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SYNTHESIS AND STABILITY OF 3-HYDROXYANAGRELIDE, A BIOLOGICALLY POTENT METABOLITE OF ANAGRELIDE[#]

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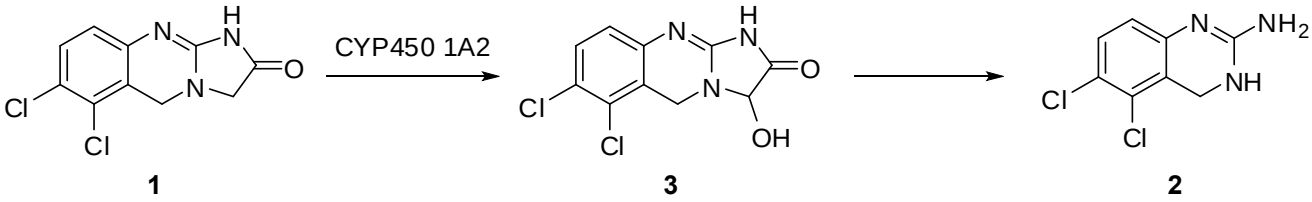
Abstract – Metabolism of 6,7-dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin-2-one (anagrelide), a drug for treating essential thrombocythemia, gives 6,7-dichloro-3-hydroxy-1,5-dihydroimidazo[2,1-*b*]quinazolin-2-one (3-hydroxy-anagrelide) and 2-amino-5,6-dichloro-3,4-dihydroquinazoline. To enable the properties of 3-hydroxyanagrelide to be fully evaluated, the racemic compound has been synthesized. In pH 7.4 aqueous buffer 3-hydroxyanagrelide readily equilibrates with an isomer, 6,7-dichloro-1-hydroxy-3,5-dihydroimidazo[1,2-*a*]-quinazolin-2-one, and is also hydrolyzed to 2-amino-5,6-dichloro-3,4-dihydro-quinazoline. 3-Hydroxyanagrelide (half-life 40 hours) was the dominant species at equilibrium and it was concluded that the equilibration and decomposition are sufficiently slow that published assays of 3-hydroxyanagrelide are reliable.

The myeloproliferative disorder essential thrombocythemia (ET) is characterized by an excess of platelets in peripheral blood.[1,2] The frequency of the disease is 2.5 per 10^5 person-years, with sufferers having a higher risk of adverse thrombotic and hemorrhagic events. Anagrelide (**1**, 6,7-dichloro-1,5-dihydroimidazo[2,1-*b*]quinazolin- 2-one) is a potent inhibitor of megakaryocytopoiesis[3-5] that is prescribed for the treatment of ET.[2,6,7] Anagrelide is a highly selective drug unlike the alternative agent hydroxyurea (hydroxycarbamide),[2,8] which causes DNA damage and has leukemogenic potential.

[#]Dedicated to Professor Ei-ichi Negishi, for his outstanding contributions to organometallic chemistry.



