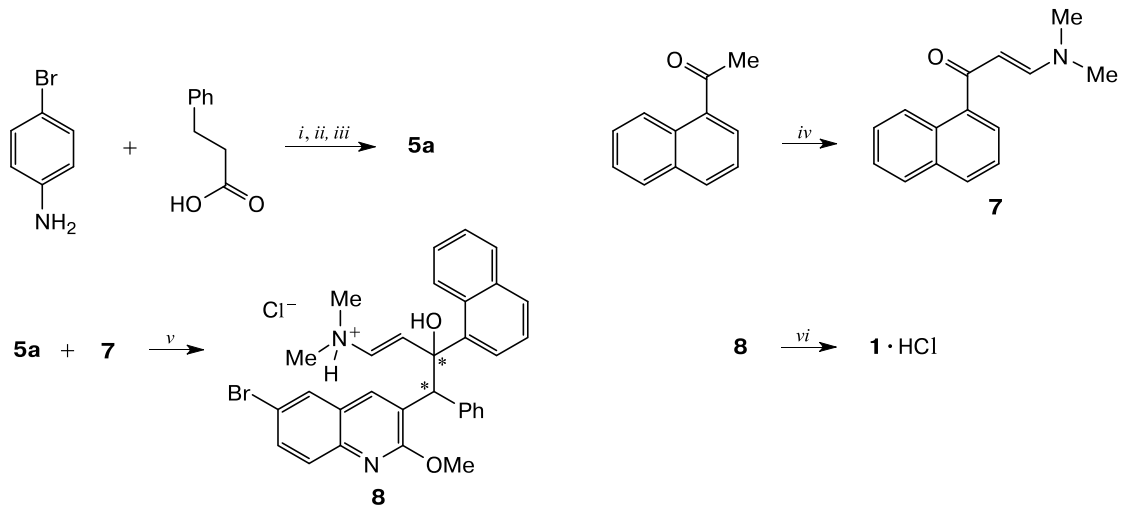
Unfortunately, this method appeared to be unsuitable for the synthesis of the target compound **2** because of instability of the chlorine atom at the quinoline ring and the formation of compound **9** as a by-product (Scheme 3).

Hence, the synthesis of the target compounds **2**—**4** using organolithium compounds according to Scheme 1 has no alternative taking into account the limiting conditions on the structure of compounds, the cost of the starting materials, and minimization of the number of synthesis steps (Scheme 4).

The key step is the synthesis of tertiary alcohols **2**—**4** from 3-dimethylamino-1-(naphthalen-1-yl)propan-1-one and substituted 3-benzyl-2-chloroquinolines. Organolithium compounds have not only nucleophilic but also basic properties. The reactions of the resulting organolithium derivative can, in principle, not only give the required tertiary alcohols, but it also can be accompanied by proton abstraction from the most acidic carbon atom in reactant **6** (Scheme 5).

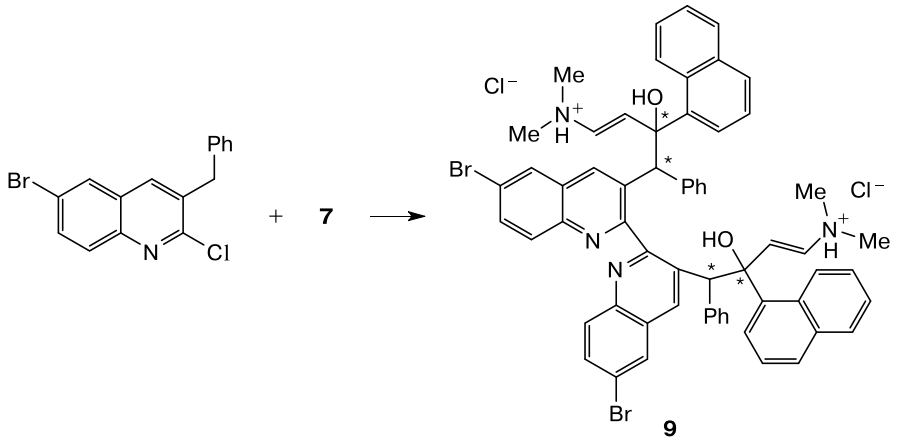
A general way to increase the yield of compounds **2**—**4** is to decrease the polarity of the reaction mixture during the synthesis. This is achieved by the addition of compound **6** to organolithium derivatives **10**—**12** in a non-polar solvent (toluene, hexane).

Scheme 2



Reagents and conditions: *i*. H_3BO_3, xylene, reflux; *ii*. Me_2NCHO, $POCl_3$, 80 °C. *iii*. MeONa/MeOH, reflux; *iv*. $Me_2NCH(OMe)_2$, xylene, reflux; *v*. Pr^i_2NLi, THF, −35 °C, then HCl. *vi*. H_2/Pd.

Scheme 3



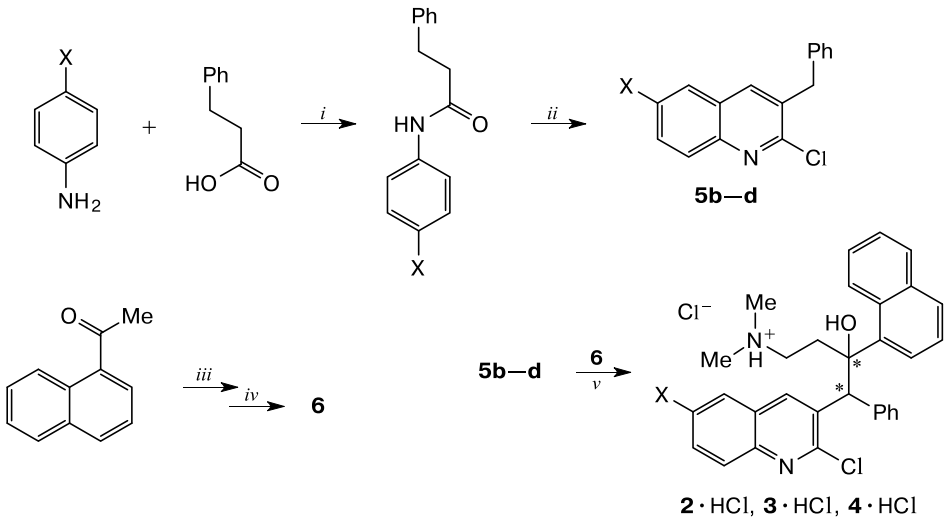
Reagents and conditions: Et_2NLi, THF, −35 °C, then HCl.

We succeeded in separating the resulting mixtures of diastereomers of **2**—**4** to individual components. Diastereomers of compounds **2** and **4** were separated by their transformation from hydrochlorides to bases, washing with boiling acetone, and recrystallization from ethyl acetate. Compound **3** (in the form of hydrochloride) was washed with chloroform, and the residue was concentrated and crystallized from ethanol.

The synthesized compounds were characterized by NMR spectroscopy, chromatography-mass spectrometry, and X-ray diffraction (Figs 1—3).

