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Studies on Quinazolines. 6.[1] Asymmetric Synthesis of (S)-(+)- and (R)-(-)-3-[[4-(2-Methoxyphenyl)piperazin-1-yl]methyl]-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazolines

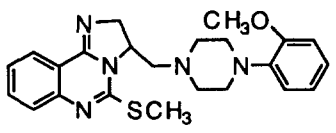
Alexander Gutcait,[2] Kuang-Chao Wang, Hsiu-Wen Liu and Ji-Wang Chern *

School of Pharmacy, College of Medicine, National Taiwan University,
No. 1, Section 1, Jen-Ai Road, Taipei, Taiwan (100), ROC.

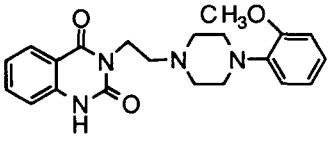
E-mail: chern@jwc.mc.ntu.edu.tw

Absract: The titled compounds have been synthesized in five steps from commercially available (R)-(+) and (S)-(-)-glycidol. The overall yield was about 29% with ee>98.5 %. Copyright © 1996 Elsevier Science Ltd

The racemic 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazoline **1**[1] has been recently synthesized as a conformational restricted analog of 3-[[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]quinazoline-2,4-dione, (SGB-1534, **2**)[3] and has been shown to exhibit high potency and selectivity toward α_1-adrenoreceptor. It is currently undergoing preclinical investigation as a antihypertensive agent. To elucidate the stereochemical requirements for biological activity, a new and efficient method for the synthesis of enantiomers of compound **1** was developed.



1

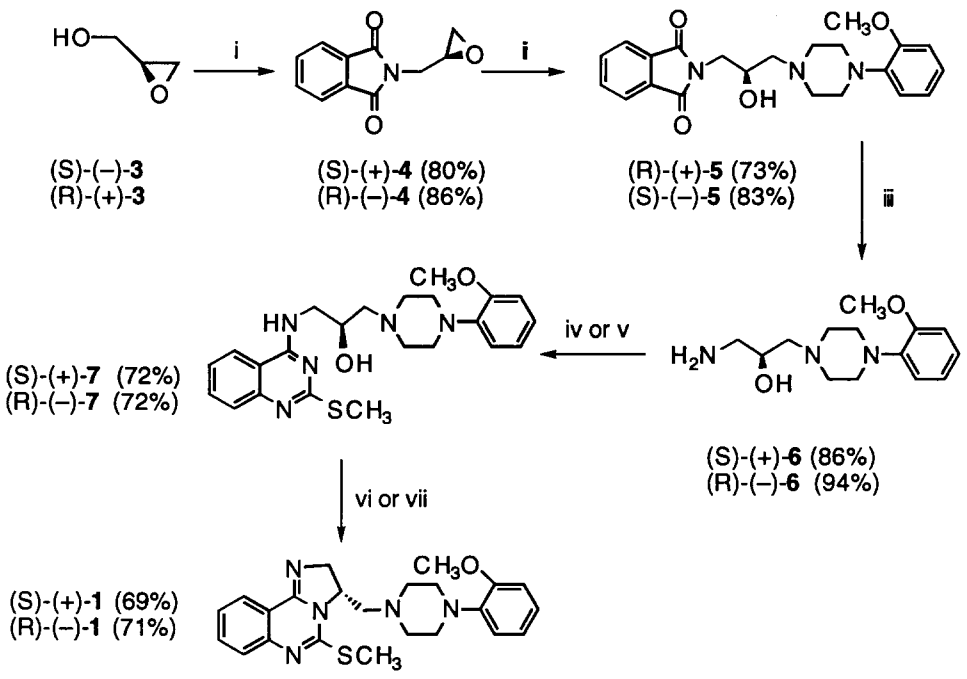


2

The synthesis began with the condensation of glycidol **3** with phthalimide under Mitsunobu reaction conditions[4] in THF at room temperature and gave the 1,2-epoxy-3-phthaloylaminopropane **4** in 80-86% yield. Glycidol was reported[5] to be unstable and undergo self-condensation in the presence of traces of acids as catalyst in epoxide ring opening. Thus, using freshly distilled glycidol is required to obtain pure compound **4** without intensive chromatographic purification. The yield was within the range of 73-83%. The condensation of epoxy derivative **4** with an equimolar amount of 4-(2-methoxyphenyl)piperazine was performed at reflux in THF for 3 days and the yield of resulting 1-phthaloylamino-3-[4-(2-methoxyphenyl)]piperazin-1-yl]propan-2-ol **5** after column chromatography was 68-72%. However, when the reaction was carried out with an excess amount of piperazine derivative, the chromatographically pure compound **5** was isolated in 73-83% yield by simply washing the crude product with ether to remove the excess piperazine.