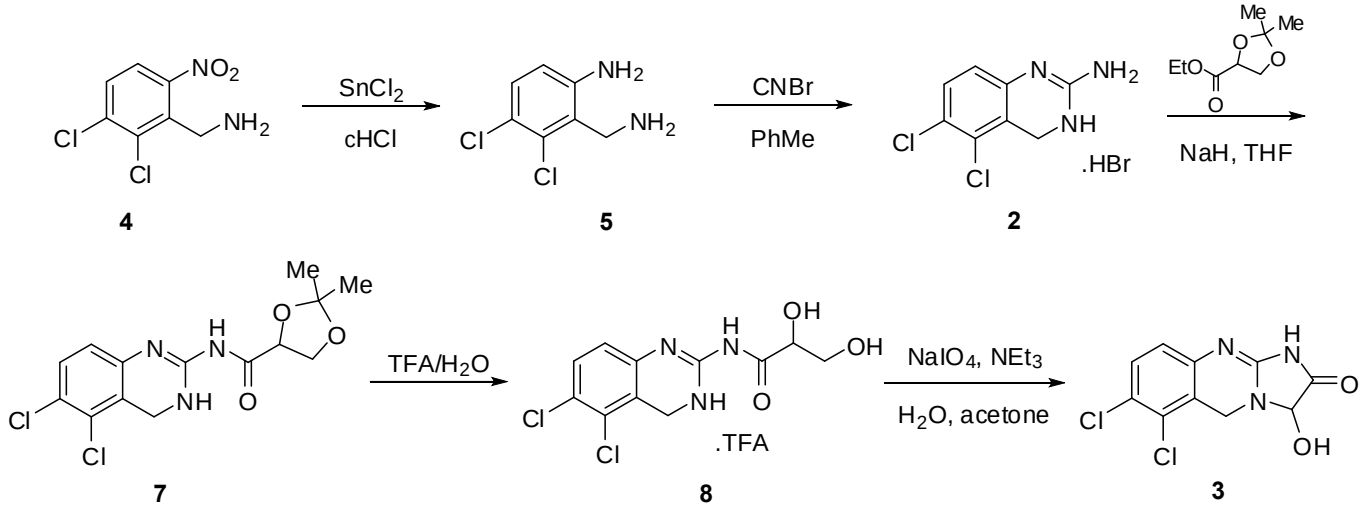
1 **3** **2**

Scheme 1. Metabolism of **1** to **3** and **2**

Studies of the metabolism of anagrelide **1** identified the metabolites 2-amino-5,6-dichloro-3,4-dihydroquinazoline **2** (RL 603) and the product of hydroxylation by cytochrome P450 1A2, 6,7-dichloro-3-hydroxy-1,5-dihydroimidazo[2,1-*b*]quinazolin-2-one (3-hydroxyanagrelide **3**).[9] The absolute configuration of metabolite **3**, assuming an excess of one enantiomer was formed, was not determined. Compound **2** probably results from the ring-opening and hydrolysis of **3** (Scheme 1). Inhibition of PDE-III by **3** is responsible for the undesirable cardiac side-effects of **1**.[2,10] Whilst **1** and **3** are similarly potent against megakaryocytopoiesis [IC_{50} values for inhibition of megakaryocytopoiesis: 27 nM (**1**); 48 nM (**3**)], the metabolite **3** is nearly 40-fold *more* potent against PDE-III [IC_{50} values for inhibition of PDE-III: 32 nM (**1**); 0.9 nM (**3**)].[9] Compound **2** has no effect on megakaryocytopoiesis and is only a weak inhibitor of PDE-III (IC_{50} 40 μM).

We have developed a reliable synthetic route (Scheme 2) to racemic **3**, which makes this biologically potent molecule readily available for the first time and enables a full determination of its pharmacological profile, in particular the activities against megakaryocyte maturation and PDE-III.[9] We show that compound **3** exhibits ring-chain tautomerism, which was not previously realized[9] and has important implications for its biological assay.

Reduction of the nitro group of 2,3-dichloro-6-nitrobenzylamine **4** with tin(II) chloride in hydrochloric acid was followed by condensation of aniline **5** with cyanogen bromide to yield **2**. Coupling of **2** with ethyl isopropylidene-glycerate **6**[11] gave acetal **7**, which was hydrolyzed with aqueous trifluoroacetic acid to diol **8**. Cleavage of diol **8** with sodium metaperiodate unmasked glyoxylic aldehyde **9**, which spontaneously cyclized to racemic 3-hydroxyanagrelide **3**. Such ring-chain tautomerism of amido-aldehydes has been previously described.[12] Despite many attempts the yield of pure, isolated **3** could never be raised above *ca*. 10%. The fundamental problem is that the cyclisation of the intermediate aldehyde **9** can proceed in two directions, with the formation of the isomer 6,7-dichloro-1-hydroxy-3,5-dihydroimidazo[1,2-*a*]quinazolin-2-one **10** being at least as favorable as **3**. Furthermore, both compounds are susceptible to hydrolysis to **2** *via* aldehyde **9**.



