Synthesis Routes Towards the Farnesyl Protein Transferase Inhibitor ZARNESTRA™

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The discovery that post-translational farnesylation of Ras oncoprotein was an essential step in exercising its biological effect led to the design of farnesyl protein transferase inhibitors (FTIs) in order to control growth of tumors bearing Ras mutations. Pre-clinical studies on murine models have confirmed their inhibitory effect on tumor growth and enabled clinical development. R115777 (ZARNESTRA™) is currently undergoing clinical evaluation and recent studies have confirmed its antitumor potential and low toxicity. We wish to describe here the chemical synthesis routes that our group have developed to access ZARNESTRA™.

Introduction

Ras was the first human transforming oncogene discovered.[1] Studies on clinical specimens have revealed a significant prevalence of Ras mutations with 25% incidence in lung, bladder and thyroid cancers[1−3] and higher incidences of 53% and more than 90% in colon[4] and pancreatic cancer,[5] respectively. The Ras oncoprotein is involved in the intracellular signaling pathways leading to cell proliferation. These initial results prompted several investigations to define therapeutic agents which targeted the aberrant cell signaling caused by the Ras oncogenes.

To function in signal transduction, Ras must attach to the plasma membrane, but the physico-chemical properties of the newly synthesized Ras protein do not induce translocation to the membrane. Post-translational modifications of Ras and related CAAX-containing proteins are required to transport these proteins to functional membrane locations within cells. The first and most important step of these modifications is catalyzed by the enzyme farnesyl protein transferase[6] (FPT). This key limiting reaction involves the covalent attachment of a 15-carbon farnesyl moiety through a thioether bond to a single cysteine of the C-terminal CAAX motif, where C is cysteine, A is any aliphatic amino acid and X is serine, methionine, glutamine or alanine. The prenylated product undergoes proteolytic cleavage of the C-terminal tripeptide followed by a methyl esterification of the new C-terminal farnesylcysteine.[7,8]

Furthermore, recent findings have highlighted the role of other prenylated proteins, such as RhoB or CENP-E and CENP-F, in tumor cell proliferation.[9,10] All of these proteins undergo this critical farnesylation step, and inhibition of FPT can suppress human tumor cell proliferation related to these proteins. Thus, FPT is a valuable pharmacological target and compounds inhibiting this enzyme could have a significant potential in cancer therapy not limited to Ras-dependent tumors.

R115777 (**1**) has emerged as a novel, selective, nonpeptide farnesyl protein inhibitor showing in vitro activity in the nanomolar range.[11] As an orally active antitumor agent **1** is currently undergoing human clinical trials.[12] We have previously described the structure-activity relationships of quinolinone-based inhibitors of FPT as part of our efforts to develop orally active FTIs.[13,14] Herein we wish to describe the synthesis routes we have developed to access **1**.

Results and Discussion

Historically, we prepared 4-(3-chlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone (**3**) by intramolecular cyclization of the amide **2** in PPA at 100 °C (Scheme 1).[15] Interestingly, ad-

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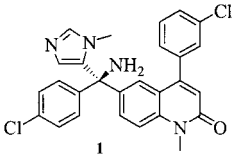
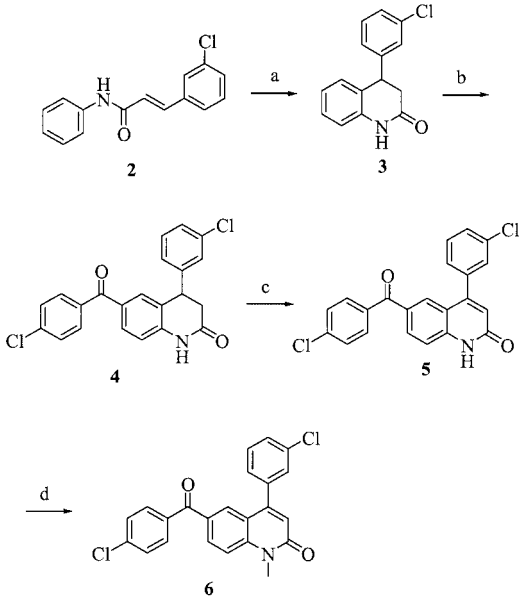


R115777 FT inhibitory activity
Lamin B CVIM peptide $IC_{50} = 0.86$ nM
K-RasB CVIM peptide $IC_{50} = 7.9$ nM

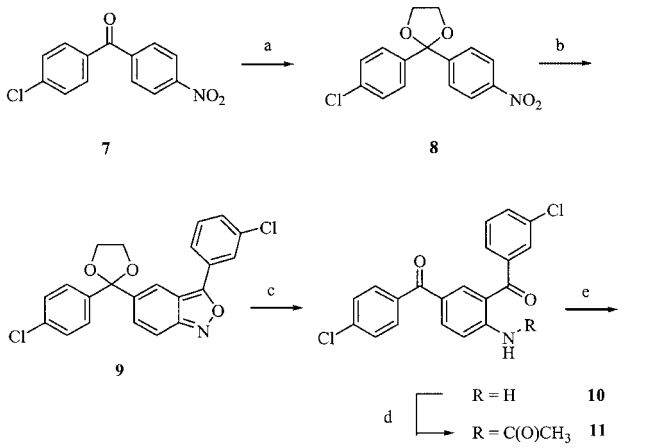
Figure 1. R115777

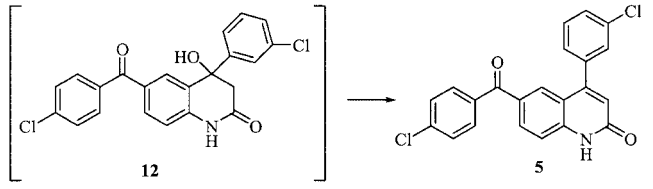
ding 4-chlorobenzoic acid to this mixture and further heating provided the appropriate quinolinone 6-isomer **4** in good yield. Derivative **4** was oxidized to **5** and *N*-methylation was performed under phase-transfer catalysis (PTC) to provide **6**.[16−18]



Scheme 1. a) Polyphosphoric acid (PPA), 100 °C, 16 h; b) 4-chlorobenzoic acid, 140 °C, 48 h (45%); c) Br_2, C_6H_5Br, 160 °C, 16 h (93%); d) CH_3I, benzyltriethylammonium chloride (BTEAC), NaOH, THF, room temp., 16 h (75%)