Crystals of compound **4** rapidly decompose in air. Hence, this compound was studied at 200 K under an argon atmosphere. The X-ray diffraction study of compound **3** was performed in a similar way. Crystals of compound **2** were studied at 295 K. The crystals of **2** and **3** are characterized by a similar arrangement of the molecules. The asymmetric unit of the crystal of **4** contains an ethanol solvent molecule in a ratio of two molecules **4** per ethanol molecule. The solvent molecules are located at lattice points (in the vicinity of inversion centers) and are disordered mainly over two positions. This weak binding of the solvent molecule to molecules **4** is responsible for crystal degradation. There is a strong intramolecular O(1)—H(1)...N(2) hydrogen bond in all molecules **2**—**4** that has an effect on the molecular conformation.

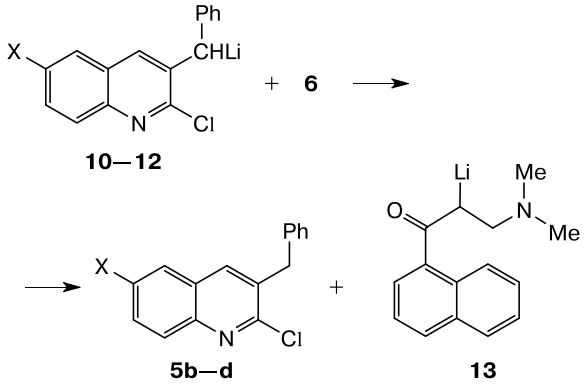
Scheme 4



X = Br (**2**, **5b**), OMe (**3**, **5c**), F (**4**, **5d**)

Reagents and conditions: *i*. H_3BO_3, xylene, reflux. *ii*. Me_2NCHO, $POCl_3$, 80 °C. *iii*. $(CH_2O)_x$, $CHCl_3$, Me_2NH_2Cl, reflux. *iv*. toluene, water, NaOH. *v*. Et_2NLi, THF, −78 °C, then HCl.

Scheme 5



X = Br (**5b**, **10**), OMe (**5c**, **11**), F (**5d**, **12**)

The bases of 4-dimethylamino-2-(naphthalen-1-yl)-1-phenyl-1-(quinolin-3-yl)butan-2-ols **2—4** were transformed to hydrocitrates. Hydrocitrates of amines **2** and **3** were subjected to biological assays. The results of assays of diastereomers of **2** hydrocitrate in the *M.tuberculosis H37Rv* strain are given in Table 1. Hydrocitrate of (1*R**,2*S**)-**2** proved to be twice as active as hydrocitrate of (1*R**,2*R**)-**2**.

At concentrations of 5 and 10 μg mL^{-1}, compound **3** caused the complete suppression of the Mtb growth throughout the experiment.

In the presence of compound **3** at concentrations of 1.25 and 2.5 μg mL^{-1}, the Mtb growth started on the 10.94±0.09 and 16.00±0.06 days, respectively, and reliably differed from the control in the absence of the substance (the delay was ~2.5 and ~7.5 days). Besides, compound **3** taken at a concentration of 2.5 μg mL^{-1} caused a reliable increase in the duration of the active cell division phase by ~8 days compared to the control.

Table 1. Results of assays of diastereomers of **2** hydrocitrate in the *M.tuberculosis H37Rv* strain

Compound	MIC/mg mL^{-1}
(1*R**,2*S**)-**2**	3.125
(1*R**,2*R**)-**2**	6.25
Bedaquiline® hydrocitrate*	1.56
Rifampicin	0.10
Isoniazid	0.10

* (1*R**,2*S**)-1-(6-Bromo-2-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrocitrate.

To sum up, we synthesized a series of new quinoline-substituted aminobutanols, separated their diastereomers, and characterized them by mass spectrometry, ^1H and ^{13}C NMR spectroscopy, and X-ray diffraction. Hydrocitrates of the derivatives were subjected to biological assays to evaluate activity against *M. tuberculosis*. Hydrocitrate of (1*R**,2*S**)-**2** proved to be twice as active as hydrocitrate of (1*R**,2*R**)-**2**. Compound **3** also exhibited antituberculosis activity.

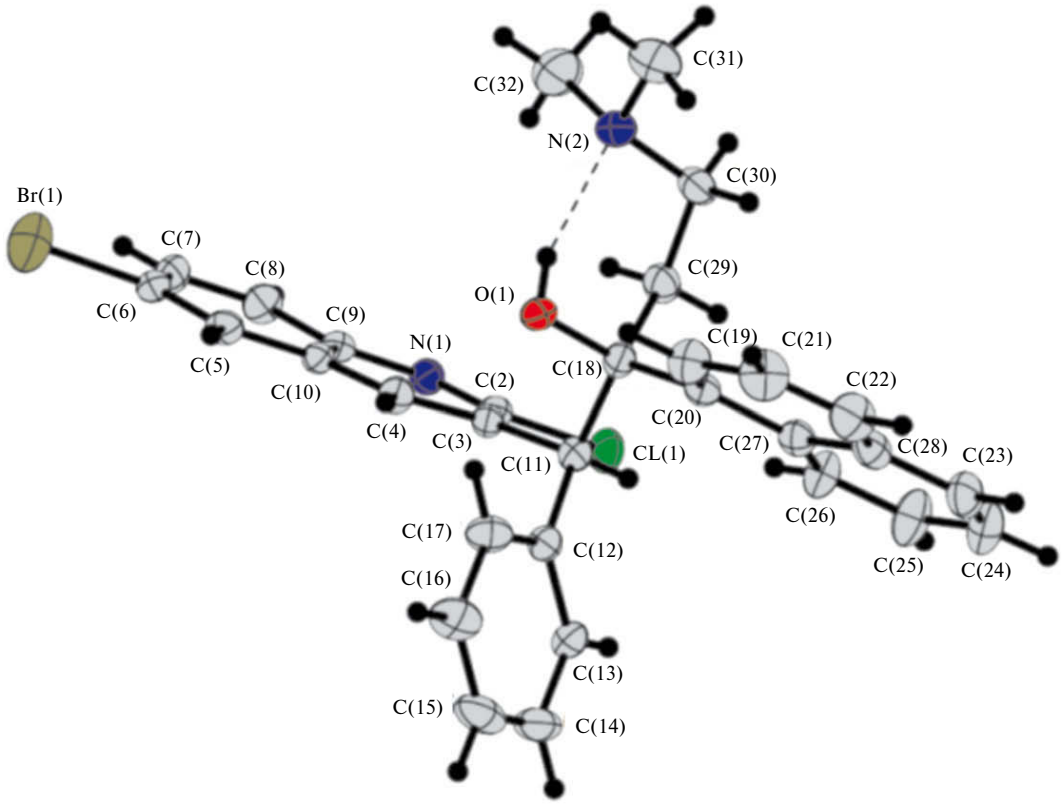


Fig. 1. Molecular structure of (1*R**,2*S**)-1-(6-bromo-2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (**2**).