Scheme 2. Synthesis of **3**

The ^{1}H NMR spectrum of **3** showed an *AB* system for the benzylic methylene, indicative of an adjacent chiral center, which rules out the possibility that **3** exists in a ring-opened aldehyde **9** or aldehyde-hydrate form. The isomer **10** resulting from the alternative possible mode of ring-closure of intermediate aldehyde **9** (Scheme 3), was isolated during chromatographic purification of **3** and exhibited similar ^{1}H NMR and mass spectral data to **3**. The crystal structure of **10** confirmed its identity (Figure 1). Treatment of **10** with acetic anhydride in pyridine yielded the diacetate **11** (Scheme 3 and Figure 2).

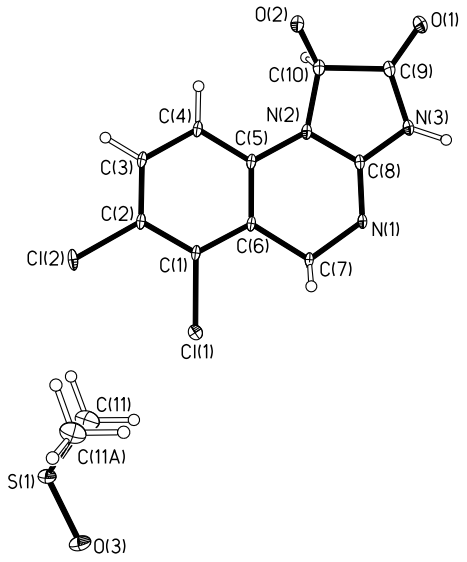


Figure 1. Molecular structure of **10** (1:1 DMSO solvate)

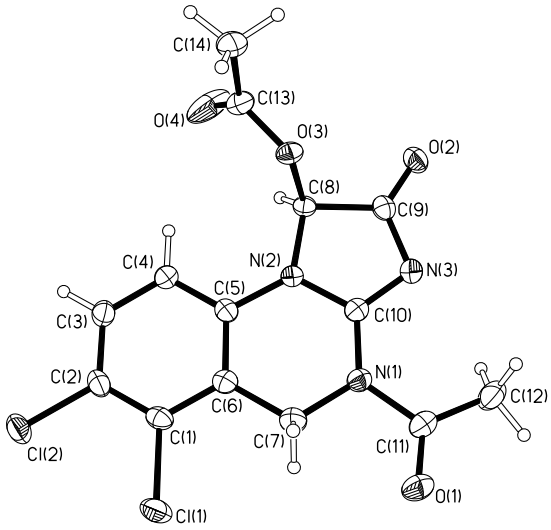
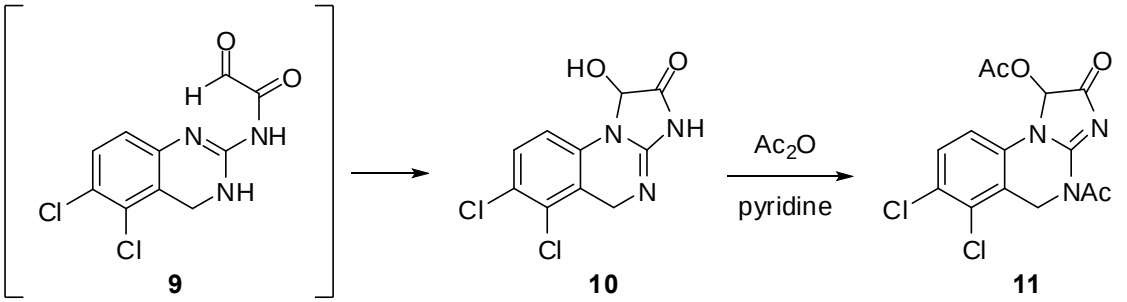


Figure 2. Molecular structure of **11**



Scheme 3. Formation of **10** and **11**

To determine if **3** was stable under the conditions and multi-day timespan of the megakaryocytopoiesis assay, the compound was incubated at 37 ºC in pH 7.4 buffer and analyzed by HPLC over the course of one week. Under these conditions the half-life of **3** was ca. 40 hours (Figure 3), with formation of mainly **2** and **10** (~ 10% of the concentration of **3**). Although **3** will decompose during the assay, it remains the dominant species and so the published[9] assays for **3** are reliable. When the stability of **10** was studied as described for **3**, after ca. 50 hours all three components (**2**, **3** and **10**) were present at similar concentrations, before both isomers were converted irreversibly into **2**. Hence, attempting to determine an IC_{50} value for inhibition of megakaryocytopoiesis by isomer **10** would not yield a valid result, as it would inevitably form a mixture with the highly potent **3** under the assay conditions.