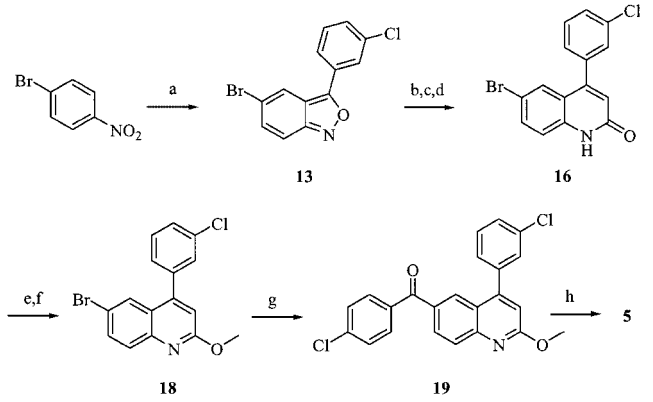
However, this scheme did not allow a wide variety of substitution on the 4-phenyl ring and we looked for an alternative synthesis of **6**. Davis and Pizzini[19] had described the synthesis of 1,2-benzisoxazoles, and reduction of these compounds to *ortho*-aminobenzophenones was known.[20] Starting from 4-chloro-4′-nitrobenzophenone (**7**), we first protected the carbonyl moiety by ketalization, then treated it with 3-chlorobenzyl cyanide to provide the 1,2-benzisoxazole **9**, which crystallized from the reaction medium and was removed by filtration. The reaction must be carried out with caution as it generates 1 equiv. of sodium cyanide as a by-product. Reduction by Lewis acid ($TiCl_3$) in a water/THF mixture removed the ketal function and provided the *ortho*-aminobenzophenone **10**, which was then acylated. The resulting amide **11** was cyclized to quinolinone **12** which was not isolated, as an excess of potassium *tert*-butoxide allowed in situ elimination to provide **5** in a good yield (Scheme 2).





Scheme 2. a) Ethylene glycol, *para*-toluenesulfonic acid (PTSA), toluene, 110 °C, 24 h (98%); b) (3-Cl-C_6H_4)CH_2CN, NaOH, MeOH, 60 °C, 1 h (86%); c) $TiCl_3$, H_2O/THF, room temp., 16 h; d) Ac_2O, toluene, 110 °C, 2 h; e) *t*BuOK (4 equiv.), DME, room temp., 3 h (87%)

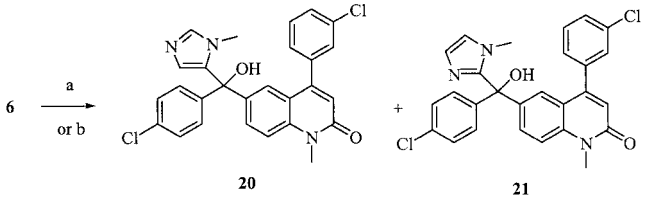
The same scheme was applied to 4-bromo-1-nitrobenzene (Scheme 3) to provide 6-bromo-4-(3-chlorophenyl)-2(1*H*)-quinolinone (**16**). Conversion of **16** into the corresponding 2-methoxyquinoline **18** was performed by chlorination using phosphorus oxychloride as solvent followed by substitution using sodium methoxide. After bromine/lithium exchange **18** was treated with 4-chloro-*N*-methoxy-*N*-methyl-



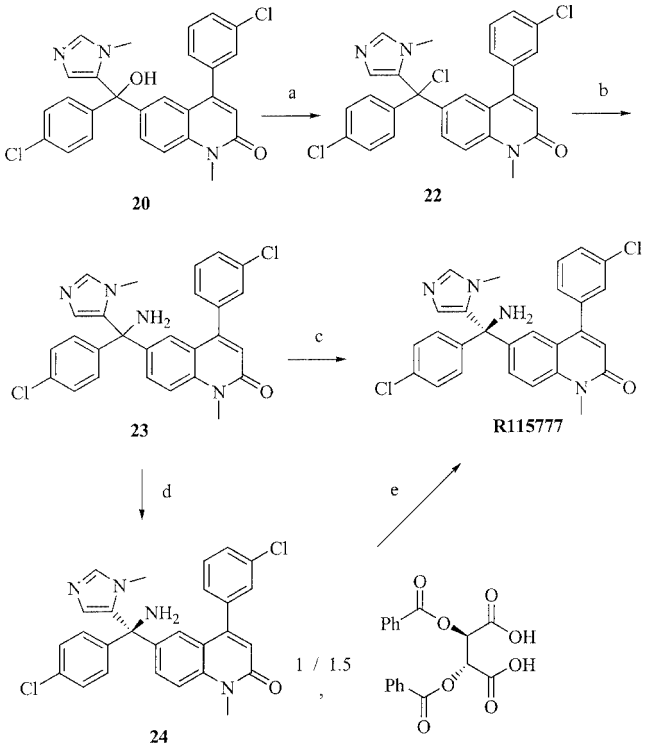
Scheme 3. a) (3-Cl-C_6H_4)CH_2CN, NaOH, MeOH, room temp., 16 h (35%); b) $TiCl_3$, H_2O/THF, room temp., 16 h (85%); c) Ac_2O, toluene, 110 °C, 2 h; d) *t*BuOK (4 equiv.), DME, room temp., 16 h (81%); e) $POCl_3$, 80 °C, 16 h; f) MeONa/MeOH, 60 °C, 16 h (86%); g) (4-Cl-C_6H_4)C(O)N(CH_3)OCH_3, *n*BuLi, THF, −70 °C, 0.5 h (75%); h) HCl (6 N), MeOH, 60 °C, 72 h, (80%)

benzamide to provide **19**. Finally, acidic cleavage of the 2-methoxy moiety gave us another route to key intermediate **5**.

The *N*-methylimidazole moiety was then introduced by the following sequence (Scheme 4): *N*-methylimidazole was deprotonated at carbon-2 by addition of *n*-butyllithium and the resulting carbanion silylated by addition of triethylsilyl chloride. Another equivalent of *n*-butyllithium at a temperature maintained below −50 °C, formed the 5-lithio-1-methyl-2-triethylsilylimidazole to which the ketone **6** was added giving **20** in moderate yield (52%), together with 5% of **21**.



Scheme 4. a) 1. *N*-methylimidazole, *n*BuLi, $ClSiEt_3$, THF, −78 °C; 2. *n*BuLi, −78 °C, **20** (52%), **21** (4%); b) 1. *N*-methylimidazole, *n*-hexyllithium, $ClSi(iBu)_3$, THF, −78 °C; 2. *n*-hexyllithium, −78 °C, **20** (75%), **21** (< 0.3%)



Scheme 5. a) $SOCl_2$ 40 °C or HCl, $SOCl_2$, *N*,*N*-dimethylimidazolidinone, room temp.; b) NH_4OH, THF, 80 °C (65%) or NH_3/MeOH, room temp. (70−75%); c) enantiomer separation by HPLC on chiral phase (32.5%); d) L-(−)-dibenzoyltartaric acid monohydrate, acetone, room temp. (37%); e) NH_4OH, EtOH, 80 °C (86%)