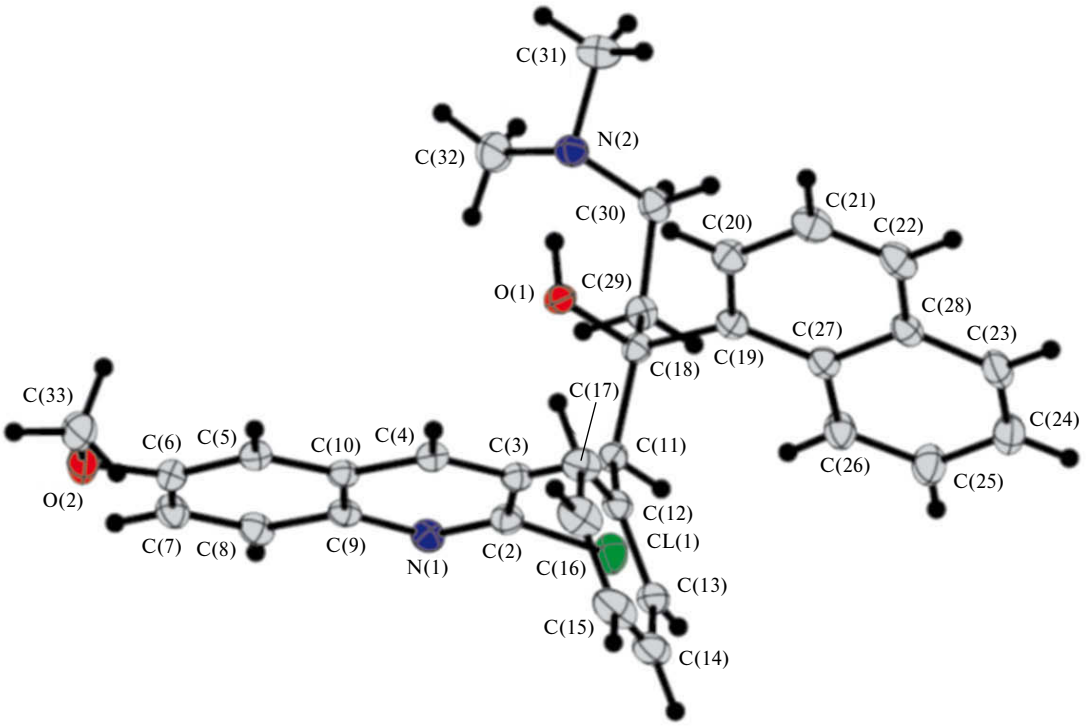


Fig. 2. Molecular structure of (1*R**,2*S**)-1-(2-chloro-6-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (**3**).

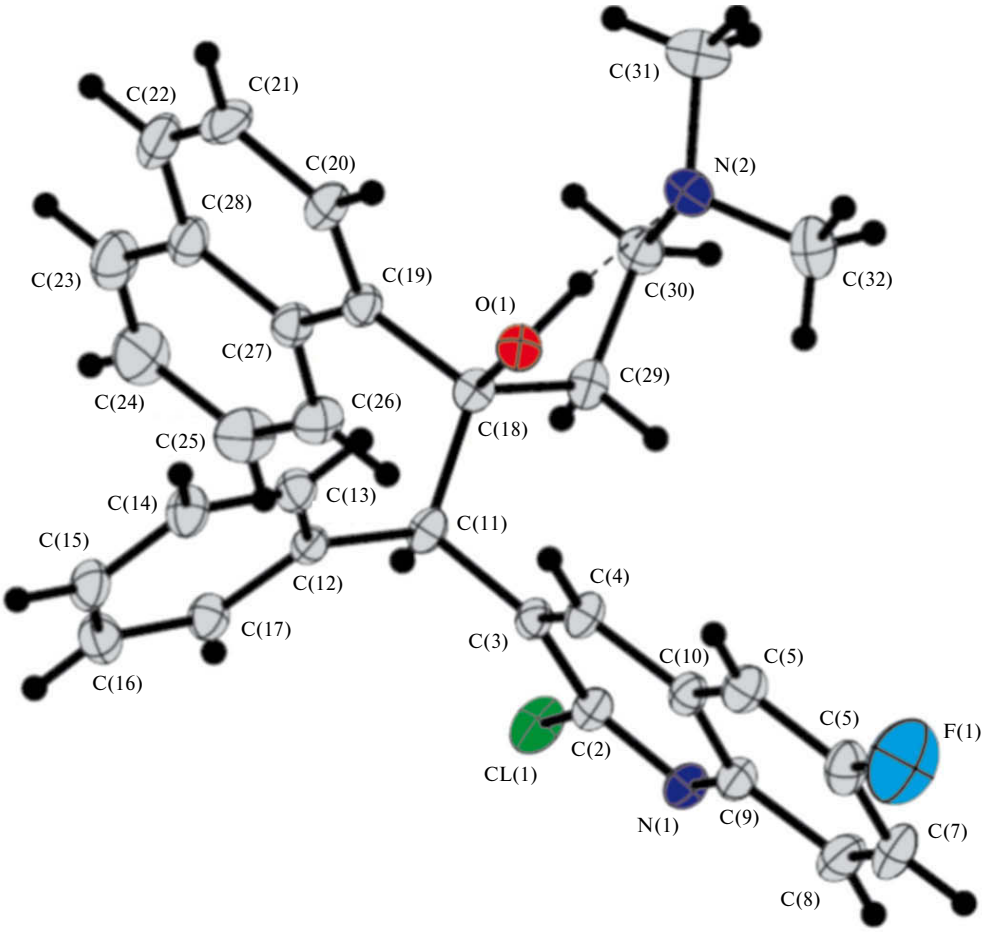


Fig. 3. Molecular structure of (1*R**,2*S**)-1-(2-chloro-6-fluoroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (**4**).

Experimental

The reaction mixtures and target compounds were analyzed by HPLC on an Agilent 1200 Series system equipped with a ReproSil-Pur Basic chromatographic column (modified silica gel C18 with a granule diameter 5 μm, geometric sizes of the column were 4.6×250 mm). The conditions of HPLC: the elution gradient (95% phase A + 5% phase B)→100% phase B during 20 min. The phase A consisted of H_2O and 0.01% trifluoroacetic acid (TFA); the phase B, of acetonitrile and 0.01% TFA. The rate of elution was 1 mL min^{-1}. The analyzed compounds were detected using a spectrophotometric detector at $\lambda = 220$ nm.

Electrospray ionization mass spectra (ESI-MS) were recorded on an Agilent MSD IonTrap 6310 mass spectrometer in positive ion mode. The pressure of the nebulizer gas was 275 MPa, the drying gas flow rate was 7 L min^{-1}, the drying gas temperature was 350 °C.

The ^1H NMR spectra were measured on a Bruker AM-360 spectrometer (working frequency 360.13 MHz) in $CDCl_3$ using the signal of the nondeuteratred solvent as the internal standard.

The melting points of the products were determined on a PTP (M) capillary-type analyzer (KlinLabPribor) and on a Mettler Toledo FP62 melting point apparatus.