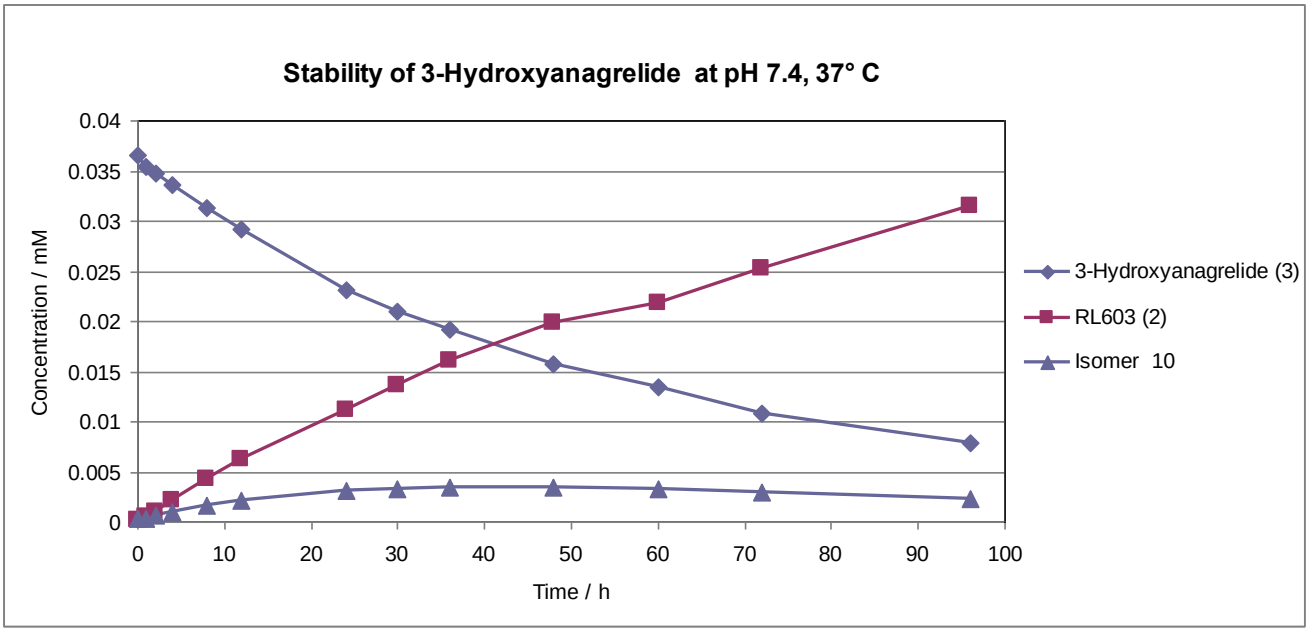


Figure 3. Equilibration of **3** with **10** and their decomposition to **2**

EXPERIMENTAL

Melting points were determined in glass capillaries and are uncorrected. NMR spectra were recorded on a Bruker spectrometer using residual solvent signals as reference. 2,3-Dichloro-6-nitrobenzylamine.HCl was purchased from Cambridge Major Laboratories. Other reagents and solvents were purchased from reputable suppliers. HPLC analyses were performed on a Shimadzu Prominence 20A instrument with diode array detection controlled by Shimadzu LCSolutions software. Solvent A was 0.5% trifluoroacetic acid in water. A linear gradient from 20 to 30% solvent B (acetonitrile) over 20 min was used [Phenomenex Luna C18 (2) column (250 × 4.6 mm, 10 μm particle size); temperature 37 °C; flow rate 1 mL min^{-1}; injection volume of 60 μL; detection wavelength 272 nm; sample concentration 0.005 mg mL^{-1} in pH 7.4 buffer containing 5% DMSO]. All time points were measured in triplicate.

