Tetrahedron: *Asymmetry* 21 (2010) 2027–2031

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis and biological evaluation of (*S*)-4-aminoquinazoline alcohols

Murat Cakici [a], Mustafa Catir [b], Semistan Karabuga [c], Hamdullah Kilic [a,*], Sabri Ulukanli [d], Medine Gulluce [e], Furkan Orhan [e]

[a] *Faculty of Sciences, Department of Chemistry, Ataturk University, 25240 Erzurum, Turkey*
[b] *Faculty of Arts and Sciences, Department of Chemistry, Erzincan University, 24100 Erzincan, Turkey*
[c] *Faculty of Science and Letters, Department of Chemistry, Kilis 7 Aralik University, 79100 Kilis, Turkey*
[d] *Faculty of Science and Letters, Department of Chemistry, Korkut Ata University, 80100 Osmaniye, Turkey*
[e] *Faculty of Sciences, Department of Biology, Ataturk University, 25240 Erzurum, Turkey*

ARTICLE INFO

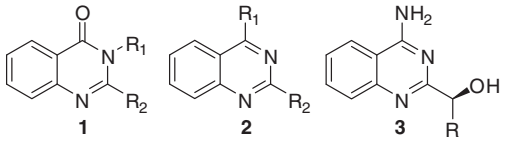
Article history:
Received 13 May 2010
Accepted 25 May 2010
Available online 21 June 2010

ABSTRACT

A simple synthetic method for the preparation of enantiomerically pure (*S*)-4-aminoquinazoline alcohols from (*S*)-quinazolinone alcohols by key steps including chlorination, nucleophilic *ipso* substitution, and deacetylation is presented. Mutagenic and antimutagenic properties of the (*S*)-4-aminoquinazoline alcohols were investigated by using *Salmonella typhimurium* TA1535, and *Escherichia coli* WP2*uvrA* tester strains at 0.01, 0.1, and 1 μg/plate concentrations. (*S*)-4-aminoquinazoline alcohols were found to be genotoxically safe at the tested concentrations. Among the tested (*S*)-4-aminoquinazoline alcohols, the best antimutagenic activity was obtained with a methyl derivative at 0.1 μg/plate dose.

1. Introduction

Quinazolin-4(3*H*)-ones **1** and related quinazolines[1–5] **2** are a class of nitrogen-containing heterocycles of considerable interest, owing to their diverse pharmacological activities including antibacterial,[6] antitubercular,[7] antifungal,[8] antihyperglycemic,[9] anti-inflammatory,[10] bronchodilatory,[11] cholinesterase inhibitory,[12] antifolate,[13] antitumor,[14] protein kinase inhibitory,[15] and many others.[16]



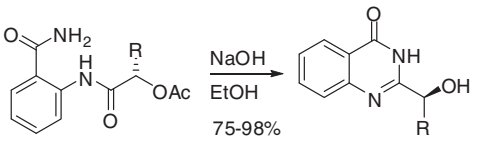
Additionally, 4-aminoquinazoline and its derivatives are useful as fungicides and anti-inflammatory, antimicrobial, and antihypertensive agents.[17–20] In particular, they are potent and highly selective inhibitors of tyrosine kinase.[21] Therefore, in recent years, the synthesis of 4-aminoquinazolines has attracted much attention.[22] Among the structural variations of quinazoline that have been reported, to the best of our knowledge, no previous studies have dealt with the preparation of optically active 4-aminoquinaozoline alcohols **3**. Recently, we reported the efficient synthesis of **5a–e** from the readily accessible enantiomerically pure (*S*)-amides **4a–e**.[23] The most challenging aspect of the synthesis was a fast and simple protocol for large-scale preparation of enantiomerically pure quinazolinone alcohols from cheap starting materials. Following this success, we envisaged that this protocol could be successfully extended to the synthesis of (*S*)-4-aminoquinazoline alcohols from (*S*)-quinazolinone alcohols **5a–e** by a reaction sequence that employs acetylation of hydroxy functionality, chlorination with $POCl_3$, and nucleophilic *ipso* substitution of chloride by ammonia; subsequent unmasking should then cleanly provide the desired (*S*)-4-aminoquinazoline alcohols **3a–e**. Herein, we report a convenient procedure for obtaining the hitherto unknown homochiral 4-aminoquinazolines **3a–e** possessing a secondary alcohol group from the readily accessible enantiomerically pure (*S*)-quinazolinone alcohols **5a–e**, and an assessment of their mutagenic and antimutagenic activities. It was found that (*S*)-4-aminoquinazoline alcohols **3a–e** have no mutagenic effects on the tested strains, and **3a–c** exhibit moderate antimutagenicity against *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG).