3-Dimethylamino-1-(naphthalen-1-yl)propan-1-one hydrochloride was transformed into the base employing sodium hydroxide (reagent grade, Khimmed) and sodium bicarbonate (reagent grade, Khimmed); toluene (special purity grade, EKOS) was distilled over sodium metal. The water content in the solvents was determined by coulometric titration using hydronal (Coulomat AG, Fluka). The following reagents and solvents were utilized: THF (stabilized ABCR GmBh, Reatorg), 2.5 *M* Bu^nLi (98%, Acros Organics), 2.5 *M* Bu^nLi (98%, ABCR), 1.6 *M* Bu^nLi (98%, Acros Organics), diethylamine* (99%, Aldrich), *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (99%, Aldrich), and hexane (reagent grade, Khimmed). Diethylamine, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, hexane, and toluene were dried and distilled over sodium metal; THF was dried over sodium metal followed by distillation or drying over activated alumina using a Pure Solve 400 solvent purification system.

Synthesis of 3-dimethylamino-1-(naphthalen-1-yl)propan-1-one (6). 3-Dimethylamino-1-(naphthalen-1-yl)propan-1-one hydrochloride (11.2 g, 0.042 mol) was dissolved in distilled water (10 mL) in a 250 mL one-neck round-bottom flask equipped with a magnetic stirrer. Toluene (100 mL) and a solution of sodium hydroxide (1.8 g, 0.045 mol) in distilled water (10 mL) were added to the resulting solution. The emulsion thus formed was vigorously stirred for 10 min at room temperature. The aque-

* We used diethylamine ($pK_b \approx 35$) instead of diisopropylamine ($pK_b \approx 34$) because of its higher basic properties and since it is more readily available on the industrial scale, being a by-product of the synthesis of triethylamine.

ous layer was separated, and the toluene layer was dried over magnesium sulfate, filtered, and concentrated. A mobile oily yellowish liquid was obtained in a yield of 9.6 g. The chromatographic retention time t_{chr} = 10.34 min. The yield of **6** was 99% according to HPLC data and ^{1}H NMR spectra. ^{1}H NMR ($CDCl_3$), δ: 2.95 (s, 6 H, 2-CH_3); 3.47 (t, 2 H, C$\underline{H}_2$—CH_2, J = 7.0 Hz); 3.75 (t, 2 H, CH_2—C$\underline{H}_2$, J = 7.0 Hz); 7.60—8.50 (m, 7 H, CH_{arom}). MS, found: m/z 228.1 $[M + H]^+$; $C_{15}H_{17}NO$; calculated M + H = 228.1.

Synthesis of a diastereomeric mixture of 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrochlorides (2—4). Two four-neck flasks were evacuated at 120 °C for 1 h. The flasks were filled with argon and cooled to 25 °C. Diethylamine (1.46 g, 0.02 mol), THF (50 mL), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (2.32 g, 0.02 mol) were placed in the first flask equipped with a thermometer and cooled to −20 °C. Then 2.5 *M* *n*-butyllithium (8 mL, 0.02 mol) was added to the resulting solution, and the mixture was stirred for 30 min and cooled to −78 °C. The corresponding 3-benzyl-2-chloroquinoline **5** (0.015 mol) was placed in the second flask and dissolved in THF (50 mL). Then the mixture was cooled to −50 °C. The first flask was connected to the second flask by a rubber tube, and the content of the first flask was poured into the second one. After the completion of the ixing of the reagents, the reaction mixture was allowed to stand for 1 h and cooled to −78 °C. Compound **6** was placed in the third flask and then it was diluted with toluene to 50 mL and cooled to −78 °C. The resulting cold solution of compound **6** in toluene was added to the reaction mixture. The mixture was kept for 3 h at −78 °C, treated with concentrated hydrochloric acid (10 mL, 0.108 mol), and heated to 25 °C. The reaction mixture was concentrated to dryness, dissolved in chloroform (100 mL), and washed with water (3×30 mL). The aqueous layer was separated, and the chloroform layer was dried over magnesium sulfate and concentrated. The dry residue was twice suspended in toluene (50 mL) and then filtered off. The resulting product was dried to constant weight.

1-(6-Bromo-2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (2). The yield of a mixture of two diastereomers of **3**·HCl was 3.62 g (40.5%), the (1*R**,2*R**)/(1*R**,2*S**) diastereomeric ratio was 60 : 40.

A mixture of diastereomer hydrochlorides was obtained as white or beige crystals with m.p. 219.4—228.1 °C (with decomp.). The chromatographic retention time t_{chr}((1*R**,2*R**)-**2**) = 16.03 min, t_{chr}((1*R**,2*S**)-**2** = 17.35 min.

^{1}H NMR of the base (1*R**,2*R**)-**2** ($CDCl_3$), δ: 1.95—2.05 (s, 7 H, CH_2—CH_2, Me); 2.07—2.16 (m, 1 H, CH_2—CH_2); 2.23—2.32 (m, 1 H, CH_2—CH_2); 2.48—2.57 (m, 1 H, CH_2—CH_2); 5.8—5.82 (s, 1 H, CH); 7.36—7.46 (m, 5 H, CH_{arom}); 7.48—7.53 (m, 2 H, CH_{arom}); 7.56—7.62 (m, 2 H, CH_{arom}); 7.74—7.84 (m, 3 H, CH_{arom}); 7.77—7.91 (m, 1 H, CH_{arom}); 8.24—8.30 (d, 1 H, CH_{arom}, J = 7.2 Hz); 8.50—8.58 (m, 2 H, CH_{arom}); 9.17 (s, 1 H, OH). ^{13}C NMR of the base (1*R**,2*R**)-**2** ($CDCl_3$), δ: 34.0 (1 C), 44.5 (2 C), 55.5 (1 C), 56.0 (1 C), 82.0 (1 C), 119.3 (1 C), 124.6 (2 C), 125.0 (1 C), 125.4 (1 C), 126.7 (1 C), 127.3 (1 C), 127.7 (2 C), 128.2 (1 C), 128.4 (1 C), 129.3 (1 C), 129.6 (2 C), 131.6 (2 C), 132.6 (1 C), 134.8 (1 C), 135.0 (2 C), 138.5 (1 C), 139.2 (1 C), 141.1 (1 C), 144.0 (1 C), 152.1 (1 C).

^{1}H NMR of the base (1*R**,2*S**)-**2** ($CDCl_3$), δ: 1.95—2.00 (s, 5 H, CH_2—CH_2, Me); 2.00—2.10 (m, 5 H, CH_2—CH_2); 6.00—6.05 (s, 1 H, CH); 6.85—6.95 (m, 3 H, CH_{arom}); 7.15—7.20 (m, 2 H, CH_{arom}); 7.25 (s, 1 H, CH_{arom}); 7.45—7.50 (m, 1 H, CH_{arom}); 7.55—7.6 (m, 1 H, CH_{arom}); 7.65—7.75 (m, 3 H, CH_{arom}); 7.80—7.85 (m, 1 H, CH_{arom}); 7.95—8.15 (m, 3 H, CH_{arom}); 8.65—8.71 (m, 1 H, CH_{arom}); 9.35 (s, 1 H, —OH). ^{13}C NMR of the base (1*R**,2*S**)-**2** ($CDCl_3$), δ: 33.0 (1 C), 44.5 (2 C), 53.5 (1 C), 56.0 (1 C), 82.0 (1 C), 124.5 (1 C), 124.8 (2 C), 125.6 (1 C), 126.0 (1 C), 126.8 (1 C), 127.2 (1 C), 127.2 (1 C), 127.3 (1 C), 127.5 (1 C), 127.8 (1 C), 128.0 (1 C), 128.2 (2 C), 129.6 (1 C), 129.8 (2 C), 134.0 (1 C), 134.5 (2 C), 140.0 (2 C), 141.0 (1 C), 146.0 (1 C), 152.0 (1 C).