The next step was conducted smoothly by treatment of compound **5** with hydrazine hydrate in ethanolic solution at room temperature to furnish 1-amino-3-[4-(2-methoxyphenyl)piperazin-1-yl]propan-2-ol **6** as monohydrate with 86-94% yield. Compound **6** turned out to be soluble in water and the precipitated phthalic acid hydrazide was filtered off from the mixture.

Scheme 1.

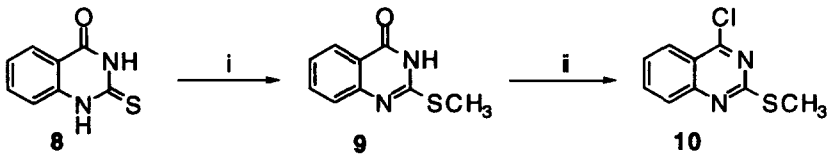


(i) Phthalimide, DEAD, Ph_3P, THF, 20 - 25 °C, 18 h; (iii) 4-(2-methoxyphenyl)piperazine, THF, reflux, 3 d; (iii) $NH_2NH_2 \cdot H_2O$, ethanol, 20 -25 °C,12 -24 h; (iv) 2,4-dimethylthioquinazoline, CH_3CN, reflux, 82-97 h, 24-56%; (v) **10**, NEt_3, THF, reflux, 7 h; (vi) MsCl, NEt_3, CH_2Cl_2, 0 to 25 °C, 7-19h, 47-69%; (vii) MsCl, NEt_3, K_2CO_3, CH_2Cl_2, 0 to 25 °C, 24 h.

Aminoalcohol **6** was then allowed to react with 2,4-dimethylthioquinazoline in acetonitrile at reflux to give 4-[(3-(4-methoxyphenyl)piperazine-1-yl)propan-2-ol-1-yl]amino-2-methylthioquinazoline **7**. But the results were variable in the yields ranging from 24 to 56% and the reaction released notorious methylthiol. We have investigated the possibility of synthesizing compound **7** by using 4-chloro-2-methylthioquinazoline **10**. Compound **10** was obtained in good yield (90-93%) starting from anthranilamide by heating with carbon disulfide in water-alcohol solution of potassium hydroxide to afford 2-mercaptoquinazolin-4-one **8** in 91% yield.[6] Compound **8** was then methylated with methyl iodide to give 2-methylthioquinazolin-2-one **9** which was subsequently converted to 4-chloro-2-methylthioquinazoline **10** in high yield (90-93%) by treating with $POCl_3$, followed by precipitation with water from acetone solution. Compound **10** was reacted smoothly with amino alcohol **6** in the presence of triethylamine to give compound **7** in 72% yield. All attempts to carry out the cyclization of **7** to compound **1** either by the Mitsunobu reaction[4] (Ph_3P, DEAD) or by treating with p-toluenesulphonylchloride (TsCl) in the presence of triethylamine were failed. It is reasonable to suggest that the failure of ring closure was probably due to the steric hindrances. This might gain some supports from the fact that the cyclization was achieved by methanesulphonylchloride (MsCl) and triethylamine. The cyclization reaction proceeded in 12-17 hours to give compound **1** with 47-69% chemical yield after chromatographical purification. It was pointed out that the reactive sulfonates form were readily converted into the chlorides as by-

product due to the action of triethylammonium chloride.[7] The addition of potassium carbonate to the reaction mixture to trap hydrogen chloride formed allowed us to obtain a chromatographically pure compound **1** in 77% yield without column chromatography.

Scheme 2.



(i) CH_3I, NaOH, H_2O, 22 °C, 76%; (ii) $POCl_3$, reflux, 1.5 h, 90 -93%.