2. Results and discussion

The starting quinazolinone alcohols **5a–e**[23] were prepared from cyclization of the corresponding enantiomerically pure (*S*)-amides **4** by NaOH in EtOH at room temperature (Scheme 1). The quinazoline alcohols **3a–e**, all of which have terminal amino groups at the 4-position of the quinazoline scaffold, were synthesized by a three-step reaction sequence starting from the enantiomerically pure quinazolinone alcohols **5a–e** as shown in Scheme 2. Hydroxy groups in (*S*)-quinazolinone alcohols **5a–e** were protected by treat-

* Corresponding author. Tel.: +90 442 231 4426; fax: +90 442 236 0948.
E-mail address: hkilic@atauni.edu.tr (H. Kilic).

0957-4166/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2010.05.040



Scheme 1. Synthesis of the (*S*)-quinazolinone alcohols **5a**–**e**.

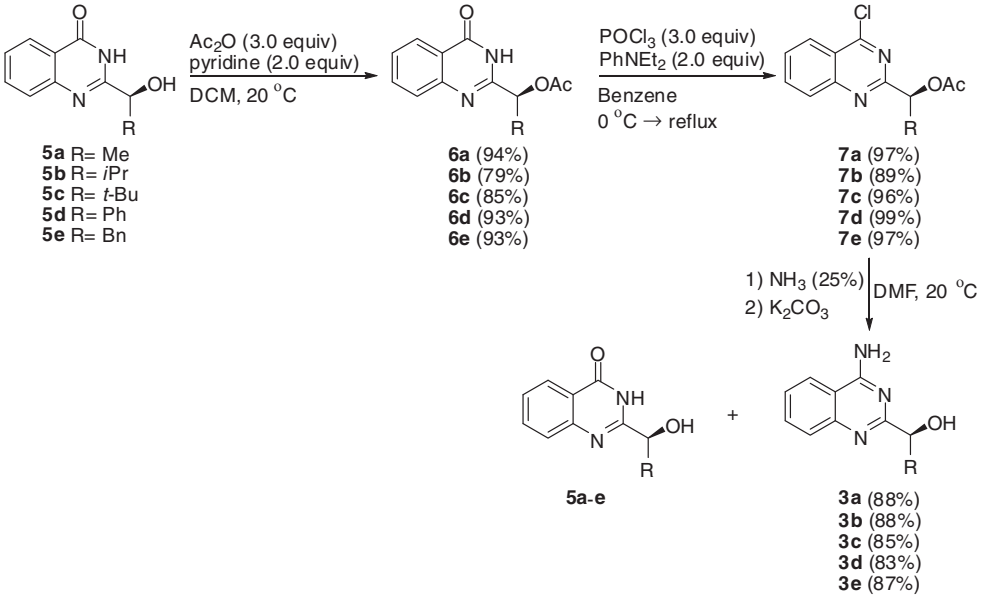
ment with acetic anhydride in the presence of pyridine (3:2) to give the corresponding acetate **6** in a yield of 79–94%.

The structural assignments of the acetates **6a**–**e** were secured on the basis of physical behavior. Thus, elemental analysis confirmed the molecular formula, while the acetate functionalities were established by their NMR and IR spectra. The enantiomeric purities of the acetates **6a**–**e** were determined by a HPLC system equipped with a Chiralyser, which revealed that the acetates **6a**–**e** have enantiomeric purities of 99%, and retain their original (*S*)-configuration with no partial racemization. However, the ^{1}H NMR (400 MHz, $CDCl_3$, and DMSO-d_6) and specific rotation of the known compound **6d**[24] were in disagreement with those reported previously. The reported synthesis of **6d** involved the initial reaction of 2-aminobenzamide with 2-acetoxy-2-phenylacetic anhydride to give **4d** that subsequently underwent cyclization to form **6d** in the absence of a base. To the best of our knowledge, the use of a strong base is required for the cyclization reaction; otherwise the reaction would stop at the stage of acylation of 2-aminobenzamide with 2-acetoxy-2-phenylacetic anhydride. We therefore concluded that the structural assignment of **6d** was incorrect and should be revised to **4d**, as established by comparison with the reported ^{1}H NMR and specific rotation data.[23] The treatment of the acetates **6a**–**e** with phosphoryl chloride in benzene for 3–4 h resulted in excellent yields of 4-chloroquinozoline acetates **7a**–**e**, which were purified by short column chromatography on silica gel using a mixture of hexane and ethyl acetate (3:1). The 4-chloroquinazoline acetates **7a**–**e** so obtained were characterized on the basis of analytical data and spectral evidence. We next turned our attention to the key intramolecular *ipso* substitution step. 4-Aminoquinazolines **3a**–**e** were synthesized by two consecutive nucleophilic substitution and hydrolysis reactions. At first, we tried a one-pot method to prepare **3a**–**e**, but we only observed substitution at C-4 and partial hydrolysis of the acetate functionality using aqueous ammonia. Therefore, we split the synthesis of **3a**–**e** into two individual steps. Firstly, the 4-chloroquinazoline acetates **7a**–**e** were coupled with aqueous ammonia at room temperature to introduce an amino group at the C-4 position. Secondly, the mixture was mixed with K_2CO_3 to give the desired 4-aminoquinazoline alcohols **3a**–**e** together with quinazoline alcohols **5a**–**e** (3–5%). The (*S*)-4-aminoquinazolinone alcohols **3a**–**e** were purified by means of column chromatography on silica gel eluting with hexane and ethyl acetate (2:1) The structure assignments of **3a**–**e** are based on their analytical and spectral data. The elemental analyses of **3a**–**e** revealed the empirical formula while the ^{13}C NMR spectrum displayed the expected carbon resonances. The ^{13}C NMR spectrum possesses the two expected carbon resonances at around 165–168 and 160–162 ppm, which confirm the presence of 4-aminoquinazoline functionality. The intense band at around 3332 cm^{-1} in the IR spectrum indicated the presence of an amino group in **3a**–**e**. Chiral HPLC analysis of **3a**–**e** shows that enantiomeric purities are around 99%.