However, carrying out this process at a temperature as low as −78 °C is inconvenient and costly on a commercial scale in view of the specialized equipment required to perform a large-scale process at such a low temperature. There was a need to improve the above reaction step so that it could be carried out in an efficient and economical manner on a commercial scale. We have discovered that improvements in yield (75%), impurity profile (less than 0.3% of **21**) and commercial ease of operation can be achieved by the use of *n*-hexyllithium in place of *n*-butyllithium and the use of triisobutylsilyl chloride in place of triethylsilyl chloride, with particularly advantageous results obtained at temperatures between −15 and 0 °C.[21] This selectivity at such relatively high temperatures is remarkable in view of suggestions in the literature that the silyl group is unsuitable as a blocking group, owing to the 2- to 5-position migration of 2-(trialkylsilyl)-substituted 5-lithio-*N*-methylimidazoles.[22,23]

Replacement of the hydroxy group by the amino moiety to reach the racemic analogue of **1** was initially achieved in two steps by first treating **20** with thionyl chloride to provide 6-[chloro(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)-methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (**22**) and then substituting the chlorine atom in **22** by aqueous ammonia to give **23** (Scheme 5). On a preparative scale this procedure was further improved by performing the chlorination step in *N*,*N*-dimethylimidazolidinone and by using ammonia in methanol at a lower temperature.[21]

The racemic compound **23** was resolved by HPLC on a Chiracel OD® column to afford the active (+)-(*R*)-enantiomer **1** (R115777). R115777 was also obtained by resolution, the racemic form **23** being treated with L-(−)-dibenzoyltartaric acid (DBTA) to obtain the diastereomeric tartrate salt **24** which is treated with aqueous ammonium hydroxide, to form the crude R115777 which is then purified by recrystallization from ethanol (Scheme 5; steps d, e).

Conclusion

R115777 can be accessed by at least three principal routes which were also applied to further broaden the SAR of quinolinone series FTIs.[13,14] An efficient synthetic process for the production of R115777 is reported allowing the large-scale preparations required for development purposes. R115777 is currently undergoing phase II trials in hematological cancers and solid tumors.

Experimental Section

General Remarks: Proton NMR spectra were recorded at 400, 300 or 200 MHz with a Bruker Avance 400, 300 or a Bruker AMC 200 spectrometer, with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and signals are reported as s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Coupling constants are given in Hertz (Hz). Electrospray mass

spectra were recorded with an Applied Biosystems API 100 spectrometer. Optical rotations were performed with a Perkin−Elmer 341 polarimeter. Elemental analyses were realized with a Fisons instrument EA1108 or EA1110. Melting points were determined with a Mettler Toledo FP62 apparatus and are uncorrected. All reactions were routinely checked by TLC on silica gel Merck 60F 254. Column chromatography was carried out on Millipore silica gel (25−45 μm). The enantiomeric purity of final compounds was monitored by HPLC using Chiracel® OD or Chiralpak® AD columns.

6-(4-Chlorobenzoyl)-4-(3-chlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone (4): *N*-Phenyl-3-(3-chlorophenyl)-2-propenamide[18] (58.6 g, 0.2275 mol) and polyphosphoric acid (580 g) were stirred at 100 °C overnight to yield crude 4-(3-chlorophenyl)-3,4-dihydro-2(1*H*)-quinolinone (**3**). 4-Chlorobenzoic acid (71.2 g, 0.455 mol) was added and the mixture was further stirred at 140 °C for 48 h, cooled, poured into ice/water and filtered. The precipitate was washed with water, then with a dilute NH_4OH solution and taken up in CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and the solvents were evaporated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 99:1:0.1). The pure fractions were collected and the solvents evaporated, and recrystallized from CH_2Cl_2/MeOH/diisopropyl ether, to afford 40 g (45%) of **4**. M.p. 195 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 22 °C): δ = 2.90 (d, ^1J = 6.9 Hz, 2 H, 3-H), 4.52 (t, ^1J = 6.8 Hz, 1 H, 4-H), 7.10 (d, ^1J = 8.3 Hz, 1 H, 8-H), 7.23 (d, ^1J = 9.7 Hz, 1 H, C_6H_4-3-Cl), 7.35−7.41 [m, 4 H, 5-H + C_6H_4-4-Cl (2 H) + C_6H_4-3-Cl (1 H)], 7.55−7.69 [m, 5 H, 7-H + C_6H_4-4-Cl (2 H) + C_6H_4-3-Cl (2 H)], 10.73 (s, NH) ppm. $C_{22}H_{15}Cl_2NO_2$ (396.28): calcd. C 66.68, H 3.82, N 3.53; found C 66.57, H 3.75, N 3.45.

6-(4-Chlorobenzoyl)-4-(3-chlorophenyl)-2(1*H*)-quinolinone (5): Bromine (3.4 mL, 0.066 mol) in bromobenzene (80 mL) was added dropwise at room temperature to a solution of **4** (26 g, 0.066 mol) in bromobenzene (250 mL) and the mixture was stirred at 160 °C overnight. The mixture was cooled to room temperature and made basic with NH_4OH. The solvents were evaporated, the residue was taken up in CH_3CN and filtered. The precipitate was washed with water and air-dried to give 24 g (93%) of **5**. M.p. 230−235 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 22 °C): δ = 6.58 (s, 1 H, 3-H), 7.47−7.60 (m, 4 H, C_6H_4-3-Cl + 8-H), 7.59 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.65 (s, 1 H, C_6H_4-3-Cl), 7.70−7.75 (m, 1 H, 5-H), 7.76 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 8.00 (dd, ^1J = 8.6 Hz and 2 Hz, 1 H, 7-H), 12.33 (s, NH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO, 22 °C): δ = 116.6 (C-8), 117.6 (C-10), 122.9 (C-3), 128.0 (C_6H_4-3-Cl), 128.9 (C_6H_4-3-Cl), 128.9 (C_6H_4-4-Cl, 2 C), 129.4 (C_6H_4-3-Cl), 129.8 (C-5), 130.0 (C-6), 131.0 (C_6H_4-3-Cl), 131.7 (C_6H_4-4-Cl, 2 C), 131.9 (C-7), 133.8 (C_6H_4-3-Cl, C−Cl), 136.2 [C_6H_4-4-Cl, C−C(O)], 137.6 (C_6H_4-4-Cl, C−Cl), 138.3 (C_6H_4-3-Cl, C-quinolinone), 142.9 (C-9), 150.2 (C-4), 161.7 (C-2), 193.3 (ketone) ppm. HR-MS: calcd. for $C_{22}H_{13}Cl_2NO_2$ 394.040; found 394.0397.