MS, found: m/z 559.92 $[M + H]^+$; $C_{31}H_{28}BrClN_2O$; calculated M + H = 560.00.

1-(2-Chloro-6-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (3). The yield of a mixture of two diastereomers of **2**·HCl was 4.62 g (56.2%), the (1*R**,2*R**)/(1*R**,2*S**) diastereomeric ratio was 40 : 60. A mixture of two diastereomer hydrochlorides was obtained as white or beige crystals with m.p. 239.1—242.9 °C (with decomp.). The chromatographic retention time t_{chr}((1*R**, 2*R**)-**3**) = 13.6 min, t_{chr}((1*R**, 2*S**)-**3**) = 14.6 min.

^{1}H NMR of the base (1*R**,2*R**)-**3** ($CDCl_3$), δ: 1.95—2.00 (s, 6 H, 2-CH_3); 2.05—2.15 (m, 2 H, CH_2—CH_2); 2.25—2.35 (m, 1 H, CH_2—CH_2); 2.50—2.55 (m, 1 H, CH_2—CH_2); 3.80—3.90 (s, 3 H, OMe); 5.80—5.85 (s, 1 H, CH); 7.00—7.05 (m, 1 H, CH_{arom}); 7.11—7.20 (m, 1 H, CH_{arom}); 7.25—7.32 (m, 2 H, CH_{arom}); 7.36—7.43 (m, 3 H, CH_{arom}); 7.55—7.62 (m, 3 H, CH_{arom}); 7.73—7.78 (m, 1 H, CH_{arom}); 7.81—7.88 (m, 2 H, CH_{arom}); 8.26—8.34 (d, 1 H, —CH_{arom}, J = 7.2 Hz); 8.52—8.59 (m, 2 H, CH_{arom}); 9.10—9.15 (s, 1 H, OH). ^{13}C NMR of the base (1*R**,2*R**)-**3** ($CDCl_3$), δ: 34.0 (1 C), 44.5 (2 C), 55.0 (1 C), 55.5 (1 C), 56.2 (1 C), 82.0 (1 C), 105.4 (1 C), 121.9 (1 C), 124.6 (1 C), 124.7 (1 C), 125.2 (1 C), 125.5 (1 C), 126.7 (1 C), 127.4 (1 C), 127.7 (2 C), 128.1 (1 C), 128.4 (1 C), 129.0 (1 C), 129.6 (1 C), 129.7 (1 C), 131.7 (2 C), 134.1 (1 C), 134.9 (1 C), 138.6 (1 C), 139.7 (1 C), 141.5 (1 C), 141.7 (1 C), 149.2 (1 C), 157.6 (1 C).

^{1}H NMR of the base (1*R**,2*S**)-**3** ($CDCl_3$), δ: 1.95—2.00 (s, 6 H, 2-CH_3); 2.00—2.15 (m, 2 H, CH_2—CH_2), 2.40—2.45 (m, 2 H, CH_2—CH_2); 3.95—4.00 (m, 3 H, OMe); 6.00—6.05 (s, 1 H, CH); 6.85—6.95 (m, 3 H, CH_{arom}); 7.15—7.40 (m, 8 H, CH_{arom}); 7.45—7.55 (m, 1 H, CH_{arom}); 7.60—7.70 (m, 2 H, CH_{arom}); 7.85—7.90 (m, 1 H, CH_{arom}); 7.90—7.95 (m, 1 H, CH_{arom}); 8.65—8.70 (s, 1 H, OH). ^{13}C NMR of the base (1*R**,2*S**)-**3** ($CDCl_3$), δ: 33.0 (2 C), 44.0 (2 C), 53.0 (1 C), 54.0 (1 C), 56.0 (1 C), 82.6 (1 C), 105.3 (1 C), 122.6 (1 C), 124.5 (1 C), 124.8 (1 C), 125.2 (1 C), 125.9 (1 C), 127.2 (1 C), 128.0 (1 C), 128.4 (1 C), 128.6 (1 C), 129.3 (1 C), 129.4 (1 C), 129.5 (1 C), 129.6 (1 C), 129.8 (2 C), 134.2 (1 C), 134.5 (1 C), 139.9 (1 C), 140 (1 C), 140.5 (1 C), 142.5 (1 C), 150 (1 C), 158 (1 C).

MS, found: m/z 511.0 $[M + H]^+$; $C_{32}H_{31}ClN_2O_2$; calculated M + H = 511.1.

1-(2-Chloro-6-fluoroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (4). The yield of a mixture of two diastereomer hydrochlorides of **4**·HCl was 2.62 g (32.6%), the (1*R**,2*R**)/(1*R**,2*S**) diastereomeric ratio was 70 : 30. A diastereomeric mixture of the hydrochloride was obtained as white or beige crystals with m.p. 220—229.1 °C (with decomp.). The chromatographic retention time t_{chr}((1*R**, 2*R**)-**2**) = 13.72 min, t_{chr}((1*R**, 2*S**)-**2**) = 14.44 min. ^{1}H NMR of the base (1*R**,2*R**)-**4** ($CDCl_3$), δ: 1.95—2.05 (m, 8 H, CH_2—CH_2, Me); 2.11—2.16 (m, 1 H, CH_2—CH_2); 2.24—2.31 (m, 1 H, CH_2—CH_2); 5.90—5.95 (s, 1 H, CH); 7.15—7.32 (m, 5 H, CH_{arom}); 7.35—7.47 (m, 3 H, CH_{arom}); 7.50—7.57 (m, 2 H, CH_{arom}); 7.60—7.68 (m, 1 H, CH_{arom}); 7.70—7.95 (m, 3 H, CH_{arom}); 8.07—8.15 (d, 1 H

CH_{arom}, J = 7.2 Hz); 8.45—8.65 (d, 1 H, CH_{arom}, J = 7.2 Hz); 9.05—9.15 (s, 1 H, —OH). ^{13}C NMR of the base (1*R**,2*R**)-**4** ($CDCl_3$) δ: 33.9 (1 C), 44.5 (2 C), 54.9 (1 C), 56.0 (1 C), 81.9 (1 C), 110.6 (d, 1 C, $\underline{C}H_{arom}$, $^2J_{C,F}$ = 21.7 Hz); 119.2 (d, 1 C, CH_{arom}, $^2J_{C,F}$ =21.7 Hz); 124.5 (1 C), 124.7 (1 C), 125.0 (1 C), 125.5 (1 C), 126.7 (1 C), 127.3 (2 C), 127.7 (2 C), 128.3 (1 C), 129.6 (2 C), 130.0 (2 C), 131.7 (1 C), 134.5 (1 C) 135.0 (1 C), 139.2 (1 C), 139.2 (1 C), 141.0 (1 C), 143.5 (1 C), 151.0 (1 C), 158.8 (d, 1 C, CF_{arom}, $^1J_{C,F}$ = 248 Hz).