(*S*)-4-Aminoquinazoline alcohols **3a**–**e** at three different concentrations (0.01, 0.1, and 1 μg/plate) showed no mutagenic effect in the mutagenicity assays performed with *Salmonella typhimurium* TA1535 and *Escherichia coli* WP2*uvrA*.[25] Antimutagenic activities of **3a**–**e** at three different concentrations (0.01, 0.1, and 1 μg/plate) were evaluated in vitro against NaN_3, and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) in *S. typhimurium* TA1535 and *E. coli* WP2*uvrA*, respectively. In the antimutagenicity assays performed with *E. coli* WP2*uvrA* strains, **3a**–**c** had moderate antimutagenic activity at 0.01 and 0.1 μg/plate, while **3d**,**e** showed no antimutagenicity at any concentration. The inhibition rates of **3a**–**c** were 31.1% (**3a** 0.1 μg/plate), 24.7% (**3b** 0.01 μg/plate), and 24.3% (**3c** 0.1 μg/plate), respectively. A plausible explanation for this observation might be that **3a**–**c** inhibit the formation of *O6*-methylguanine.

3. Conclusion

In summary, a highly efficient and general approach to enantiomerically pure 4-aminoquinazoline alcohols with an (*S*)-configuration



Scheme 2. Synthesis of the (*S*)-4-aminoquinazoline alcohols **3a**–**e**.

starting from readily accessible compounds has been established. The total yield of this synthetic route from **5** to **3** was over 60%, and the compounds were purified by either recrystallization or short column chromatography on silica gel in each step. Based on the biological activity assays, (*S*)-4-aminoquinazoline alcohols **3a–e** are genotoxically safe at the tested concentrations. In addition, **3a–c** exhibit moderate antimutagenicity. It is evident from this study that antimutagenicity decreases as steric hindrance increases in the proximity of the hydroxy functionality.

4. Experimental

4.1. General

Reagents and solvents were purchased from standard chemical suppliers and were purified to match the reported physical and spectral data. Melting points were determined with a Gallenkamp apparatus. Solvents were concentrated at reduced pressure (ca. 20 °C, 20 Torr). IR spectra were obtained on KBr pellets with a Perkin–Elmer apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 MHz, 100 MHz) spectrometer in $CDCl_3$. Elemental analyses were obtained with a Leco CHNS 932 analyzer. Enantiomeric excesses were determined by HPLC analysis using a chiral column with *n*-hexane–*i*PrOH eluent, and detection was performed at 210–254 nm. Optical rotations were measured with a Bellingham + Stanley, ADP220, 589 nm spectropolarimeter in a 1 dm tube; concentrations are given in g/100 mL. A polarimetric Chiralyser detector was used to assess the specific rotation sign of the enantiomer formed. Column chromatography was performed on silica gel. Mutagenicity and antimutagenicity tests were carried out as described in the literature.[25]

4.2. General procedure for the acetates 6a–e

To a solution of (*S*)-**5** (26.3 mmol) in 50 mL of CH_2Cl_2 were added pyridine (52.6 mmol) and acetic anhydride (78.9 mmol). The resulting mixture was stirred at room temperature for 3–5 h and then quenched by the addition of saturated $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure and the resulting solid was recrystallized from ethanol to afford (*S*)-acetate **6** in a yield of 79–94%.