6-(4-Chlorobenzoyl)-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (6): Iodomethane (6.2 mL, 0.1 mol) was added to a mixture of **5** (20 g, 0.05 mol) and benzyltriethylammonium chloride (5.7 g, 0.025 mol) in THF (200 mL) and NaOH (10 N) (200 mL). The mixture was stirred at room temperature overnight, EtOAc was added and the mixture was decanted. The organic layer was washed with water, dried ($MgSO_4$), filtered and the solvents were evaporated to dryness. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH, 99.75:0.25:0.1). The pure fractions were collected and the solvents evaporated, to afford 12.3 g (75%) of **6**. M.p. 155 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 3.73 (s, 3 H, CH_3), 6.69 (s, 1 H, 3-H), 7.47−7.67 (m, 3 H, C_6H_4-3-Cl), 7.57(d, ^1J = 2 Hz, 1 H, 5-H), 7.61 (d, ^1J = 8.5 Hz, 2 H, C_6H_4-4-Cl), 7.73−7.82 (m, 1 H, C_6H_4-3-Cl), 7.76 (d, ^1J = 8.5 Hz, 2 H, C_6H_4-4-Cl), 7.79 (d, ^1J = 8.7 Hz, 1 H, 8-H), 8.06 (dd, ^1J = 8.6 Hz and 2 Hz, 1 H, 7-H) ppm. $C_{23}H_{15}Cl_2NO_2$ (408.29): calcd. C 67.66, H 3.70, N 3.43; found C 67.72, H 3.64, N 3.34.

2-(4-Chlorophenyl)-2-(4-nitrophenyl)-1,3-dioxolane (8): A mixture of 4-chloro-4′-nitrobenzophenone[24] (**7**) (10 g, 0.0382 mol), ethylene glycol (4.3 mL, 0.0764 mol) and *para*-toluenesulfonic acid (PTSA) (3.6 g, 0.19 mol) in toluene (150 mL) was stirred and refluxed with azeotropic removal of water for 24 h. The mixture was washed with 10% aq. K_2CO_3 and then with water. The organic layer was dried ($MgSO_4$), filtered and the solvents were evaporated to afford 11.42 g (98%) of **8**. M.p. 111 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 4.03 (s, 4 H), 7.42 (d, ^1J = 8.6 Hz, 2 H, C_6H_4Cl), 7.47 (d, ^1J = 8.6 Hz, 2 H, C_6H_4Cl), 7.71 (d, ^1J = 8.7 Hz, 2 H, $C_6H_4NO_2$), 8.21 (d, ^1J = 8.6 Hz, 2 H, $C_6H_4NO_2$) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 22 °C): δ = 65.4 (CH_2−O), 107.8 (O−C−O), 124.0 (C-3′, C-5′), 127.4 (C-2′, C-6′), 128.0 (C-2, C-6), 128.8 (C-3, C-5), 133.5 (C−Cl), 140.6 (C-1), 147.6 (C−NO_2), 149.2 (C-1′) ppm.

3-(3-Chlorophenyl)-5-[2-(4-chlorophenyl)-1,3-dioxolan-2-yl]-2,1-benzisoxazole (9): 8 (25 g, 0.0818 mol) and 3-chlorobenzyl cyanide (17.4 mL, 0.147 mol) were added to a mixture of NaOH (16.4 g, 0.409 mol) in MeOH (100 mL). The mixture was stirred and refluxed until complete dissolution (1 h). Ice and then ethanol were added. The product was allowed to crystallize from the mixture. The precipitate was filtered, washed with ethanol and dried to afford 58 g (86%) of **9**. M.p. 120 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 4.07 (s, 4 H, OCH_2), 7.33 (dd, ^1J = 9.3 Hz and 1.3 Hz, 1 H, 6-H), 7.42 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.55 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.61−7.72 (m, 2 H, C_6H_4-3-Cl), 7.70 (d, ^1J = 8.6 Hz, 1 H, 7-H), 8.04−8.07 (m, 3 H, 4-H + C_6H_4-3-Cl) ppm. $C_{22}H_{15}Cl_2NO_3$ (412.28): calcd. C 64.09, H 3.67, N 3.40; found C 64.40, H 3.65, N 3.40. HR-MS: calcd. for $C_{22}H_{15}Cl_2NO_3$ 412.051; found 412.052. ***Caution!*** The reaction generates sodium cyanide. Cyanide-containing layers are typically decomposed by the addition of 1 equiv. of aqueous H_2O_2 at a pH range of 9.5−10.5, and at a temperature range of 30−50 °C. At higher pH (> 11) the reaction may slow down, and cause H_2O_2 to decompose. After decomposition, the cyanide content is checked and should be < 3 ppm. If not, an additional amount of H_2O_2 is added.

[2-Amino-5-(4-chlorobenzoyl)phenyl](3-chlorophenyl)methanone (10): Titanium(III) chloride (350 mL, 15% w/w solution in H_2O, 0.34 mol) was added at room temperature to a mixture of **9** (58 g, 0.14 mol) in THF (350 mL). The mixture was stirred at room temperature overnight, then poured on ice and extracted with CH_2Cl_2. The organic layer was separated, washed with 10% aq. K_2CO_3, dried ($MgSO_4$), filtered and the solvent was evaporated to afford 61 g (100%) of **10**. M.p. 142 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 7.00 (d, ^1J = 8.6 Hz, 1 H, 6-H), 7.53−7.57 (m, 4 H), 7.63−7.72 (m, 5 H), 7.82 (dd, ^1J = 8.6 Hz and 1.9 Hz, 1 H, 5-H), 8.01 (s, NH2) ppm. $C_{20}H_{13}Cl_2NO_2$ (370.24): calcd. C 64.88, H 3.54, N 3.78; found C 64.88, H 3.40, N 3.74.

***N*-[2-(3-Chlorobenzoyl)-4-(4-chlorobenzoyl)phenyl]acetamide (11):** Acetic anhydride (29 mL, 0.284 mol) was added to a mixture of **10** (52.6 g, 0.142 mol) in toluene (510 mL). The mixture was stirred at 120 °C for 20 h. The solvent was evaporated to dryness to afford 60 g of **11**. ^{1}H NMR (400 MHz, [D$_5$]pyridine, 22 °C): δ = 2.12 (s, 3 H, CH_3), 7.36 (t, ^1J = 7.8 Hz, 1 H, C_6H_4-3-Cl 5′-H), 7.52 (d, ^1J = 8.4 Hz, 2 H, C_6H_4-4-Cl 3′-H + 5′-H), 7.51−7.56 (m, 1 H,

C_6H_4-3-Cl 4′-H), 7.81−7.87 (m, 1 H, C_6H_4-3-Cl 6′-H), 7.86 (d, ^1J = 8.4 Hz, 2 H, C_6H_4-4-Cl 2′-H + 6′-H), 8.04 (m, 1 H, C_6H_4-3-Cl 2′-H), 8.11 (dd, ^1J = 8.6 Hz and 2 Hz, 1 H, 5-H), 8.21 (d, ^1J = 2 Hz, 1 H, 3-H), 8.48 (d, ^1J = 8.6 Hz, 1 H, 6-H) 11.39 (s, NH) ppm. ^{13}C NMR (101 MHz, [D$_5$]pyridine, 22 °C): δ = 25.1 (CH_3), 123.4 (C-6), 127.9 (C-4), 129.6 (C_6H_4-3-Cl C-2′), 129.9 (C_6H_4-4-Cl C-3′ + C-5′), 130.9 (C_6H_4-3-Cl C-6′), 131.1 (C_6H_4-3-Cl C-5′), 132.6 (C_6H_4-4-Cl C-2′ + C-6′), 132.8 (C-2), 133.7 (C_6H_4-3-Cl C-4′), 134.8 (C-3), 135.3 (C_6H_4-3-Cl C-1′), 135.7 (C-5), 137.0 (C_6H_4-4-Cl C-1′), 139.6 (C_6H_4-4-Cl C-4′), 140.7 (C_6H_4-3-Cl C-3′), 143.7 (C−NH), 172.5 (NH−C=O), 194.0 (3-Cl−C_6H_4−C=O), 195.9 (4-Cl−C_6H_4−C=O) ppm. $C_{22}H_{15}Cl_2NO_3$ (412.28): calcd. C 64.09, H 3.67, N 3.40; found C 64.27, H 3.89, N 3.32.