^{1}H NMR of the base (1*R**,2*S**)-**4** ($CDCl_3$), δ: 1.95—2.05 (s, 5 H, CH_2—CH_2, Me); 2.05—2.20 (m, 5 H, CH_2—CH_2, Me); 6.00—6.05 (s, 1 H, CH); 6.85—6.95 (s, 3 H, CH_{arom}); 7.15—7.25 (m, 2 H, CH_{arom}); 7.30—7.47 (m, 1 H, CH_{arom}); 7.45—7.55 (m, 3 H, CH_{arom}); 7.60—7.75 (m, 2 H, CH_{arom}); 7.85—7.92 (d, 1 H, CH_{arom}, J = 7.2 Hz); 8.00—8.10 (m, 2 H, CH_{arom}); 8.64—8.70 (d, 2 H, CH_{arom}, J = 7.2 Hz); 9.30—9.35 (s, 1 H, OH). ^{13}C NMR of the base (1*R**,2*S**)-**4** ($CDCl_3$), δ: 33.4 (1 C), 44.5 (2 C), 53.9 (1 C), 56.2 (1 C), 82.5 (1 C), 111.0 (d, 1 C, CH_{arom}, $^2J_{C,F}$ = 21.7 Hz); 120.0 (d, 1 C, CH_{arom}, $^2J_{C,F}$ = 21.7 Hz); 124.4 (1 C), 124.7 (1 C), 125.4 (1 C), 125.8 (1 C), 127.0 (1 C), 127.6 (2 C), 127.7 (3 C), 127.8 (1 C), 128.0 (1 C), 130.0 (1 C), 130.5 (2 C), 135.0 (2 C), 140.0 (1 C), 140.5 (1 C), 141.0 (1 C), 143.5 (1 C), 151.8 (1 C), 159.0 (d, 1 C, CF_{arom}, $^1J_{C,F}$ = 248 Hz).

MS, found: m/z 499.5 $[M + H]^+$; $C_{31}H_{28}FClN_2O$; calculated M + H = 499.5.

Isolation and separation of diastereomers of 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ols. Step 1. Preparation of diastereomers of bases 2 or 4. A 25% aqueous ammonia solution (25 mL) was added to a suspension of a mixture of diastereomers of the appropriate hydrochloride (20 g, 0.034 mol) in chloroform (200 mL), and the mixture was stirred for 15—20 min. The resulting emulsion was separated using a separatory funnel. The lower (chloroform) layer was washed with distilled water (50 mL). The aqueous extracts were combined and washed with chloroform (50 mL). The organic layers were combined and concentrated using a rotary evaporator at room temperature. The resulting beige powder was thoroughly ground and dried *in vacuo* at 25 °C.

Step 2. Separation of diastereomers of bases 2 or 4. The dried base (100 g) of a diastereomeric mixture of **2** or **4** was suspended in acetone (1 L). The suspension was refluxed for 15—20 min with moderate stirring, cooled to 5 °C, and kept in a refrigerator at 5—10 °C overnight. The white precipitate of the (1*R**,2*R**)-diastereomer was suction-filtered, washed with ice-cold acetone (70 mL), and dried to constant weight at 25 °C. The yield of (1*R**,2*R**)-**2** with a chromatographic purity ≥98% was 45.4 g. The yield of (1*R**,2*R**)-**4** with a chromatographic purity ≥98% was 50.4 g.

After the filtration, the mother liquor was concentrated at 30 °C. The beige-brown flocculent precipitate (50 g) was dissolved in boiling ethyl acetate (330 mL). The resulting dark-red solution was slowly cooled to room temperature and kept at 0—5 °C overnight. The white coarsely-crystalline precipitate that formed was suction-filtered, washed with ice-cold acetone (50 mL), and dried to constant weigh. The yield of (1*R**,2*S**)-**2** with a chromatographic purity ≥98% was 33 g. The yield of (1*R**,2*S**)-**4** with a chromatographic purity ≥98% was 25.3 g.

Synthesis of (1*R,2*S**)-diastereomers of 1-(6-bromo-2-chloro-3-quinolyl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrocitrate (2 · $C_6H_8O_7$).** Citric acid monohydrate (12.4 g, 0.059 mol) was dissolved in ethanol (150 mL). The solution was mixed with the base of (1*R**,2*S**)-**2** (30 g, 0.054 mol) under vigorous stirring. The resulting suspension was kept at 5—10 °C overnight, filtered, and washed with ethanol (50 mL). The product was dried to constant weight at 40—45 °C overnight. Hydrocitrate **2** · $C_6H_8O_7$ was obtained as a white crystalline powder in a yield of 35.7 g. The filtrate, which was obtained after the isolation of the product, was concentrated to 2/3 of the initial volume and kept at 5—10 °C overnight. The precipitate that formed was filtered off. The yield of the second crop was 1.8 g. The total yield was 35.6 g (93%), the chromatographic purity ≥98%.

Isolation and separation of diastereomers of 1-(2-chloro-6-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol (3). Step 1. Preparation of (1*R,2*R**)-1-(2-chloro-6-methoxyquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrochloride, (1*R**,2*R**)-3 · HCl.** A diastereomeric mixture of **3** hydrochloride (1.8 g, 0.0033 mol) was suspended in chloroform (30 mL) for 1 h. The suspension was filtered off. The yield of diastereomer (1*R**,2*R*)-**3** · HCl was 0.7 g; the chromatographic purity ≥88%. The precipitate that formed was repeatedly separated. The yield of (1*R**,2*R**)-**3** · HCl with a chromatographic purity ≥98% was 0.5 g. The residues were concentrated to constant weight and were used for the preparation of the diastereomer (1*R**,2*S**)-**3**.

Step 2. Preparation of hydrochloride of (1*R,2*S**)-3.** A diastereomeric mixture of **3** hydrochloride (1.2 g, 0.0022) was dissolved in ethanol (40 mL) under reflux. The solution was cooled to 2 °C and allowed to stand overnight. The precipitate that formed was filtered off, washed with ethanol (40 mL) cooled to 0 °C, and dried to constant weight at room temperature. The yield of hydrochloride of (1*R**,2*S**)-**3** with a chromatographic purity 95% was 0.6 g. The precipitate that formed was repeatedly crystallized. The yield of hydrochloride of (1*R**,2*S**)-**3** with a chromatographic purity ≥98% was 0.3 g. The residues were concentrated to constant weight and were used for the preparation of the diastereomer (1*R**,2*R**)-**3**.