4.2.1. (*S*)-1-(4-Oxo-3,4-dihydroquinazolin-2-yl)ethyl acetate 6a

Crystallization from EtOH gave a white powder. Yield: 94%; mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.51 (br s, 1H), 8.27 (dd, J = 8.1, 1.4 Hz, 1H), 7.78 (ddd, J = 8.3, 7.0, 1.4 Hz, 1H), 7.73 (dd, J = 8.3, 1.2 Hz, 1H), 7.50 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 5.80 (q, J = 6.7 Hz, 1H), 2.24 (s, 3H), 1.72 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.3, 163.5, 154.5, 148.9, 135.0, 127.9, 127.3, 126.5, 121.4, 70.3, 21.3, 19.0; IR (KBr, cm^{-1}) 3176, 3126, 3046, 2980, 2918, 1749, 1681, 1608, 1468, 1369, 1230, 1094, 1050. Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.34; H, 5.17; N, 11.91; $[\alpha]_D^{20} = -70.9$ (*c* 1, EtOH); ee: 99%; retention time: 13.9 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 225 nm.

4.2.2. (*S*)-2-Methyl-1-(4-oxo-3,4-dihydroquinazolin-2-yl)propyl acetate 6b

Crystallization from EtOH gave a white powder. Yield: 79%; mp 173–175 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.39 (br s, 1H), 8.27 (ddd, J = 8.1, 1.5, 0.6 Hz, 1H), 7.77 (ddd, J = 8.2, 6.8, 1.5 Hz, 1H), 7.73 (ddd, J = 8.2, 1.5, 0.6 Hz, 1H), 7.49 (ddd, J = 8.1, 6.8, 1.5 Hz, 1H), 5.51 (d, J = 5.87 Hz, 1H), 2.44 (m, 1H), 2.26 (s, 3H), 1.05 (d, J = 5.3 Hz, 3H), 1.03 (d, J = 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.5, 163.2, 153.7, 148.9, 134.9, 127.9, 127.1, 126.4, 121.4, 78.1, 32.4, 21.1, 18.9, 17.7; IR (KBr, cm^{-1}) 3188, 3137, 3076, 2969, 2924, 2868, 1751, 1670, 1611, 1469, 1371, 1227, 1031. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 66.35; H, 6.03; N, 10.79; $[\alpha]_D^{20} = -64.2$ (*c* 1, EtOH); ee: 99%; retention time: 7.5 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 225 nm.

4.2.3. (*S*)-2,2-Dimethyl-1-(4-oxo-3,4-dihydroquinazolin-2-yl)propyl acetate 6c

Crystallization from EtOH gave a white powder. Yield: 85%; mp 157–159 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.94 (br s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 7.82–7.70 (m, 2H), 7.49 (ddd, J = 8.0, 6.4, 1.8 Hz, 1H), 5.40 (s, 1H), 2.25 (s, 3H), 1.10 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.3, 163.0, 152.6, 148.7, 134.9, 128.1, 127.2, 126.4, 121.6, 80.7, 35.7, 26.4, 21.1; IR (KBr, cm^{-1}) 3181, 3135, 3078, 2970, 1750, 1670, 1612, 1470, 1371, 1335, 1235, 1137, 1058, 1028. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.47; H, 6.56; N, 10.23; $[\alpha]_D^{20} = -19.2$ (*c* 0.52, EtOH); ee: 99%; retention time: 7.0 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 225 nm.

4.2.4. (*S*)-(4-Oxo-3,4-dihydroquinazolin-2-yl)(phenyl)methyl acetate 6d

Crystallization from EtOH gave a white powder. Yield: 93%; mp 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.72 (br s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.83–7.71 (m, 2H), 7.66 (d, J = 6.7 Hz, 2H), 7.50 (ddd, J = 8.1, 6.2, 2.2 Hz, 1H), 7.42–7.30 (m, 3H), 6.69 (s, 1H), 2.31 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 12.65 (br s, 1H), 8.09 (dd, J = 8.0, 1.1 Hz, 1H), 7.82–7.78 (m, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.59–7.57 (m, 2H), 7.52–7.45 (m, 1H), 7.43–7.31 (m, 3H), 6.38 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.7, 163.5, 153.3, 149.0, 135.9, 135.0, 129.3, 129.1, 128.1, 127.4, 127.3, 126.4, 121.5, 75.5, 21.2; IR (KBr, cm^{-1}) 3070, 2967, 2924, 2874, 1741, 1616, 1570, 1482, 1372, 1344, 1312, 1236, 1034. Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.29; H, 4.93; N, 9.62; $[\alpha]_D^{20} = +49.0$ (*c*1, EtOH); ee: 99%; retention time: 13.8 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 225 nm.