It is of interest to note that the enantiomers of compound **1** had very good solubility in several solvents such as acetonitrile, isopropanol and ethanol when compare to racemic compound **1** which was crystallized from the above mentioned solvents. Thus, when the acetonitrile solutions of enantiomers **(S)-1** and **(R)-1** are mixed together by having one of them in excess amount, the racemic **(RS)-1** will precipitate immediately and quantitatively as a fine crystalline solid. However, only the one that is used in excess remained in filtrate solution. This would make it possible to obtain consistancy in enantiomeric purity of the synthesized compounds. Simple treatment of the sample with acetonitrile can be applied to separate the enantiomers **(S)-1** or **(R)-1** from the crystalline racemic **(RS)-1** by filtration. By HPLC analysis, the enantiomers of **1** obtained after evaporation of acetonitrile solution had more than 98.5% ee. The optical purity of starting materials influences only on the yield of pure enantiomers **1**.

High solubility of the enantiomers of **1** in comparison to their racemate can be explained most likely by the absence of crystalline structure of considered compounds. It is corroborated with the observation of the temperature zone of fair solid-to-liquid transition which is characteristic for glass-like state of compounds, instead of critical melting points for crystalline compounds.

The homochiral compounds were subjected to α_1-adrenoceptor binding affinity assay. The preliminary results illustrated that the affinity of enantiomer **(S)-1** to α_1-adrenoceptor (Ki = 1.88 nM) is 295-fold better than that of enantiomer **(R)-1** (Ki = 544 nM), whereas, the racemic **(RS)-1** showed a Ki value of 3.55 nM.[8]

In summary, we have demonstrated the ready availability of **(R)-(+)** and **(S)-(-)**-glycidol and their efficiency in the preparation of the enantiomers of 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazoline. The total yield of compound **1** after five steps-synthesis was about 29% from glycidol **3**. For the extension of this work it is currently applied to the synthesis of several chiral compounds for pharmacological evaluation in our laboratory.

EXPERIMENTAL SECTION

Analytical samples were homogeneous by thin-layer chromatography (TLC) and afforded spectroscopic data which are consistent with the assigned structures. Melting points were obtained on a capillar Electrothermal apparatus and are uncorrected. ^1H and ^{13}C nuclear magnetic resonance spectra were obtained using either a Varian AM-300 or Brucker AMX-400 spectrometer. Chemical shifts were reported in parts per

million (δ, ppm) using $CHCl_3$ (δ_H 7.26) or DMSO (δ_H 2.49) as internal standard. EI mass spectrums were recorded on JEOL JMS-D300 mass spectrometer from National Taiwan University, Taipei. Elemental analyses for C, H, and N were carried out on a Perkin-Elmer 240 Elemental Analyzer in National Taiwan University, Taipei and were within +0.4% of the theoretical values. Optical rotations were measured with a Jasco DIP-370 digital polarimeter in a 1 dm cell. Enantiomeric excess was determined by HPLC using CHIRALCEL OD (Daicel) column (eluent: hexane/isopropyl alcohol/triethylamine = 80/20/0.2). Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel, 60F-254, Merck) and spots were visualized with UV light and/or phosphomolybdic acid-ethanol. Column chromatography was performed with Kieselgel 60 (70-230 mesh) silica gel (Merck). All nonaqueus reactions were performed in oven-dried glassware and under atmosphere of dry nitrogen or argon. All starting materials were obtained from commercial suppliers (Aldrich, Jannsen, Merck Fluka) and used without purification. Glycidol was purchased from Aldrich and were distilled before using. Mesyl chloride was distilled *in vacuo* and kept under argon atmosphere. Solvents were purchased from Baker Analysed, Lab-scan and Alphs Chem Co. and had a HPLC quality. Solvents were dried according the methods described in [9].

4-(2-Methoxyphenyl)piperazine. The mixture of 1-(2-methoxyphenyl) piperazine hydrochloride (6.86 g, 30 mmol), aq. NaOH (2.5N, 36 mL, 90 mmol) and chloroform (30 mL) was vigorously stirred for 0.5 h. Chloroform layer was separated and stirred with water (50 mL) for another 0.5 h. Chloroform layer after separation was filtrated through Na_2SO_4 (2g) and evaporated *in vacuo* to dryness. The oil residue was dried *in vacuo* (2 mm Hg, 1h, 80 °C) to give 5.50 g (95%) of 4-(2-methoxyphenyl)piperazine as slightly yellow oil. It was used in synthesises without further purification.