6-Amino-2,3-dichlorobenzylamine 5: To a solution of tin(II) chloride dihydrate (87.6 g, 388 mmol) in conc. HCl (100 mL) was added portionwise a slurry of 2,3-dichloro-6-nitrobenzylamine hydrochloride **4** (20.0 g, 77.7 mmol) in conc. HCl (100 mL), keeping the temperature below 45 °C. The reaction mixture was heated at 45 °C for 2 h, then cooled to −5 °C and the resulting white solid collected using suction filtration. The solid was added to ice-water (100 mL) and the mixture basified (pH 12) with solid NaOH. CH_2Cl_2 (150 mL) was added and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (5 × 70 mL), and the organic extracts were combined and washed with water (5 × 70 mL), then dried ($MgSO_4$) and concentrated to yield the title compound as a yellow solid which was used without further purification (10.6 g, 72%). R_f 0.24 (EtOAc). δ_H (300 MHz; $CDCl_3$) 7.16 (d, J = 8.6 Hz, 1H, ArH), 6.55 (d, J = 8.6 Hz, 1H, ArH), 4.65 (br s, 2H, $ArNH_2$), 4.12 (s, 2H, CH_2), 1.38 (br s, 2H, NH_2). δ_C (75 MHz; $CDCl_3$) 146.7 (aromatic C-N), 132.6 (aromatic C-Cl), 129.4 (aromatic C-H), 125.8 (aromatic C-Cl), 122.0 (aromatic *C*-CH_2), 115.4 (aromatic C-H), 41.5 (benzylic C). *m/z* (EI) 190.0068 (M^+, 95%. $C_7H_8{}^{35}Cl_2N_2$ requires 190.0065), 173 (100), 146 (36).

2-Amino-5,6-dichloro-3,4-dihydroquinazoline. HBr 2: To a stirred solution of 6-amino-2,3-dichloro-benzylamine **5** (10.0 g, 52.4 mmol) in toluene (400 mL) was added dropwise a solution of cyanogen bromide (6.11 g, 57.6 mmol) in toluene (70 mL), forming a white precipitate. The mixture was stirred at room temperature for 1 h, at 75 °C for 30 min and finally at reflux for 1 h. The reaction mixture was allowed to cool to room temperature and was stirred overnight. The white precipitate was collected using suction filtration, washed with toluene then petrol, dissolved in MeOH and pre-absorbed onto silica. Medium pressure chromatography on silica (CH_2Cl_2 - MeOH - conc. aq. NH_3, 80 : 18 : 2) yielded the title compound as a white solid hydrobromide salt (7.1 g, 47%). δ_H (300 MHz; DMSO-d_6) 8.49 (br s, 1H, NH), 7.69 (br s, 2H, NH_2), 7.54 (d, J = 8.6 Hz, 1H, ArH), 6.99 (d, J = 8.6 Hz, 1H, ArH), 4.53 (s, 2H, CH_2). δ_C

(75 MHz; DMSO-d_6) 152.3 (guanidine C), 133.8 (aromatic C-N), 130.2 (aromatic C-H), 129.3 (aromatic C-Cl), 126.6 (aromatic C-Cl), 118.8 (aromatic *C*-C), 115.6 (aromatic C-H), 40.8 (benzylic C, obscured by solvent peak). *m/z* (EI) 215.0014 (organic cation M^+, 69%. $C_8H_7{}^{35}Cl_2N_3$ requires 215.0017), 214 (100), 197 (14), 174 (10). (Anal. Found: C, 32.10; H, 2.72; N, 13.99. $C_8H_8BrCl_2N_3$ requires C, 32.36; H, 2.72; N, 14.15).