4.2.5. (*S*)-1-(4-Oxo-3,4-dihydroquinazolin-2-yl)-2-phenylethyl acetate 6e

Crystallization from EtOH gave a white powder. Yield: 93%; mp 121–123 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.19 (br s, 1H), 8.28 (dd, J = 8.1, 1.0 Hz, 1H), 7.93–7.63 (m, 2H), 7.52 (ddd, J = 8.1, 6.7, 1.7 Hz, 1H), 7.30–7.15 (m, 5H), 5.90 (dd, J = 8.1, 4.8 Hz, 1H), 3.44 (dd, J = 14.1, 4.8 Hz, A part of AB system, 1H), 3.31 (dd, J = 14.1, 8.1 Hz, B part of AB system, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.1, 163.1, 153.4, 148.8, 135.8, 135.0, 129.8, 128.6, 127.9, 127.3, 127.3, 126.5, 121.5, 74.1, 39.5, 21.0; IR (KBr, cm^{-1}) 3182, 3137, 3031, 2918, 1750, 1671, 1610, 1470, 1370, 1336, 1226, 1135, 1049. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.16; H, 5.33; N, 9.15; $[\alpha]_D^{20} = -16.5$ (*c* 1, EtOH); ee: 99%; retention time: 15.8 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 225 nm.

4.3. General procedure for the preparation of 7a–e

To a solution of (*S*)-**6** (12.93 mmol) in dry benzene (30 mL) were added $PhNEt_2$ (25.86 mmol) and then $POCl_3$ (38.8 mmol) at room temperature. The reaction mixture was then refluxed for 3–4 h, cooled to room temperature, and diluted with EtOAc (50 mL). The mixture was washed successively with icy water (40 mL), 2 M HCl (40 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4, and evaporated under reduced pressure (20 °C,

15 mbar). Purification by column chromatography (silica gel, hexane–EtOAc, 3:1) gave 4-chloroquinazoline acetate **7** in a yield of 89–99%.

4.3.1. (*S*)-1-(4-Chloroquinazolin-2-yl)ethyl acetate 7a

Crystallization from hexane–EtOAc gave a white powder. Yield: 97%; mp 75–77 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.24 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.93 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 5.95 (q, J = 6.8 Hz, 1H), 2.20 (s, 1H), 1.72 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.7, 164.4, 163.1, 151.4, 135.1, 128.9, 128.9, 125.9, 122.9, 73.1, 21.3, 19.8. IR (KBr, cm^{-1}) 3075, 2987, 2936, 1744, 1616, 1572, 1557, 1480, 1371, 1309, 1237, 1086. Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.49; H, 4.42; N, 11.17. Found: C, 57,67; H, 4.29; N, 11.23; $[\alpha]_D^{20} = -98.7$ (c 1, CH_2Cl_2).

4.3.2. (*S*)-1-(4-Chloroquinazolin-2-yl)-2-methylpropyl acetate 7b

Colorless liquid. Yield: 89%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (dd, J = 8.4, 1.0 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.93 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.68 (ddd, J = 8.4, 7.0, 1.0 Hz, 1H), 5.64 (d, J = 6.0 Hz, 1H), 2.59–2.44 (m, 1H), 2.21 (s, 3H), 1.00 (d, J = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.1, 163.3, 162.8, 151.3, 135.0, 129.0, 128.8, 125.9, 122.8, 81.0, 32.2, 21.1, 19.3, 17.6. IR (KBr, cm^{-1}) 3070, 2967, 2924, 2874, 1741, 1616, 1570, 1481, 1372, 1312, 1236, 1034; MS (FAB) m/z 279 (MH^+); HRMS (FAB); calcd for $C_{14}H_{16}ClN_2O_2$ [MH^+] 279.0900; found: 279.0896; $[\alpha]_D^{20} = -86.7$ (c 1, CH_2Cl_2).

4.3.3. (*S*)-1-(4-Chloroquinazolin-2-yl)-2,2-dimethylpropyl acetate 7c

Colorless liquid. Yield: 96%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.23 (ddd, J = 8.3, 1.4, 0.6 Hz, 1H), 8.05 (ddd, J = 8.5, 1.1, 0.6 Hz, 1H), 7.92 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.68 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 5.53 (s, 1H), 2.18 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 171.2, 162.7, 162.1, 151.2, 134.9, 129.0, 128.8, 125.9, 122.9, 83.7, 35.4, 26.6, 21.2. IR (KBr, cm^{-1}) 2966, 2908, 2863, 1741, 1616, 1570, 1481, 1372, 1310, 1242, 1059, 1028; MS (FAB) m/z 293 (MH^+); HRMS (FAB); calcd for $C_{15}H_{18}ClN_2O_2$ [MH^+] 293.1057; found: 293.1052; $[\alpha]_D^{20} = -17.0$ (c 1, CH_2Cl_2).