1,2-Epoxy-3-phthaloylaminopropane (S)-(+)-3. To a stirred solution of phthalimide (1.93 g, 13.11 mmol) in dry THF (20 mL) was added triphenylphosphine (3.44 g, 13.11 mmol) followed by (S)-(+)-glycidol (1.12 g, 15.08 mmol) and diethyl azodicarboxylate (2.28 g, 13.11 mmol). The reaction mixture was stirred for 18h at room temperature and the solvent was removed *in vacuo*. The residue was stirred with ether (50 mL) for 2h and the precipitate was removed by filtration. The filtrate was evaporated *in vacuo* and the residue was purified by column chromatography (eluent: ethyl acetate/chloroform = 1/10) to give 1.48 g (80 %) of **(S)-(+)-3** as colourless solid: mp 102-103 °C; $[\alpha]_D^{26}$ +9 (c 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.87-7.82 (m, 2H, Ar-H), 7.76-7.71 (m, 2H, ArH), 3.95 (dd, 1H, *J* = 14.3, 5.1 Hz, CH_2O), 3.80 (dd, 1H, *J* = 14.3 Hz, CH2O), 3.25-3.20 (m, 1H, CHO), 2.78 (pseudo t, 1H, *J* = 4.4 Hz, NCH_2), 2.68 (dd, 1H, *J* = 4.80, 2.61 Hz, NCH_2); ^{13}C NMR ($CDCl_3$) δ 168.56, 134.71, 132.50, 124.02, 49.65, 46.68, 40.22

Compound **(R)-(-)-3** was obtained in 86 % yield using a similar procedure which afforded **(S)-(+)-3** as colourless solid: mp 102 °C; $[\alpha]_D^{26}$ -9 (c 2.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.90-7.84 (m, 2H, ArH), 7.77-7.71 (m, 2H, ArH), 3.96 (dd, *J* = 14.4, 5.0 Hz), 3.81 (dd, 1H, *J* = 14.4, 5.0 Hz), 3.27-3.21 (m, 1H, CHO), 2.81 (dd, 1H, *J* = 4.6, 4.1 Hz), 2.70 (dd, 1H, *J* = 4.8, 2.5 Hz); ^{13}C NMR ($CDCl_3$) δ 168.58, 134.73, 132.50, 124.03, 49.65, 46.70, 40.23; MS *m/z* 203 (M^+). Anal. Calc. for $C_{11}H_9NO_3$: C 64.92; H 4.46; N 6.89. Found C 64.70; H 4.37; N 6.92.

1-Phthaloylamino-3-[4-(2-methoxyphenyl)]piperazin-1-yl]propan-2-ol (R)-(+)-5. Procedure 1. To a stirred solution of 4-(2-methoxyphenyl)piperazine (5.07 g, 26.37 mmol) in dry THF (50 mL) was added **(S)-(+)-4** (4.15 g, 20.42 mmol) and the mixture was heated under reflux for 3 days. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluent: methanol/ethyl acetate/dichloromethane = 1/1/20) to give 5.47 g (68 %) of **(R)-(+)-5** as colorless solid: mp 155-157 °C;

$[\alpha]_D^{26}$ +8 (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.88-7.83 (m, 2H, ArH), 7.75-7.71 (m, 2H, ArH), 7.02-6.90 (m, 4H, ArH), 4.12-4.06 (m, 1H, CH), 3.85-3.77 (m, 5H, CH_3, CH_2), 3.06 (br s, 4H, NCH_2), 2.87-2.44 (m, 7H, NCH_2, CH_2, OH); ^{13}C NMR ($CDCl_3$) δ 169.13, 152.78, 141.65, 134,58, 132.62, 123.94, 123.59, 121.53, 118.76, 111.74, 65.47, 62.13, 55.92, 54.02, 51.28, 42.61; MS *m/z* 395 (M^+). Anal. Calcd. for $C_{22}H_{25}N_3O_4$: C 66.82; H 6.37; N 10.60. Found C 66.86; H 6.34; N 10.43.