Ethyl 2,3-isopropylidene-glycerate 6: To an ice-cooled, mechanically-stirred solution of 1,2-*O*-isopropylideneglycerol (18.8 mL, 20.0 g, 152 mmol) in water (800 mL) was added solid KOH (16.8g, 300 mmol) followed by solid $KMnO_4$ (34.0 g, 216 mmol) portionwise over 2 h. Stirring was continued overnight, and the resulting brown slurry was filtered under vacuum. The filter cake was washed with further water (2 × 100 mL) and the combined aqueous liquors decolorized with sodium metabisulfite and concentrated to dryness under vacuum at 50 °C. The resulting white residue was broken up with a spatula, suspended in anhydrous DMF (120 mL), treated with ethyl iodide (19.2 mL, 37.4 g, 240 mmol) and stirred overnight. The resulting opaque mixture was poured into water, extracted with ether (3 × 100 mL) and the combined organic layers washed with water (5 × 50 mL), dried ($MgSO_4$) and concentrated to yield the title compound as a colorless oil (10.8 g, 41%). δ_H (300 MHz; $CDCl_3$) 4.52 (dd, *J* = 8.0, 5.2 Hz, 1H, CH), 4.20 – 4.15 (m, 3H, OCH_2 + CH), 4.04 (dd, *J* = 8.0, 5.2 Hz, 1H, CH), 1.52 (s, 3H, CH_3) 1.42 (s, 3H, CH_3), 1.23 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$).

Isopropylidene-glyceric acid (5,6-dichloro-3,4-dihydroquinazolin-2-yl)amide 7: To a suspension of 2-amino-5,6-dichloro-3,4-dihydroquinazoline hydrobromide **2** (5.05 g, 17.0 mmol) in anhydrous THF (100 mL) under N_2 was added NaH (1.50 g of a 60 wt % dispersion, 37.4 mmol) and the mixture was heated at 50 °C for 30 min. After cooling to room temperature, ethyl 2,3-isopropylidene-glycerate **6** (3.15 g, 18.1 mmol) was added, and the mixture was stirred for 2 ½ days. The reaction was quenched with water and partitioned between water and EtOAc. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), silica (*ca*. 10 g) was added and the suspension was concentrated to dryness. Medium pressure chromatography on silica (EtOAc - petrol, 40 : 60 → 50 : 50) yielded the title compound as an off-white solid (3.20 g, 55%). An analytical sample was recrystallised from Et_2O - EtOAc. R_f 0.44 (EtOAc). δ_H (300 MHz; $CDCl_3$) 7.16 (d, *J* = 8.5 Hz, 1H, ArH), 6.61 (d, *J* = 8.5 Hz, 1H, ArH), 4.65 (s, 2H, benzylic CH_2), 4.47 (dd, *J* = 7.4, 5.4 Hz, 1H, CH), 4.22 (t, *J* = 8.0 Hz, 1H, CH), 4.06 (dd, *J* = 7.4, 5.4 Hz, 1H, CH), 1.45 (s, 3H, CH_3), 1.32 (s, 3H, CH_3). δ_C (75 MHz; $CDCl_3$) 177.7 (C=O), 152.3 (guanidine C), 139.6 (aromatic C-N), 130.2 (aromatic C-Cl), 129.9 (aromatic C-Cl), 127.4 (aromatic *C*-C), 119.8 (aromatic C-H), 119.4 (aromatic C-H), 111.9 (acetal C), 76.2 (CHO), 68.0 (CH_2O), 42.2 (benzylic C), 26.5 (CH_3), 25.6 (CH_3). *m/z* (EI) 343.0486 (M^+, 32%. $C_{14}H_{15}{}^{35}Cl_2N_3O_3$ requires 343.0491), 242 (83), 199 (100), 149 (90). (Anal. Found C, 48.77; H, 4.53; N,

12.19. $C_{14}H_{15}Cl_2N_3O_3$ requires C, 48.85; H, 4.39; N, 12.21). mp 154 – 156 °C.