Preparation of the base of diastereomer (1*R,2*S**)-3.** Hydrochloride of (1*R**,2*S**)-**3** (0.5 g, 0.001 mol) was suspended in chloroform (20 mL). Then a 25% aqueous ammonia solution (3 mL) was added to the suspension at 25 °C, and the mixture was stirred for 15—20 min. The resulting suspension was separated using a separatory funnel. The lower (chloroform) layer was washed with distilled water (50 mL). The aqueous extracts were combined and washed with a fresh portion of chloroform (50 mL). The organic layers were combined and concentrated using a rotary evaporator at 25 °C. The resulting beige powder was dried *in vacuo* at room temperature.

X-ray diffraction study of compounds 2—4. Single crystals of all compounds were grown from chloroform. The X-ray diffraction data sets for compounds **2—4** were collected on a STOE diffractometer equipped with a Pilatus100K semiconductor detector, a microfocus X-ray source (Cu-Kα, λ = 1.54086 Å), and a focusing multilayered thin-film monochromator. The X-ray diffraction data were processed using the STOE X-AREA 1.67 software (STOE & Cie GmbH, Darmstadt, Germany, 2013). The integrated intensities were processed with the LANA program (implemented in the X-Area software) to minimize the differences of intensities of symmetry-equivalent reflections (multi-scan method).

Crystallographic data and the X-ray data collection statistics for compounds **2—4** are summarized in Table 2.

The structures were solved and refined with the SHELX(1) program package. The positional parameters of nonhydrogen

Table 2. Crystallographic data and the X-ray data collection statistics for compounds **2—4**

Parameter	**2**	**3**	**4**
Molecular formula	$C_{31}H_{28}BrClN_2O$	$C_{32}H_{31}ClN_2O_2$	$C_{31}H_{28}ClFN_2O$
M	559.91	511.04	498.00
T/K	293(2)	293(2)	293(2)
Space group	*P*21/*c*	*P*21/*c*	$P\bar{1}$
Crystal system	Monoclinic	Monoclinic	Triclinic
a/Å	15.6337(5)	15.8639(3)	9.7451(3)
b/Å	9.5020(2)	9.3739(2)	12.1285(5)
c/Å	19.0902(7)	18.8059(6)	13.1246(5)
β/deg	108.347(2)	108.347(2)	68.184(3)
Z	4	4	2
V/Å^3	2691.72(15)	2654.41(12)	1387.75(10)
d_x/mg m^{-3}	1.382	1.279	1.194
μ/mm^{-1}	3.194	3.194	1.469
λ/Å	1.54086	1.54086	1.54086
Number of reflections			
measured	18802	18733	5330
unique	4646	4954	2388
R_{int}	0.052	0.1186	0.0488

atoms were refined by the full-matrix method with anisotropic displacement parameters. The crystal structure of **4** was refined using the SQUEEZE procedure. The hydrogen atoms (except for the proton H(1) at the oxygen atom (O(1)) were positioned geometrically and refined using a riding model. In all structures, the hydrogen atom H(1) was located in difference Fourier maps and its parameters were freely refined. The molecular geometry was calculated using the SHELX program package. The graphical representations and figures were made using the DIAMOND(2) software. The crystallographic data were deposited with the Cambridge Crystallographic Data Centre and are available, free of charge, at www.ccdc.cam.ac.uk/data_request/cif (CADS 1920402 (**2**), 1920404 (**3**), 1920399 (**4**)).

Synthesis of diastereomeric 1-(2-chloroquinolin-3-yl)-4-dimethylamino-2-(naphthalen-1-yl)-1-phenylbutan-2-ol hydrocitrates (2—4) (general procedure). Citric acid monohydrate (12.4 g, 0.059 mol) was dissolved in rectified ethanol (150 mL). The solution was mixed with the base of the (1*R**,2*S**)- or (1*R**,2*R**)-diastereomer of compounds **2—4** (0.054 mol) under vigorous stirring. The resulting suspension was kept at 5—10 °C overnight, filtered, and washed with ethanol (50 mL). The reaction product was dried to constant weight at 40—45 °C overnight. The yields of hydrocitrates of diastereomers (1*R**,2*R**)-**2** and (1*R**,2*S**)-**2** were 34.5 g (83%) and 30.3 g (77%), respectively; the yield of hydrocitrate of diastereomer (1*R*,2*S*)*-**3** was 33.2 g (86%); the yields of hydrocitrates of diastereomers (1*R**,2*R**)-**4** and (1*R**,2*S**)-**4** were 34 g (89%) and 35.3 g (93.9%), respectively.

***In vitro* evaluation of inhibitory concentrations of compound 2 for mycobacteria in liquid Dubos medium from changes in the optical density at 600 nm.** To evaluate the dynamic effect of hydrocitrates of diastereomers of **2** on the growth of *Mycobacterium tuberculosis* (Mtb), the periodic culturing was performed in 200 μL of the liquid medium (Dubos broth). The Dubos broth was prepared according to the manufacturer's instructions from Difco (USA). After the autoclaving of the salt base diluted in distilled water, the flasks containing the medium were cooled to 52—54 °C, and then 5% sterile bovine serum albumin (BSA) and sodium oleate were added. The solution was distributed in wells of a 96-well flat-bottom plate. The evaluation was performed using the laboratory *M. tuberculosis* H37Rv strain sensitive to all antituberculosis agents. A suspension of single mycobacterial cells in the same growth phase was seeded in wells containing Dubos broth supplemented with the substances under study at different

Table 3. Growth of the control cultures *M.tuberculosis* H37Rv in the Bactec MGIT 960 system (without the addition of the substances and with exposure to rifampicin)

τ/day	Without the substance		Rifampicin (1 μg mL^{-1})	
	Average	SD*	Average	SD*
1	0	0	0	—
2	0	0	0	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
9	78	6	0	0
10	585	42	0	0
11	2680	626	0	0
12	6541	1901	0	0
13	11273	3132	0	0
14	15419	3772	0	0
15	17931	3837	0	0
16	18859	3557	0	0
17	19103	3358	0	0
18—42	19131	3318	0	0

* SD is a standard deviation.

concentrations (50, 25, 12.5, 6.25, 3.125, 1.56, 0.78, 0.39, 0.2, and 0.1 μg mL^{-1}) and the control agents rifampicin (R) and isoniazid (H) at the same concentrations. Each concentration of the substances was tested in triplicate; of the control samples, in duplicate. The Mtb culture grown in a medium without the addition of substances, served as the positive control. The incubation was performed at 37 °C for 18 days (the results were recorded until the positive control of the stationary growth phase or the maximum bacterial concentration was reached). The growth of the periodic culture of Mtb was monitored by changes in optical density (*D*) in the suspension, which was measured every 1—2 days with a Sigma plate reader at 600 nm, after the

Table 4. Growth of the control cultures *M.tuberculosis* H37Rv in the Bactec MGIT 960 system in the presence of compound **3** at concentrations of 0.15—10 μg mL^{-1}