Compound **(S)-(-)-5** was obtained in 72 % yield using a similar procedure which afforded **(R)-(+)-5**: $[\alpha]_D^{28}$ -8 (c 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.90-7.84 (m, 2H, ArH), 7.75-7.71 (m, 2H, ArH), 7.03-6.84 (m, 4H, ArH), 4.12-4.05(m, 1H, CH), 3.79-3.72 (m, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.06 (br s, 4H, NCH_2), 2.87-2.44 (m, 7H, NCH_2, CH_2, OH); ^{13}C NMR ($CDCl_3$) δ 169.13, 152.78, 141.63, 134,59 132.62, 123.94, 123.61, 121.53, 118.76, 111.71, 65.46 62.13, 55.92, 54.13, 51.26, 42.61; MS *m/z* 395 (M^+). Anal. Calcd for $C_{22}H_{25}N_3O_4 \cdot 0.5H_2O$: C 65.33; H 6.48; N10.39. Found C 65.05; H 6.31; N 10.24.

Procedure 2. To a stirred solution of 4-(2-methoxyphenyl)piperazine (6.03 g, 31.0 mmol) in dry THF (150 mL) was added **(R)-(-)-4** (5.49 g, 27.0 mmol) and the mixture was heated under reflux for 3 days. The solvent was removed *in vacuo* and the residue was stirred in ether (200 mL) for 3 h. The precipitate was collected by filtration and washed with ether (50 mL) to afford 7.81 g (73 %) of **(S)-(-)-5**.

Compound **(R)-(+)-5** was obtained in 83 % yield using a similar procedure which afforded **(S)-(-)-5**.

1-Amino-3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-2-ol (S)-(+)-6. To a stirred suspension of **(R)-(+)-5** (7.0 g, 17.7 mmol) in ethanol (180 mL) was added hydrazine monohydrate (4.31 mL, 88.7 mmol) and the solution was stirred at 25 °C for 12 h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in water (125 mL) and the solution was extracted with $CHCl_3$ (2 x 125 mL). The extracts were filtered through Na_2SO_4 (20 g) and evaporated to dryness to give slightly yellow oil which was crystallized after stirring with ether (60 mL) to afford 4.03 g (86 %) of **(S)-(+)-6** as white crystalline solid: mp 76-80 °C; $[\alpha]_D^{26}$ +22.3 (c 2.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.03-6.85 (m, 4H, ArH), 3.86 (s, 3H, OCH_3), 3.72-3.77 (m, 1H, CHOH), 2.87-2.80 (m, 3H), 2.68-2.61 (m, 3H), 2.46-2.40 (m, 2H), 2.23 (br. s, 3H, NH_2, OH, exchangeable with D_2O). Anal. Calcd. for $C_{14}H_{23}N_3O_2 \cdot H_2O$: C 59.34; H 8.89; N 14.82. Found C 59.50; H 9.06; N 14.83.

Compound **(R)-(-)-6** was obtained in 94% yield using a similar procedure which afforded **(S)-(+)-6**: $[\alpha]_D^{26}$ -22.3 (c 1.9, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.04-6.85 (m, 4H, ArH), 3.86 (s, 3H OCH_3), 3.78-3.73 (m, 1H, CHOH), 2.90-2.81 (m, 3H), 2.68-2.60 (m, 3H), 2.50-2.36 (m, 2H), 2.30 (br. s, 3H, NH_2, OH, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 152.79, 141.70, 123.60, 121.54, 118.76, 111.71, 68.37, 62.07, 55.92, 54.09, 51.29, 45.41; MS *m/z* 265 (M^+). Anal. Calcd. for $C_{14}H_{23}N_3O_2 \cdot 0.5H_2O$: C 61.29; H 8.82; N 15.32. Found C 61.41; H 8.83; N 15.11.

4-[(3-(4-Methoxyphenyl)piperazine-1-yl)propan-2-ol-1-yl]amino-2-methylthio-quinazoline (S)-(+)-7. The solution of 2,4-dimethylthioquinazoline (0.7 g, 3.15 mmol) and **(S)-(+)-6** (0.76 g, 2.86 mmol) in acetonitrile (25 mL) was heated under reflux for 4 days. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (ethyl acetate as eluent) to give 0.41 g (33 %) of **(S)-(+)-7** as slightly yellow solid: mp > 78 °C dec.; $[\alpha]_D^{28}$ +6 (c 2.9, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O) δ 7.70-7.63 (m, 3H, ArH), 7.35-7.29 (m, 1H, ArH), 7.04-6.86 (m, 4H, ArH), 4.09-4.06 (m, 1H, CHOH), 3.95 (dd, 1H, J = 3.30, 13.75 Hz , CH_2), 3.87 (s, 3H, OCH_3), 3.63 (dd, 1H, J = 6.0, 13.9 Hz , CH_2), 3.11 (br s, 4H, NCH_2), 2.88-2.84 (m, 2H, NCH_2), 2.67-2.51 (m, 7H, SCH_3, NCH_2, CH_2); ^{13}C