6-(4-Chlorobenzoyl)-4-(3-chlorophenyl)-2(1*H*)-quinolinone (5): *t*BuOK (62.8 g, 0.56 mol) was added to a solution of **11** (57.7 g, 0.14 mol) in 1,2-dimethoxyethane (550 mL). The mixture was stirred at room temperature for 3 h, then H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated. The residue was crystallized from Et_2O. The precipitate was filtered and dried to afford 47.8 g (87%) of **5** (already described above).

5-Bromo-3-(3-chlorophenyl)-2,1-benzisoxazole (13): NaOH (24.8 g, 0.62 mol) was dissolved in MeOH (100 mL) and the mixture was cooled to room temperature. 1-Bromo-4-nitrobenzene (25 g, 0.124 mol), followed by 3-chlorobenzyl cyanide (26.3 mL, 0.223 mol), was added dropwise, the temperature rose to 50 °C and the mixture was stirred at room temperature overnight. The mixture was poured into water and ice, the precipitate was filtered, washed with water and extracted with CH_2Cl_2 and MeOH. The organic layer was dried ($MgSO_4$), filtered and the solvents were evaporated to dryness. The residue was taken up in Et_2O, filtered and dried to afford 13.3 g (35%) of **13**. Using mechanical stirring enabled us to raise the yield to 60%. M.p. 163 °C. ^{1}H NMR (400 MHz, [D$_5$]pyridine, 22 °C): δ = 7.39 (dd, ^1J = 9.6 Hz and 1.5 Hz, 1 H, 6-H), 7.43 (t, ^1J = 7.7 Hz, 1 H, C_6H_4-3-Cl 5′-H), 7.49 (ddd, ^1J = 7.7 Hz 1.1 Hz and 1.1 Hz, 1 H, C_6H_4-3-Cl 4′-H), 7.62 (d, ^1J = 9.6 Hz, 1 H, 7-H), 7.90 (ddd, ^1J = 7.7 Hz 1.1 Hz and 1.1 Hz, 1 H, C_6H_4-3-Cl 6′-H), 8.09 (dd, ^1J = 1.1 Hz and 1.1 Hz, 1 H, C_6H_4-3-Cl 2′-H), 7.26 (br. s, 1 H, 4-H) ppm. ^{13}C NMR (101 MHz, [D$_5$]pyridine, 22 °C): δ = 115.9 (C−Br), 117.5 (C-7), 119.1 (C-9), 122.9 (C-4), 125.0 (C_6H_4-3-Cl C-6′), 126.6 (C_6H_4-3-Cl C-2′), 129.5 (C−Cl), 130.7 (C_6H_4-3-Cl C-4′), 131.2 (C_6H_4-3-Cl C-5′), 135.0 (C-6), 134.4 (C_6H_4-3-Cl C-1′), 156.5 (C=N), 162.5 (C−O) ppm. HR-MS: calcd. for $C_{13}H_7BrClNO$ 307.948; found 307.943.

(2-Amino-5-bromophenyl)(3-chlorophenyl)methanone (14): Titanium(III) chloride (1050 mL, 15% w/w solution in H_2O, 1.0 mol) was added at room temperature to a solution of **13** (120 g, 0.386 mol) in THF (1350 mL) and the mixture was stirred at room temperature for 2 h. The mixture was poured into water and ice and extracted with CH_2Cl_2. The organic layer was decanted, washed with 10% aq. K_2CO_3, dried ($MgSO_4$), filtered and the solvents were evaporated to yield 102 g (85%) of **14**. M.p. 110 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 6.87 (d, ^1J = 9.7 Hz, 1 H, 3-H), 7.28 (d, ^1J = 2 Hz, 1 H, 6-H), 7.31 (s, 2 H, NH2), 7.42 (dd, ^1J = 9.7 Hz and 2 Hz, 1 H, 4-H), 7.48−7.69 (m, 4 H, C_6H_4Cl) ppm.

***N*-[4-Bromo-2-(3-chlorobenzoyl)phenyl]acetamide (15):** A solution of **14** (101.9 g, 0.328 mol) and acetic anhydride (61.6 mL, 0.656 mol) in toluene (1200 mL) was stirred and refluxed overnight. The solvents were evaporated and the product was used without further purification to yield 116 g (quant.) of **15**. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 1.72 [s, 3 H, C(O)CH_3], 7.34 (d, ^1J = 9.3 Hz, 1 H, 3-H), 7.52 (d, ^1J = 2.6 Hz, 1 H, 6-H), 7.57(m, 3 H, C_6H_4Cl), 7.71 (m, 1 H, C_6H_4Cl), 7.78 (dd, ^1J = 9.3 Hz and 2.6 Hz, 1 H, 4-H), 10.17 (s, 1 H, NH) ppm.

6-Bromo-4-(3-chlorophenyl)-2(1*H*)-quinolinone (16): *t*BuOK (183 g, 1.635 mol) was added portionwise at room temperature to a solution of **15** (115.6 g, 0.328 mol) in 1,2-dimethoxyethane (1200 mL) and the mixture was stirred at room temperature overnight. The solvents were evaporated to dryness, the residue was poured into water and ice and decanted. The oily residue was taken up in diisopropyl ether, the precipitate was filtered, washed with EtOAc, acetonitrile and diethyl ether and dried, yielding 88.6 g (81%) of **16**, M.p. 266 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 6.50 (s, 1 H, 3-H), 7.35 (s, 1 H, 5-H), 7.36 (d, ^1J = 8.6 Hz, 1 H, 8-H), 7.45 (d, ^1J = 6.5 Hz, 1 H, C_6H_4Cl), 7.58−7.63 (m, 3 H, C_6H_4Cl), 7.71 (dd, ^1J = 8.6 Hz and 2 Hz, 1 H, 7-H), 12.08 (s, NH) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 22 °C): δ = 114.0 (C−Br), 118.4 (C-8), 120.3 (C-10), 123.2 (C-3), 127.8 (C_6H_4Cl), 128.1 (C-5), 128.7 (C_6H_4Cl), 129.3 (C_6H_4Cl), 131.0 (C_6H_4Cl), 133.7 (C−Cl), 133.9 (C-7), 138.4 (C_6H_4Cl, C-quinolinone), 138.7 (C-9), 149.1 (C-4), 161.2 (C=O) ppm. HR-MS: calcd. for $C_{15}H_9BrClNO$ 333.963; found 333.965.