4.3.4. (*S*)-(4-Chloroquinazolin-2-yl)(phenyl)methyl acetate 7d

Colorless liquid. Yield: 99%; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.19 (ddd, J = 8.4, 1.4, 0.6 Hz, 1H), 8.06 (ddd, J = 8.5, 1.0, 0.6 Hz, 1H), 7.91 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.68–7.61 (m, 3H), 7.40–7.28 (m, 3H), 6.86 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 163.2, 162.9, 151.4, 137.2, 135.1, 129.0, 128.9, 128.8, 128.8, 128.1, 125.9, 122.9, 78.4, 21.3; IR (KBr, cm^{-1}) 3066, 3031, 2930, 1745, 1615, 1568, 1482, 1371, 1311, 1233, 1045; MS (FAB) m/z 313 (MH^+); HRMS (FAB); calcd for $C_{17}H_{14}ClN_2O_2$ [MH^+] 313.0744; found: 313.0741; $[\alpha]_D^{20} = +52.0$ (c 1, CH_2Cl_2).

4.3.5. (*S*)-1-(4-Chloroquinazolin-2-yl)-2-phenylethyl acetate 7e

Crystallization from hexane–EtOAc gave a white powder. Yield: 97%; mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.26 (ddd, J = 8.4, 1.4, 0.6 Hz, 1H), 8.05 (ddd, J = 8.5, 1.1, 0.6 Hz, 1H), 7.95 (ddd, J = 8.5, 7.0, 1.4 Hz, 1H), 7.71 (ddd, J = 8.4, 7.0, 1.1 Hz, 1H), 7.35–7.25 (m, 5H), 7.25–7.19 (m, 1H), 6.07 (dd, J = 9.6, 4.3 Hz, 1H), 3.44 (dd, J = 14.1, 4.3 Hz, A part of AB system, 1H), 3.30 (dd, J = 14.1, 9.6 Hz, B part of AB system, 1H), 2.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 170.6, 163.2, 163.1, 151.4, 137.1, 135.1, 129.6, 129.0, 129.0, 128.5, 126.9, 126.0, 123.0, 77.3, 40.2, 21.1; IR (KBr, cm^{-1}) 3070, 3019, 2930, 1744, 1611, 1570, 1482, 1371, 1315, 1233, 1067. Anal. Calcd for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.25; H, 4.58; N, 8.61; $[\alpha]_D^{20} = -35.5$ (c 1, CH_2Cl_2).

4.4. General procedure for the preparation of 3a–e

To a solution of (*S*)-4-chloroquinazolin acetate **7** (9.58 mmol) in 25 mL of DMF was added 50 mL of NH_3 (25% in water) and the resulting mixture was stirred at room temperature for 12 h. Upon completion of the ipso substitution of chloride by ammonia (TLC monitoring), K_2CO_3 (19.16 mmol) was added to this solution and the mixture was stirred for an additional 36 h to remove the acetyl group. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. Purification by column chromatography (silica gel, hexane–EtOAc, 2:1) gave 4-aminoquinazoline alcohol **3** in a yield of 83–88%.

4.4.1. (*S*)-1-(4-Aminoquinazolin-2-yl)ethanol 3a

Crystallization from EtOH gave a white powder. Yield: 88%; mp 174–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 8.20 (d, J = 8.2 Hz, 1H), 7.85 (br s, 2H), 7.76–7.70 (m, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.46–7.40 (m, 1H), 4.93 (d, J = 4.9 Hz, 1H), 4.58 (qd, J = 6.5, 4.9 Hz, 1H), 1.39 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 168.8, 162.8, 150.1, 133.5, 127.7, 125.7, 124.2, 113.9, 69.9, 23.6; IR (KBr, cm^{-1}) 3335, 3103, 1664, 1574, 1558, 1507, 1367, 1348, 1311, 1055. Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.25; H, 5.85; N, 21.85; $[\alpha]_D^{20} = -66.5$ (c 1, EtOH); ee: 99%; retention time: 23.0 min, Chiralcel OD, 90:10 n-hexane–iPrOH, flow rate of 1 ml/min, 254 nm.

4.4.2. (*S*)-1-(4-Aminoquinazolin-2-yl)-2-methylpropan-1-ol 3b

Crystallization from EtOH gave a white powder. Yield: 88%; mp 139–140 °C; δ 7.91–7.79 (m, 1H), 7.75 (m, 2H), 7.54–7.37 (m, 1H), 5.96 (br s, 2H), 4.54–4.62 (m, 2H), 2.45–2.21 (m, 1H), 1.13 (d, J = 6.9 Hz, 1H), 0.74 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.6, 161.6, 149.6, 133.6, 128.3, 126.0, 122.0, 113.3, 77.4, 33.8, 20.2, 15.5; IR (KBr, cm^{-1}) 3336, 3202, 2963, 2868, 1640, 1618, 1575, 1504, 1463, 1366, 1324, 1143, 1015, 911; Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.17; H, 6.89; N, 19.17; $[\alpha]_D^{20} = -56.6$ (c 1, EtOH); ee: 99%; retention time: 16.3 min, Chiralcel OD, 90:10 n-hexane–iPrOH, flow rate of 1 ml/min, 210 nm.