τ/day	0.15		0.312		0.625		1.25		2.5		5		10	
	Average	SD*	CAverage	SD*	Average	SD*	Average	SD*	Average	SD*	Average	SD*	Average	SD*
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
9	48	4	48	23	0	0	0	0	0	0	0	0	0	0
10	427	49	469	102	88	61	0	0	0	0	0	0	0	0
11	1545	87	2355	607	577	351	0	0	0	0	0	0	0	0
12	3779	189	6269	1576	2059	1459	51	69	0	0	0	0	0	0
13	6686	279	10989	2257	4665	2984	412	305	0	0	0	0	0	0
14	9693	368	14994	2382	7699	4278	1555	1124	0	0	0	0	0	0
15	11840	350	17366	2179	10287	4910	3452	2028	0	0	0	0	0	0
16	12986	332	18177	1908	11938	4850	5779	2572	0	0	0	0	0	0
17	13520	326	18327	1780	12727	4446	7953	2575	0	0	0	0	0	0
18	13687	280	18334	1771	13026	4129	9500	2168	0	0	0	0	0	0
19	13718	282	18334	1771	13144	3961	10375	1681	0	0	0	0	0	0
20	13723	283	18334	1771	13205	3876	10806	1367	0	0	0	0	0	0
21	13728	287	18334	1771	13233	3836	10992	1223	1	1	0	0	0	0
22	13729	288	18334	1771	13234	3834	11066	1149	63	88	0	0	0	0
23	13731	291	18334	1771	13234	3834	11085	1128	236	333	0	0	0	0
24	13732	292	18334	1771	13234	3834	11091	1119	696	891	0	0	0	0
25	13732	292	18334	1771	13234	3834	11091	1119	1614	1906	0	0	0	0
26	13732	292	18334	1771	13234	3834	11091	1119	2960	3184	0	0	0	0
27	13732	292	18334	1771	13234	3834	11091	1119	4374	4098	0	0	0	0
28	13732	292	18334	1771	13234	3834	11091	1119	5657	4420	0	0	0	0
29	13732	292	18334	1771	13234	3834	11091	1119	6624	4221	0	0	0	0
30	13732	292	18334	1771	13234	3834	11091	1119	7345	3761	0	0	0	0
31	13732	292	18334	1771	13234	3834	11091	1119	7824	3352	0	0	0	0
32	13732	292	18334	1771	13234	3834	11091	1119	8139	3120	0	0	0	0
33	13732	292	18334	1771	13234	3834	11091	1119	8309	2951	0	0	0	0
34	13732	292	18334	1771	13234	3834	11091	1119	8409	2823	0	0	0	0
35	13732	292	18334	1771	13234	3834	11091	1119	8481	2724	0	0	0	0
36	13732	292	18334	1771	13234	3834	11091	1119	8541	2642	0	0	0	0
37	13732	292	18334	1771	13234	3834	11091	1119	8589	2583	0	0	0	0
38	13732	292	18334	1771	13234	3834	11091	1119	8624	2543	0	0	0	0
39	13732	292	18334	1771	13234	3834	11091	1119	8644	2517	0	0	0	0
40—42	13732	292	18334	1771	13234	3834	11091	1119	8648	2512	0	0	0	0

* SD is a standard deviation.

preliminary stirring of the well content. The statistically significant differences between the average optical densities in the wells containing the test substances and the optical densities in the control wells and the percentage of inhibition of the culture growth by the substances were determined in the maximum growth phase using the optical densities measured on the last day of observations (18th day).

The statistically significant differences between the average values were estimated using the Student t-criterion. The results were processed with the BIOSTAT 3.03 program (Praktika, Moscow, 1998). The reliable differences were with $p \leq 0.01$.

The percentage of inhibition was determined by the formula:

$$I = \frac{[D_{18}^{av}(\text{Comp}) - D_0^{av}(\text{Contr})] \cdot 100}{D_{18}^{av}(\text{Contr}) - D_0^{av}(\text{Contr})},$$

where I (%) is the inhibition $D_{18}^{av}(\text{Comp})$ is the average optical density in the wells containing the test substancees on the last day of observations (18th day), $D_0^{av}(\text{Contr})$ and $D_{18}^{av}(\text{Contr})$ are the average optical densities in the control wells at the beginning of observations (first day) and on the last day of observations (18th day), respectively.

The optical densities were recalculated to find the minimum inhibitory concentrations (MIC) (see Table 1).

Evaluation of bacteriostatic activity (growth inhibitory concentrations) of hydrocitrate of compound 3 by monitoring the growth of the *M. tuberculosis* H37Rv strain in the liquid Middlebrook 7H9 broth base. The antimycobacterial activity of hydrocitrate of **3** was studied by monitoring the growth dynamics of the H37Rv strain in the enriched *Middlebrook* 7H9 broth medium in the presence of different concentrations of hydrocitrate of compound **3** (0.15, 0.312, 0.625, 1.25, 2.5, 5, and 10 μg mL^{-1}) compared to the growth of this strain in the medium containing the first-line drug (rifampicin) at the critical concentration. Suspensions of mycobacteria were seeded at a concentration of 10^5 cfu mL^{-1} (cfu is a colony-forming unit that is used to estimate the number of viable mycobacterial cells; one colony corresponds to one cell). Each concentration, including the control test tubes without substances and the test tubes containing rifampicin, was analyzed in triplicate.

The growth of mycobacteria in culture was detected using a Bactec MGIT 960 automated growth detection system (BD, USA) in special MGIT tubes containing bound fluorophore under a semipermeable membrane on the bottom of the tube. The fluorophore release and light emission at a particular wavelength are directly proportional to the oxygen uptake of mycobacterial cells.

The growth of mycobacteria in culture media was detected at one-hour intervals using the Epicenter software (BD, USA). The dynamics of cell division of mycobacteria was expressed in relative fluorescence units (RFU). The duration of the experiment was 42 days according to the Becton Dickinson protocol. Then all grown cultures were tested for species specificity (for belonging to the *Mycobacterium tuberculosis*). The specificity of growth of mycobacteria was controlled by the visual inspection of positive test tubes (medium transparence, the presence of stippling and culture cloud on the bottom of test tube), Ziehl—Neelsen microscopy, seeding on blood agar (no growth on blood agar), and DNA identification (positive results of IS6110 PCR. assay).

The bacteriostatic activity was evaluated based on specific growth inhibition in the medium containing a particular concentration of the substance during 42 days. The minimum concentration of compound **3**, at which the culture growth was not detected, was taken as the minimum inhibitory concentration (MIC). At concentrations lower than MIC, the negative effect on the growth of *M.tuberculosis* H37Rv was evaluated. This effect may be manifested as follows:

1) retardation of the onset of the culture growth compared to the concentrations in the absence of the test substances;

2) an increase in the duration of the phase of active division compared to the control, which is indicative of a decrease in the mycobacterial cell division rate in the culture.

It should be noted that the RFU value recorded with the Epicenter program once the mycobacterial growth curve reaches a plateau has no value in evaluating antituberculosis activity of the substance because it depends on the instrumental parameters, which are not related to the dynamics of Mtb growth and does not reflect the dependence on the increase in cfu of Mtb.

The results of detection of mycobacterial growth in the control and test samples are given in Tables 3 and 4.

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