6-Bromo-2-chloro-4-(3-chlorophenyl)quinoline (17): 16 (56 g, 0.16 mol) was stirred and refluxed in phosphorus oxychloride (500 mL) overnight. The solvents were evaporated to dryness, the residue was taken up in ice and water, made basic with NH_4OH and extracted with CH_2Cl_2. The organic layer was decanted, dried ($MgSO_4$), filtered and the solvents were evaporated. The residue was crystallized in CH_2Cl_2/Et_2O, filtered and dried to afford 46.9 g (83%) of **17**. M.p. 136 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 7.56 (ddd, ^1J = 7 Hz 1.5 Hz and 1.5 Hz, 1 H, C_6H_4-3-Cl 6′-H), 7.62 (dd, ^1J = 8 Hz, 1 H, C_6H_4-3-Cl 5′-H), 7.64−7.66 (m, 1 H, C_6H_4-3-Cl 4′-H), 7.67 (s, 1 H, 3-H), 7.68−7.71 (m, 1 H, C_6H_4-3-Cl 2′-H), 7.86 (s, 1 H, 5-H), 7.88−8.02(m, 2 H, 7-H + 8-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 22 °C): δ = 121.3 (C-9), 123.5 (C-3), 126.6 (C-10), 127.7 (C-5), 128.6 (C_6H_4-3-Cl C-6′), 129.5 (C_6H_4-3-Cl C-2′), 129.6 (C_6H_4-3-Cl C-4′), 131.1 (C-8 + C_6H_4-3-Cl C-5′), 134.0 (C_6H_4-3-Cl C-3′), 134.4 (C-7), 137.7 (C_6H_4-3-Cl C-1′), 146.6 (C−Br), 149.2 (C-4), 150.5 (N=C−Cl) ppm. HR-MS: calcd. for $C_{15}H_8BrCl_2N$ 351.9295; found 351.9304.

6-Bromo-4-(3-chlorophenyl)-2-methoxyquinoline (18): Sodium methoxide (30% w/w in MeOH, 96 mL, 0.16 mol) was added to a solution of **17** (56 g, 0.16 mol) in MeOH (500 mL) and the mixture was stirred and refluxed overnight. The solvents were evaporated to dryness, the residue was taken up in CH_2Cl_2, washed with water and decanted. The organic layer was dried ($MgSO_4$), filtered and the solvents were evaporated. The residue was taken up in Et_2O and diisopropyl ether, the precipitate was filtered and dried, to afford 48 g (86%) of **18**. M.p. 137 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 4.02 (s, 3 H, CH_3), 7.04 (s, 1 H, 3-H), 7.49 (dt, ^1J = 7 Hz and 1.5 Hz, 1 H, C_6H_4-3-Cl 6′-H), 7.59−7.67 (m, 3 H, C_6H_4-3-Cl), 7.69 (s, 1 H, 5-H), 7.80−7.83 (m, 2 H, 7-H + 8-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 22 °C): δ = 53.8 (OCH_3), 114.2 (C-3), 117.5 (C-9), 125.0 (C-10), 127.4 (C-5), 128.4 (C_6H_4-3-Cl C-6′), 129.2 (C_6H_4-3-Cl C-2′ + C-4′), 130.0 (C8), 131.0 (C_6H_4-3-Cl C-5′), 133.2 (C-7), 133.9 (C−Cl), 138.7 (C_6H_4-3-Cl C-1′), 145.6 (C−Br), 148.7 (C-4), 162.2 (N=C−O) ppm. HR-MS: calcd. for $C_{16}H_{11}BrClNO$ 347.9791; found 347.9788.

(4-Chlorophenyl)-[4-(3-chlorophenyl)-2-methoxyquinolin-6-yl]-methanone (19): *n*-Butyllithium (2 mL, 0.0316 mol) was added dropwise at −70 °C to a mixture of **18** (1 g, 0.00287 mol) in THF (10 mL). The mixture was stirred at −70 °C for 30 min and a solu-

tion of 4-chloro-*N*-methoxy-*N*-methylbenzamide[25] (0.49 g, 0.00244 mol) in THF (3 mL) was added. The mixture was stirred at −70 °C for 30 min, hydrolyzed and extracted with CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel (CH_2Cl_2/cyclohexane, 50:50). The pure fractions were collected and the solvents evaporated to afford 0.74 g (75%) of **19**. M.p. 146 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 22 °C): δ = 3.09 (s, 3 H, CH_3), 7.14 (s, 1 H, 3-H), 7.56−7.60 (m, 3 H, C_6H_4-3-Cl), 7.63 (d, ^1J = 8.7 Hz, 2 H, C_6H_4-4-Cl), 7.72 (s, 1 H, C_6H_4-3-Cl), 7.84 (d, ^1J = 8.7 Hz, 2 H, C_6H_4-4-Cl), 8.01 (d, ^1J = 9.5 Hz, 1 H, 8-H), 8.05 (d, ^1J = 2 Hz, 1 H, 5-H), 8.11 (dd, ^1J = 9.5 Hz and 2 Hz, 1 H, 7-H) ppm. ^{13}C NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 53.9 (OCH_3), 114.1, 122.2, 128.4, 128.8 (2 C), 129.2 (2 C), 129.6, 129.8, 130.8, 131.7 (2 C), 132.1, 133.6, 134.0, 137.6, 138.4 (C_6H_4-3-Cl, C-quinoline), 149.2 (C-9), 150.3 (C-4), 163.5 (C-2), 193.8 (C=O) ppm. $C_{23}H_{15}Cl_2NO_2$ (408.283): calcd. C 67.66, H 3.70, N 3.43; found C 67.11, H 3.69, N 3.35.

6-(4-Chlorobenzoyl)-4-(3-chlorophenyl)-2(1*H*)-quinolinone (5): A mixture of **19** (0.4 g, 0.001 mol) in 6 N HCl (4 mL) and MeOH (2 mL) was stirred and refluxed for 72 h, poured on ice, filtered, washed several times with water, then with 2-propanol/diethyl ether and dried to afford 0.31 g (80%) of **5** (already described).