4.4.3. (*S*)-1-(4-Aminoquinazolin-2-yl)-2,2-dimethylpropan-1-ol 3c

Crystallization from EtOH gave a white powder. Yield: 85%; mp 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.83 (d, J = 8.4 Hz, 1H), 7.78–7.72 (m, 2H), 7.44 (ddd, J = 8.3, 7.1, 1.3 Hz, 1H), 6.04 (br s, 2H), 4.59 (d, J = 6.0 Hz, 1H), 4.35 (d, J = 6.0 Hz, 1H), 1.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.7, 160.5, 149.4, 133.2, 128.2, 125.8, 121.6, 113.0, 80.5, 36.6, 26.3; IR (KBr, cm^{-1}) 3333, 3159, 2957, 1660, 1636, 1616, 1576, 1508, 1361, 1321, 1016; Anal. Calcd for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.63; H, 7.48; N, 17.79; $[\alpha]_D^{20} = -57.0$ (c 1, EtOH); ee: 99%; retention time: 19.1 min, Chiralcel OD, 90:10 n-hexane–iPrOH, flow rate of 1 ml/min, 210 nm.

4.4.4. (*S*)-(4-Aminoquinazolin-2-yl)(phenyl)methanol 3d

Crystallization from EtOH gave colorless needles. Yield: 83%; mp 168–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.87 (d, J = 8.4 Hz, 1H), 7.78 (ddd, J = 8.4, 6.8, 1.5 Hz, 1H), 7.57–7.42 (m, 4H), 7.40–7.31 (m, 3H), 5.88 (br s, 2H), 5.65 (s, 1H), 5.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 161.7, 149.0, 142.8, 133.4, 128.3, 128.1, 127.9, 127.6, 126.1, 121.6, 113.2, 75.1; IR (KBr, cm^{-1}) 3332, 3182, 1638, 1574, 1503, 1454, 1372, 1323, 1041; Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.63; H, 5.46; N, 16.68; $[\alpha]_D^{20} = +30.4$ (c 1, EtOH); ee: 99%; retention time: 31.4 min, Chiralcel OD, 90:10 n-hexane–iPrOH, Flow rate of 1 ml/min, 220 nm.

4.4.5. (*S*)-1-(4-Aminoquinazolin-2-yl)-2-phenylethanol 3e

Crystallization from EtOH gave a white powder. Yield: 87%; mp 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.81 (d, J = 8.3 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.30–7.20 (m, 4H), 7.20–7.14 (m, 1H), 5.96 (br s, 2H), 4.96 (dd, J = 8.2, 3.7 Hz, 1H), 4.65 (br s, 1H), 3.40 (dd, J = 13.8, 3.7 Hz, 1H), 3.01 (dd, J = 13.8, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.1, 161.4, 149.5, 138.5, 133.4, 129.6, 128.0, 126.1, 125.9, 121.7, 113.0, 73.9, 43.3; IR (KBr, cm^{-1}) 3336, 3198, 1636, 1617, 1574, 1503, 1454, 1374, 1321, 1058; Anal. Calcd for $C_{16}H_{15}N_3O$: C, 72.43; H, 5.70; N, 15.84, found: C, 72.23; H, 5.79; N, 15.67; $[\alpha]_D^{20} = -40.5$ (*c* 1, EtOH); ee: 99%; retention time: 36.1 min, Chiralcel OD, 90:10 *n*-hexane–*i*PrOH, flow rate of 1 ml/min, 220 nm.

Acknowledgments

The financial support from the Scientific and Technological Research Council of Turkey (TUBITAK) (TBAG-108T116) is gratefully acknowledged. In addition, the authors would like to thank Dr. Graham Eaton from the Leicester University for the HRMS measurements.