NMR ($CDCl_3$) δ 159.43, 152.83, 150.89, 141.59, 133.44, 127.66, 125.03, 123.71, 121.56, 118.75, 113.36, 111.81, 66.17, 61.92, 55.96, 54.25, 54.12, 51.25, 45.14, 14.69. Anal. Calcd. for $C_{23}H_{29}N_5O_2S \cdot 0.5H_2O$: C 61.58 H 6.74; N 15.61. Found C 61.44; H 6.72; N 15.68.

Compound **(R)-(-)-7** was obtained in 72% yield using a similar procedure which afforded **(S)-(+)-7** : $[\alpha]_D^{28}$ -6 (c 2.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.70-7.66(m, 3H, ArH), 7.35-7.30 (m, 1H, ArH), 7.05-7.00 (m, 1H, ArH), 7.05-6.86 (m, 3H, Ar-H), 6.46 (t, 1H, J = 5.0 Hz, NH), 4.11-4.05 (m, 1H, CHOH), 3.95 (ddd, 1H, J = 3.6, 5.3, 13.7 Hz , CH_2), 3.87 (s, 3H, OCH_3), 3.65 (ddd, 1H, J = 5.4, 5.4, 13.7 Hz , CH_2), 3.11 (br s, 4H, NCH_2), 2.91-2.86 (m, 2H, NCH_2), 2.68-2.64 (m, 2H), 2.62 (s, 3H, SCH_3), 2.58-2.48 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 159.41, 152.82, 150.89, 141.59, 133.45, 127.67, 125.03, 123.71, 121.55, 118.74, 113.35, 111.78, 66.13, 61.90, 55.96, 54.12, 54.12, , 51.25, 45.11, 14.71; MS *m/z* 439 (M^+) Anal. Calcd. for $C_{23}H_{29}N_5O_2S \cdot H_2O$: C 60.37; H 6.39; N 15.30.Found C 60.51; H 6.57; N 15.21.

2-Methylthioquinazolin-4(3H)-one 9. To a solution of 2-mercaptoquinazolin-4(3H)-one **8** (4.45 g, 25 mmol) and NaOH (1.1 g, 27.5 mmol) in water (125 mL) was added methyl iodide (1.72 mL, 27.5 mmol) and the mixture was stirred at 25 °C for 3 h. The precipitate was collected by filtration, washed with water (3 x 20 mL) and dried in vacuum desiccator over silica gel for 24 h to give 3.66 g (73 %) of **9** as colorless solid: mp 224-225 °C (lit.[10] mp 213-214 °C). An analytical sample was recrystallized from methanol-water: mp 225 °C; ^1H NMR ($CDCl_3$) δ 11.25 (br s, 1H, NH), 8.27 (dd, 1H, J = 1.25, 6.3 Hz, ArH), 7.62 (d, 1H, J = 7.3 Hz), 7.44-7.38 (m, 1H, ArH), 2.70 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 163.73, 155.76, 149.77, 135.50, 127.30, 126.96, 126.40, 120.37, 13.97.

4-Chloro-2-methylthioquinazoline 10. Procedure 1. The mixture of quinazolinone **9** (1.92 g, 10 mmol) and $POCl_3$ (4.7 mL, 50 mmol) was stirred for 15 min at room temperature and the suspension was heated under reflux for 1.5 h. After cooling to the room temperature, the mixture was poured into a mixture of ice (40 g) and methylene chloride (20 mL) with vigorously stirring for 5 min. The organic layer was then separated and washed with 5% aq K_2CO_3 (2 x 20 mL). The organic layer was dried with Na_2SO_4 (3 g) and then was filtered through of 1g silica gel. The filtrate was evaporated *in vacuo* to give 1.91 g (91 %) of compound **10** as colorless solid: mp 107-108 °C; ^1H NMR ($CDCl_3$) δ 8.15-8.12 (m, 1H, ArH), 7.85-7.83 (m, 2H, ArH), 7.58-7.52 (m, 1H, ArH), 2.67 (s 1H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 152.38, 135.79, 135.75, 127.72, 127.63, 127.58, 126.69, 126.64, 14.99. Anal. Calcd. for $C_8H_7ClN_2S$: C 48.37; H 3.55; N 14.10. Found C 48.32; H 3.60; N 14.04.