4-(3-Chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone (20): Under dry N_2 flow, 1-methylimidazole (4.83 g, 0.058 mol) was dissolved in THF (100 mL), and the solution was cooled to −75 °C before dropwise addition of *n*-butyllithium (1.6 M in hexane, 36.7 mL, 0.059 mol) at a temperature maintained below −70 °C. The mixture was stirred for 15 min, triethylsilyl chloride (9.87 mL, 0.058 mol) was added dropwise at −70 °C. The reaction mixture was warmed to room temperature (20 °C) and then stirred for 30 min. The mixture was cooled to −75 °C, *n*-butyllithium (1.6 M in hexane, 36.7 mL, 0.059 mol) was added dropwise at a temperature maintained below −70 °C, and this mixture was stirred for 1 h at a temperature below −70 °C, then warmed to −15 °C, then re-cooled to −75 °C. A solution of **6** (20 g, 0.048 mol) in THF (40 mL) was then added dropwise at a temperature maintained below −70 °C, the reaction mixture was stirred for 1 h and warmed to −50 °C. Water (100 mL) was added dropwise. The aqueous layer was extracted with EtOAc, the organic layer was dried ($MgSO_4$) and the solvents were evaporated and the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH/NH_4OH, 97:3:0.1) to afford 12.4 g (52%) of **20**. M.p. 234 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 3.35 (s, 3 H, CH_3 imidazole), 3.67 (s, 3 H, CH_3 quinolinone), 6.06 (s, 1 H, $4_{Imidazole}$-H), 6.58 (s, 1 H, 3-H), 6.90 (s, 1 H, OH), 7.17 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.21 (d, ^1J = 1.8 Hz, 1 H, 5-H), 7.29 (ddd, ^1J = 7.3 Hz 1.6 Hz and 1.6 Hz, 1 H, C_6H_4-3-Cl), 7.36 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.41 (dd, ^1J = 1.6 Hz and 1.6 Hz, 1 H, C_6H_4-3-Cl), 7.50 (dd, ^1J = 7.3 Hz and 8.2 Hz, 1 H, C_6H_4-3-Cl), 7.54 (ddd, ^1J = 8.2 Hz 1.8 Hz and 1.8 Hz, 1 H, C_6H_4-3-Cl), 7.62 (s, 1 H, $2_{Imidazole}$-H), 7.62 (m, 2 H, 7-H + 8-H) ppm. $C_{27}H_{21}Cl_2N_3O_2$ (490.39): calcd. C 66.13, H 4.32, N 8.57; found C 66.19, H 4.29, N 8.45. A second fraction gave 0.23 g (4%) of **4-(3-Chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]-1-methyl-2(1*H*)-quinolinone (21):** M.p. 154 °C. ^{1}H NMR (200 MHz, [D$_6$]DMSO, 22 °C): δ = 3.42 (s, 3 H, $CH_{3Imidazole}$), 3.69 (s, 3 H, CH_3 quinolinone), 6.57 (s, 1 H, 3-H), 6.72 (d, ^1J = 1 Hz, 1 H imidazole), 6.99 (s, 1 H, OH), 7.12 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.14 (d, ^1J = 1 Hz, 1 H imidazole), 7.18 (s, 1 H, 5-H), 7.31 (ddd, ^1J = 9.6 Hz 1.5 Hz and 1.5 Hz, 1 H, C_6H_4-3-Cl), 7.33 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.40 (dd, ^1J = 1.5 Hz and 1.5 Hz, 1 H, C_6H_4-3-Cl), 7.50 (dd, ^1J = 8 Hz and 9.6 Hz, 1 H, C_6H_4-3-Cl), 7.54 (ddd, ^1J = 8 Hz 1.5 Hz and 1.5 Hz, 1 H, C_6H_4-3-Cl), 7.61 (m, 2 H, 7-H + 8-H) ppm. ^{13}C NMR (101 MHz, [D$_6$]DMSO, 22 °C): δ = 29.6 ($N_{Quinolinone}-CH_3$), 34.6 ($N_{Imidazole}-CH_3$), 77.4 (C−OH), 115.1 (C-8), 118.1 (C-10), 121.2 (C-3), 123.9 (CH−$N_{Imidazole}$−Me), 125.0 (C-5), 125.6 (CH=$N_{Imidazole}$), 127.9 (C_6H_4-3-Cl C-6′), 127.9 (C_6H_4-4-Cl C-3′ + C-5′), 128.8 (C_6H_4-3-Cl C-2′), 128.9 (C_6H_4-4-Cl C-2′ + C-6′), 129.0 (C_6H_4-3-Cl C-4′), 130.8 (C_6H_4-3-Cl C-5′), 131.1 (C-7), 132.0 (C_6H_4-4-Cl C-Cl), 133.6 (C_6H_4-3-Cl C-Cl), 138.6 (C_6H_4-3-Cl C-1′), 139.3 (C-9), 139.9 (C-6), 144.8 (C_6H_4-4-Cl C-1′), 149.0 (C-4), 149.4 (N=C−N), 160.8 (C=O) ppm. HR-MS: calcd. for $C_{27}H_{21}Cl_2N_3O_2$ 490.1089; found 490.1085.

Alternative Procedure: Dry tetrahydrofuran (110 ml) was added to 1-methylimidazole (7.6 mL, 0.0946 mol) and the resulting solution cooled to −15 °C. *n*-Hexyllithium (2.5 M in hexane, 37.8 mL, 0.0946 mol) was added, while the temperature was maintained between −5 and 0 °C. After addition, the reaction mixture was stirred for 15 min while cooling to −12 °C. Triisobutylsilyl chloride (26.2 mL 0.0964 mol) was added, while the temperature was maintained between −5 and 0 °C. After addition, the reaction mixture was stirred for 15 min, while being cooled to −13 °C. *n*-Hexyllithium (2.5 M in hexane, 37.2 mL, 0.0930 mol) was added, while the temperature during addition was maintained between −5 and 0 °C (some precipitation occurred). After addition, the reaction mixture was stirred for 15 min while cooled to −14 °C. Dry tetrahydrofuran (128 mL) was added to **6** (26.22 g, 0.0642 mol) and stirred until dissolution. This solution was added to the reaction mixture, while the temperature during addition was maintained between −5 and 0 °C. After addition, the reaction mixture was stirred between −5 and 0 °C for 15 min. Water (128 mL) was added to the reaction mixture, followed by acetic acid (10.6 mL). The mixture was then heated to 40 °C and stirred for 2 h. The layers were separated and the organic layer washed with water (32 mL). Water (64 mL) and aqueous NaOH 50% (7.8 mL) were added to the organic layer which was stirred at room temperature for 1 h. The layers were separated and the organic layer concentrated under reduced pressure to yield 51.08 g (75.6%) of 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone (**20**).