5,6-Dichloro-2-(2,3-dihydroxypropionylamino)-3,4-dihydroquinazolinium trifluoroacetate 8: To a suspension of isopropylidene-glyceric acid (5,6-dichloro-3,4-dihydroquinazolin-2-yl)amide **7** (3.2 g, 9.3 mmol) in water (30 mL) was added trifluoroacetic acid until the mixture just clarified (~15 mL). The mixture was stirred for 1 h. The trifluoroacetic acid and water were removed under reduced pressure at 40 °C to leave a viscous orange oil. Trituration with THF induced crystallization of the product, and the suspension was left at 4 °C overnight to complete the crystallization. The product was collected by suction filtration to yield the title compound as an off-white solid (2.9 g, 74%). An analytical sample was recrystallized from EtOAc - MeOH. R_f 0.50 (EtOAc – MeOH, 9 : 1). δ_H (300 MHz; DMSO-d_6) 7.59 (d, J = 8.7 Hz, 1H, ArH), 7.07 (d, J = 8.7 Hz, 1H, ArH), 4.75 (s, 2H, benzylic CH_2), 4.24 (t, J = 3.5 Hz, 1H, C*H*OH), 3.67 (d, J = 3.5 Hz, 2H, CH_2OH). δ_C (75 MHz; DMSO-d_6) 176.1 (C=O), 159.1 (quartet, J = 33 Hz, $CF_3CO_2^-$), 149.0 (guanidine C), 132.8 (aromatic C-N), 130.4 (aromatic C-Cl), 129.3 (aromatic C-Cl), 127.8 (aromatic *C*-C), 118.9 (aromatic C-H), 117.1 (quartet, J = 295 Hz, CF_3), 116.8 (aromatic C-H), 73.4 (CHOH), 63.7 (CH_2OH), 41.9 (benzylic C). *m/z* (EI) 303.0159 (organic cation M^+, 11%. $C_{11}H_{11}{}^{35}Cl_2N_3O_3$ requires 303.0178), 242 (12), 214 (100) 199 (25). (Anal. found C, 37.28; H, 2.67; N, 9.89. $C_{13}H_{12}Cl_2F_3N_3O_5$ requires C, 37.34; H, 2.89; N, 10.05). mp 160 – 163 °C.

rac.-6,7-Dichloro-3-hydroxy-1,5-dihydroimidazo[2,1-*b*]quinazolin-2-one 3 and rac.-6,7-dichloro-1-hydroxy-3,5-dihydroimidazo[1,2-*a*]quinazolin-2-one 10: To a suspension of 5,6-dichloro-2-(2,3-dihydroxypropionylamino)-3,4-dihydroquinazolinium trifluoroacetate **8** (1.75g, 4.22 mmol) in acetone (50 mL) and water (10 mL) in an oversized flask was added $NaIO_4$ (1.81 g, 8.45 mmol) dissolved in water (10 mL) in one portion. After 5 min, triethylamine (0.56 mL, 404 mg, 4.0 mmol) was added dropwise (precipitation), and the mixture was vigorously stirred 1 h. Silica (~ 5 g) was added and the mixture was concentrated to dryness at 40 °C (caution, bumping) to leave the crude product pre-absorbed. This was subjected to medium pressure chromatography on silica (EtOAc – MeOH, 98 : 2 → 90 : 10 in 2% increments, then 90 : 10 → 80 : 20 in 5% increments). The fractions were analyzed by TLC (THF – MeOH, 9 : 1). The appropriate fractions were combined and concentrated, and the resulting samples of 3-hydroxyanagrelide **3** and isomer **10** were suspended in Et_2O – MeCN (3 : 1) with the aid of sonication, transferred by pipette onto filter papers in Buchner funnels, and washed sequentially with water, MeCN and Et_2O. Drying under high vacuum at 50 °C yielded the title compounds in yields of approximately 5 – 10% each.