Procedure 2. When the reaction mixture was poured into ice with vigorously stirring, the precipitate was collected by filtration and washed with 5% aq. K_2CO_3 (2 x 50 mL), water (100 mL). The crude product was dissolved in acetone (100 mL) and reprecipitated with water (100 mL) to give 1.73 g (82 %) of compound **10** as colorless needles: mp 108-109 °C.

Procedure 3. To a stirred suspension of quinazoline **9** (0.5 g, 2.60 mmol) and triphenylphosphine (0.82 g, 3.12 mmol) in dichloromethane was added carbon tetrachloride (2.5 mL) and the resulting suspension was stirred at 20-25 °C. After 6h, the reaction was completed (TLC) and filtrated through the column of silica gel (2.5 x 15 cm) using dichloromethane as eluent. The right fraction was collected and evaporated *in vacuo.* The residue was dissolved in acetone (10 mL) and reprecipitated with water (30 mL) to afford a white crystalline solid which was dried *in vacuo* over $CaCl_2$ to give 0.46 g (83 %) of compound **27**: mp 108 °C.

(S)-(+)-3-[(4-(2-Methoxyphenyl)piperazin-1-yl]methyl-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazoline (S)-(+)-1. To a solution of amino alcohol **(S)-7** (1.72 g, 3.9

mmol) in dry methylene chloride under an argon atmosphere at 0 °C was added triethylamine (2.73 mL, 19.6 mmol). The mixture was stirred for 15 min and methanesulfonylchloride (0.40 mL, 5.1 mmol) was added over the period of 30 min. The mixture was stirred at 0 °C for 1 h and at 25 °C for 7 h. Then it was diluted with methylene chloride (20 mL) and washed sequentially with water (50 mL), sat. aq. $NaHCO_3$ (20 mL) and water (20 mL). The organic layer was filtrated through Na_2SO_4 (2 g) and concentrated to afford crude product which was purified by flash chromatography using ethyl acetate as eluent. The residue that obtained after evaporation of solvent was stirred with acetonitrile (2 mL) for 1 h and the precipitate was collected to give 0.148 g (9.0 %) of racemic **(RS)-1** mp 172-173 °C (lit[1] 173-174 °C); $[\alpha]_D^{26}$ +5.72 (c 0.278, $CHCl_3$), HPLC analysis indicated that the racemic mixture contained 55.7 % of **(S)-1** and 44.7 % of **(R)-1**.

The filtrate was evaporated *in vacuo* and the residue was heated at 60-70 °C *in vacuo* (5 mm) to afford 1.13 g (69 %, ee>98.5 %) of **(S)-(+)-1** as colorless solid foam: mp. 58-61 °C (softing), 62-63 °C (transparent); $[\alpha]_D^{26}$ +39.6 (c 4.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.96 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 7.52 (t, J = 7.7 Hz, 1H, Ar-H), 7.41 (d, J = 8.0 Hz, 1H, ArH), 7.24 (t, J = 8.4 Hz, 1H, ArH), 6.98-6.85 (m, 4H, ArH), 4.50-4.42 (m, 1H, (S)-CH) 4.20-4.10 (m, 2H, $=NCH_2$), 3.86 (s, 3H, OCH_3), 3.09 (m, 4H), 2.91-2.8 (m, 3H), 2.71-2.55 (m, 3H), 2.65 (s, 3H, SCH_3); ^{13}C NMR ($CDCl_3$) δ 154.90, 154.47, 152.82, 147.16, 141.82, 133.517, 126.35, 125.92, 125.72, 123.52, 121.56, 118.79, 117.67, 111.77, 60.42, 59.95, 57.08, 55.94, 54.51, 54.38, 51.16, 14.15; MS *m/z* 421 (M^+). Anal. Calcd. for $C_{23}H_{27}N_5OS \cdot 0.5H_2O$: C 64.16; H 6.55; N 16.27. Found C 64.37; H 6.49; N 16.25.