References

1. Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202.
2. Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787–9826.
3. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
4. Brown, D. J. *The Chemistry of Heterocyclic Compounds, Volume 55, Quinazolines: Supplement 1*; John Wiley & Sons: NY, 1996.
5. Eguchi, S. *Top. Heterocycl. Chem.* **2006**, *6*, 113–156.
6. Tran, T. P.; Ellsworth, E. L.; Stier, M. A.; Domagala, J. M.; Showalter, H. D. H.; Gracheck, S. J.; Shapiro, M. A.; Joannides, T. E.; Singh, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4405–4409.
7. (a) Kunes, J.; Bazant, J.; Pour, M.; Waisser, K.; Slosarek, M.; Janota, J. *Farmaco* **2000**, *55*, 725–729; (b) Kunes, J.; Spulak, M.; Waisser, K.; Slosarek, M.; Janota, J. *Pharmazie* **2000**, *55*, 858–859.
8. Dandia, A.; Singh, R.; Sarawgi, P. *J. Fluorine Chem.* **2005**, *126*, 307–312.
9. Ram, V. J.; Farhanullah; Tripathi, B. K.; Srivastava, A. K. *Bioorg. Med. Chem.* **2003**, *11*, 2439–2444.
10. Gineinah, M. M.; El-Sherbeny, M. A.; Nasr, M. N.; Maarouf, A. R. *Arch. Pharm. Pharm. Med. Chem.* **2002**, *11*, 556–562.
11. Jindal, D. P.; Bhatti, R. S.; Ahlawat, S.; Gupta, R. *Eur. J. Med. Chem.* **2002**, *37*, 419–425.
12. Decker, M. *Eur. J. Med. Chem.* **2005**, *40*, 305–313.
13. Gangjee, A.; Kothare, M.; Kisliuk, R. L. *J. Heterocycl. Chem.* **2000**, *37*, 1097–1102.
14. Forsch, R. A.; Wright, J. E.; Rosowsky, A. *Bioorg. Med. Chem.* **2002**, *10*, 2067–2076.
15. Levitzki, A. *Acc. Chem. Res.* **2003**, *36*, 462–469.
16. Abdel-Jalil, R. J.; Aldoqum, H. M.; Ayoub, M. T.; Voelter, W. *Heterocycles* **2005**, *65*, 2061–2070.
17. Seijas, J. A.; Vazquez-Tato, M. P.; Martinez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215–2217.
18. (a) Johne, S. In *The Alkaloids, Chemistry and Pharmacology*; Brossi, A., Ed.; Quinazoline Alkaloids; 1986; Vol. 29, Chapter 2, pp 99–140; (b) Nakagami, K.; Yokoi, S.; Nishimura, K.; Nagai, S.; Honda, T.; Oda, K.; Fujii, K.; Kobayashi, R.; Kojima, M. US 4323680, 1982; (c) Haley, G. J. US 5373011, 1994.
19. (a) Palanki, M. S. S.; Suto, M. J. US 5939421, 1999.; (b) Myers, M. R.; Spada, A. P.; Maguire, M. P.; Persons, P. E.; Zilberstein, A.; Hsu, C.-Y.-J.; Johnson, S. E. US 5714493, 1998.
20. (a) Nauta, W. T. US 3980650, 1976; (b) Mizogami, S.; Hiranuma, H.; Sekiya, T.; Hanazuka, M. US 4607034, 1986.
21. Denny, W. A. *Farmaco* **2001**, *56*, 51–56.
22. (a) Yoon, D. S.; Ying, H.; Stark, T. M.; Haber, J. C.; Gregg, B. T.; Stankovich, S. B. *Org. Lett.* **2004**, *6*, 4775–4778; (b) Yang, X.; Liu, H.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *Synlett* **2010**, 101–106; (c) Okano, M.; Mito, J.; Maruyama, Y.; Masuda, H.; Niwa, T.; Nakagawa, S. I.; Nakamura, Y.; Matsuura, A. *Bioorg. Med. Chem.* **2009**, *17*, 119–132; (d) Abouzid, K.; Shouman, S. *Bioorg. Med. Chem.* **2008**, *16*, 7543–7551; (e) Liu, G.; Sun, L.; Liu, C. P.; Ji, C. N.; Wen, Q. W.; Ma, S. M. *J. Heterocycl. Chem.* **2008**, *45*, 759–764; (f) Liu, G.; Hu, D. Y.; Jin, L. H.; Song, B. A.; Yang, S.; Liu, P. S.; Bhadury, P. S.; Ma, Y.; Luo, H.; Zhou, X. *Bioorg. Med. Chem.* **2007**, *15*, 6608–6617; (g) Liu, G.; Yang, S.; Song, B. A.; Xue, W.; Hu, D. Y.; Jin, L. H.; Lu, P. *Molecules* **2006**, *11*, 272–278.
23. Catir, M.; Cakici, M.; Karabuga, S.; Ulukanli, S.; Sahin, E.; Kilic, H. *Tetrahedron: Asymmetry* **2009**, *20*, 2845–2853.
24. Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295–1310.
25. (a) Mortelmans, K.; Riccio, E. S. *Mutat. Res., Fundam. Mol. Mech. Mutagen* **2000**, *455*, 61–69; (b) Mortelmans, K.; Zeiger, E. *Mutat. Res., Fundam. Mol. Mech. Mutagen* **2000**, *455*, 29–60.