(+-)-6-[Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (23): 20 (3 g, 0.0061 mol) was added at room temperature to thionyl chloride (25 mL). The mixture was stirred at 40 °C overnight. The solvent was evaporated to dryness to give 3.49 g of 6-[chloro(4-chlorophenyl)-(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)quinolinone monohydrochloride (**22**). The product was used without purification in the next step. A mixture of **22** (22.2 g, 0.0408 mol) in THF (200 mL) was poured quickly into NH_4OH (200 mL). The mixture was stirred and refluxed at 80 °C for 30 min and then decanted. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and the solvent was evaporated. The residue (21.9 g) was purified by column chromatography on silica gel (toluene/2-propanol/NH_4OH, 79:20:1). The pure fractions were collected and the solvent was evaporated. The residue (13 g, 65%) was crystallized from CH_2Cl_2/MeOH/CH_3CN. The precipitate was filtered and dried to afford 10.3 g (52%) of **23**. M.p. 214 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 3.10 (s, NH_2), 3.38 (s, 3 H, $CH_{3Imidazole}$), 3.68 (s, 3 H, $CH_{3Quinolinone}$), 5.92 (s, 1 H, $4_{Imidazole}$-H), 6.55 (s, 1 H, 3-H), 6.94 (d, ^1J = 1.6 Hz, 1 H, 5-H), 7.14 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl),

7.23 (d, ^1J = 7.5 Hz, 1 H, C_6H_4-3-Cl), 7.35 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.36 (s, 1 H, C_6H_4-3-Cl), 7.45 (d, ^1J = 7.5 Hz, 1 H, C_6H_4-3-Cl), 7.49 (dd, ^1J = 7.5 Hz and 7.5 Hz, 1 H, C_6H_4-3-Cl), 7.55 (s, 1 H, $2_{Imidazole}$-H), 7.65 (d, ^1J = 9.6 Hz, 1 H, 8-H), 7.80 (dd, ^1J = 9.6 Hz and 2 Hz, 1 H, 7-H) ppm. HR-MS: calcd. for $C_{27}H_{22}Cl_2N_4O$ 489.1249; found 489.1241.

(+)-(*R*)-6-[Amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (1, R115777): 23 (4 g) was separated into its enantiomers by chiral column chromatography on Chiralcel OD® (25 cm; eluent: 100% ethanol; flow: 0.5 mL/min; wavelength: 220 nm). The pure fractions were collected and the solvents evaporated. The residue was crystallized from 2-propanol. The precipitate was filtered to yield 1.3 g (32.5%) of **1**. M.p. 234 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 22 °C): δ = 3.10 (s, NH_2). 3.38 (s, 3 H, $CH_{3Imidazole}$), 3.68 (s, 3 H, $CH_{3Quinolinone}$), 5.92 (s, 1 H, $4_{Imidazole}$-H), 6.55 (s, 1 H, 3-H), 6.94 (d, ^1J = 1.6 Hz, 1 H, 5-H), 7.14 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.23 (d, ^1J = 7.5 Hz, 1 H, C_6H_4-3-Cl), 7.35 (d, ^1J = 8.6 Hz, 2 H, C_6H_4-4-Cl), 7.36 (s, 1 H, C_6H_4-3-Cl), 7.45 (d, ^1J = 7.5 Hz, 1 H, C_6H_4-3-Cl), 7.49 (dd, ^1J = 7.5 Hz and 7.5 Hz, 1 H, C_6H_4−3Cl), 7.55 (s, 1 H, $2_{Imidazole}$-H), 7.65 (d, ^1J = 9.6 Hz, 1 H, 8-H), 7.80 (dd, ^1J = 9.6 Hz and 2 Hz, 1 H, 7-H) ppm. $C_{27}H_{22}Cl_2N_4O$ (489.41): calcd. C 66.26, H 4.53, N 11.45; found C 66.32, H 4.38, N 11.38. *ee* > 99% (HPLC). $[\alpha]^D_{20}$ = +22.86 (*c* = 0.98 MeOH).

Large-Scale Synthesis of R115777

a) A 1-L reaction vessel was charged with **20** (105.4 g, 0.2 mol, hydrochloric acid salt) and *N*,*N*-dimethylimidazolidinone (400 mL) was added at 22 °C. The mixture was stirred vigorously at 22 °C for 15 min and became homogeneous. Thionyl chloride (32.1 mL) was added to the reaction mixture over 10 min, the reaction temperature rising from 22 to 40 °C. After addition of the thionyl chloride, the reaction mixture was cooled from 40 to 22 °C and stirred at the latter temperature for 3 h to provide a solution of 4-(3-chlorophenyl)-6-[chloro-(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone (**21**).

b) Ammonia in methanol (7 N, 429 mL) was cooled to 5 °C in a 3-L reaction vessel and the solution obtained in stage a) added, while stirring, over 10 min, with an exothermic reaction, the temperature rising from 5 to 37 °C. After the addition was complete, the reaction mixture was cooled to 22 °C and stirred for 20 h. Water (1000 mL) was then added over 20 min, the addition being slightly exothermic, so the reaction mixture was cooled to maintain the temperature below 30 °C. The mixture was then stirred at 22 °C for 22 h, the resulting precipitate filtered and the precipitate washed with water (3 × 100 mL) to provide 67.9−72.8 g (70−75%) of **23**.

c) A 3-L reaction vessel was charged with **23** (146.8 g, 0.3mol) and L-(−)-dibenzoyltartaric acid monohydrate (301.1 g, 0.8mol), acetone (1200 mL) and the reaction mixture was stirred vigorously at 22 °C for 10 min to form a solution which was seeded with 100 mg of the final tartrate salt product (obtained from previous screening experiments) and then stirred at 22 °C for 22 h. The resulting precipitate was filtered, washed with acetone (2 × 75 mL) and the product dried at 50 °C in vacuo to yield 114.7 g (37%) of *R*-(−)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone [*R*-(*R**,*R**)]-2,3-bis-(benzoyloxy)butanedioic acid (1:1.5) (**24**). *ee* = 97% (HPLC).

d) 24 (41.08 g, 0.04mol) and ethanol (80 mL) were stirred at 22 °C for 15 min. Concentrated aqueous ammonium hydroxide (12.0 mL) was added over 2 min, and the reaction mixture stirred at 25 °C for 1 h. Water (160 mL) was added at 25 °C over 10 min and the mixture heated to reflux and stirred at reflux for 1 h. The reaction mixture was then cooled to 20 °C and stirred for 16 h at this temperature. The product was filtered, washed with water (2 × 8 mL) and dried at 50 °C in vacuo to yield 16.87 g (86%) of **1**. Ethanol (265 mL) was added to **1** (19.9 g, 0.04mol) and the mixture warmed while stirring to reflux temperature (78 °C) and then stirred at reflux temperature for 15 min before cooling the solution to 75 °C. Activated carbon (1.0 g of Norit A Supra) was then added to the mixture which was stirred at reflux temperature for 1 h, filtered while warm and the filter then washed with warm ethanol (20 mL). The filtrate and wash solvent were combined (the product spontaneously crystallized at 48 °C), and the mixture warmed to reflux temperature and concentrated by removing 203 mL of ethanol. The resulting suspension was cooled to 22 °C, stirred at 22 °C for 18 h, cooled to 2 °C and stirred at 2 °C for a further 5 h. The precipitate was filtered, washed with ethanol (4 mL) and the product dried at 50 °C in vacuo to yield 17.25 g (86%) of R115777.

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