Compound **(R)-1** was obtained in 71 % yield using a similar procedure which afforded **(S)-2**: $[\alpha]_D^{26}$ -39.6 (c 4.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.96 (dd, J = 1.4, 7.9 Hz, 1H, ArH), 7.52 (t, J = 7.1 Hz, 1H, ArH), 7.41 (d, J = 8.2 Hz, 1H, ArH), 7.24 (t, J = 7.1 Hz, 1H, ArH), 7.03-6.85 (m, 4H, ArH), 4.50-4.42 (m, 1H, (S)-CH), 4.21-4.10 (m, 2H, $=NCH_2$), 3.86 (s, 3H, OCH_3), 3.09 (m, 4H), 2.91-2.8 (m, 3H), 2.71-2.55 (m, 2H), 2.65 (s, 3H, SCH_3), 2.59-2.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 154.90, 154.47, 152.82, 147.16, 141.83, 133.51, 126.35, 125.92, 125.71, 123.51 121.56, 118.78, 117.67, 111.75, 60.43, 59.99, 57.08, 55.94, 54.51, 51.16, 14.15; MS *m/z* 421 (M^+). Anal. Calcd. for $C_{23}H_{27}N_5OS \cdot 0.5H_2O$: C 64.16; H 6.55; N 16.27. Found C 64.45; H 6.54; N 15.94.

Procedure 2. To a stirred suspension of amino alcohol **(S)-(+)-7** (2.54 g, 5.57 mmol), potassium carbonate (2.31 g, 16.72 mmol) and triethylamine (2.33 mL, 16.72 mmol) in dry methylene chloride (170 mL) at +2 °C was dropwise added MsCl (0.56 mL, 7.25 mmol) over a period for 0.5 h. The mixture was stirred for 1 h at 2 °C and for 24 h at 25 °C. It was washed with water (70 mL) and the aqueous layer was extracted with dichloromethane (50 mL). The combined organic extracts was dried over Na_2SO_4 (5 g) and evaporated to dryness. Acetonitrile (30 mL) was added to the residue and after stirring for 40 min the precipitate was collected by filtration to give 0.57 g (24 %) of **(RS)-1**: m.p. 173-174 °C (lit.[1] 173-174 °C) . Acetonitrile solution was evaporated, the residue was heated *in vacuo* (2 mm Hg, 50 °C) to give 1.80 g (75 %, ee>98.5 %) of **(S)-(+)-1** as colorless solid foam.

Compound **(R)-(-)-1** was obtained in 72 % yield using a similar procedure which afforded **(S)-(+)-1**.

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REFERENCES

1. Previous paper in this series: Chern, J.-W.; Tao, P.-L.; Yen, M.-H.; Lu, G.-Y.; Shiau, C.-Y.; Lai, Y.-J.; Chien, S.-L.; Chan, C.-H. *J. Med. Chem.* **1993,** 36, 2196-2207.
2. On leave from Riga Technical University, Department of Organic Chemistry, Faculty of Chemical Engineering, Azenes St. 14/24, Riga, LV 1048, LATVIA.
3. (a) Nagano, H; et al. Eur.Pat. 89 065,1983,Chugai Pharmaceutical Co., Ltd; Chem. Abstr. **1984,** 100, 6574p. (b) Imagawa,J.; Sakai, K. *Eur. J. Pharmacol.* **1986,** 131, 257-264.
4. Mitsunobu, O. *Synthesis.* **1981,** 1-28.
5. (a) Haanson, R. M. *Chem. Rev.* **1991**, 91, 437-475. (b) Johnson, R. A. In *Encyclopedia of Reagents for Organic Synthesis ;* Paquette , L.A.; Eds.; Jon Willey & Sons, Inc.: New York, 1995; Vol. 4, pp. 2609-2613.
6. Zakerinia, M.; Davary, M.; Hakimelahi ,G. H. *Helv. Chim. Acta.* **1990**, 73, 912-915.
7. Tanabe, Y.; Yamamoto, H.; Yoshida, Y.; Miyawaki, T.; Utsumi, N. *Bull. Chem. Soc. Jpn.* **1995**; 68, 297-300.
8. Chern, J.-W.; Gutcait, A.; Wang, K.-C.; Liu, H.-W. (to be published results).
9. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1989.
10. Hu, M.-K.; Liu, K.-C.; Hsu, L.-Y.; Shih, B-J. *Chin. Pharm. J.*, 1991, 43, 83-87.

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