3-Hydroxyanagrelide 3: δ_H (300 MHz; DMSO-d_6) 11.40 (broad s, 1H, NH), 7.47 (d, J = 8.7 Hz, 1H, ArH), 6.96 (d, J = 8.7 Hz, 1H, OH), 6.91 (d, J = 8.7 Hz, 1H, ArH), 5.01 (d, J = 8.7 Hz, 1H, C*H*OH), 4.58 + 4.47 (*AB* system, J = 14.6 Hz, 2H, benzylic CH_2). δ_C (75 MHz; DMSO-d_6) 177.1 (C=O), 157.0 (guanidine C),

140.2 (aromatic C-N), 130.0 (aromatic C-Cl), 129.5 (aromatic C-Cl), 125.3 (aromatic *C*-C), 120.4 (aromatic C-H), 120.1 (aromatic C-H), 81.3 (hemi-aminal C), 41.9 (benzylic C). *m/z* (EI) 270.9924 (M^+, 100 %. $C_{10}H_7{}^{35}Cl_2N_3O_2$ requires 270.9915), 214 (86), 199 (34). (Anal. Found C, 44.06; H, 2.44; N, 14.98. $C_{10}H_7Cl_2N_3O_2$ requires C, 44.14; H, 2.59; N, 15.44).

6,7-Dichloro-1-hydroxy-3,5-dihydroimidazo[1,2-*a*]quinazolin-2-one 10: δ_H (300 MHz; DMSO-d_6) 9.40 (s, 1H, NH), 7.59 (d, *J* = 8.8 Hz, 1H, ArH), 7.15 (d, *J* = 9.2 Hz, 1H, OH), 6.99 (d, *J* = 8.8 Hz, 1H, ArH), 5.38 (d, *J* = 9.2 Hz, 1H, C*H*OH), 4.62 + 4.56 (*AB* system, *J* = 16.8 Hz, 2H, benzylic CH_2). δ_C (75 MHz; DMSO-d_6) 182.9 (C=O), 163.0 (guanidine C), 134.0 (aromatic C-N), 129.97 (aromatic C-Cl), 129.3 (aromatic C-Cl), 125.2 (aromatic *C*-C), 118.9 (aromatic C-H), 113.1 (aromatic C-H), 79.9 (hemi-aminal C), 41.5 (benzylic C). *m/z* (EI) 270.9917 (M^+, 100%. $C_{10}H_7{}^{35}Cl_2N_3O_2$ requires 270.9915), 214 (87), 199 (35). (Anal. Found C, 39.97; H, 3.40; N, 13.85. $C_{10}H_7Cl_2N_3O_2$.1.5 H_2O requires C, 40.16; H, 3.37; N, 14.05).

Acetic acid 4-acetyl-6,7-dichloro-2-oxo-1,2,4,5-tetrahydroimidazo[1,2-*a*]quinazolin-1-yl ester 11: To a suspension of 6,7-dichloro-1-hydroxy-3,5-dihydro-imidazo[1,2-*a*]quinazolin-2-one **10** (50 mg, 0.18 mmol) in anhydrous pyridine (4 mL) under N_2 was added acetic anhydride (38 μL, 41 mg, 0.40 mmol) dropwise. The mixture was stirred overnight, then the solvent was evaporated and the residue suspended in THF with warming and sonication. Silica (*ca*. 1 g) was added and the suspension was concentrated by rotary evaporation to leave the crude product pre-absorbed. Medium pressure chromatography on silica (eluting with EtOAc) yielded the title compound as a white powder (30 mg, 47%). R_f 0.80 (EtOAc). δ_H (300 MHz; $CDCl_3$) 7.73 (d, *J* = 8.8 Hz, 1H, ArH), 6.93 (d, *J* = 8.8 Hz, 1H, ArH), 6.68 (s, 1H, CHOCO), 5.48 + 4.58 (*AB* system, *J* = 16.4 Hz, 2H, benzylic CH_2), 2.64 (s, 3H, CH_3CON), 2.16 (s, 3H, CH_3COO); δ_C (75 MHz; $CDCl_3$) 180.6 (O*C*OCH_3), 171.4 (C=O), 169.5 (N*C*OCH_3), 167.0 (guanidine C), 132.3 (aromatic C-N), 130.7 (aromatic C-Cl), 129.4 (aromatic C-Cl), 127.0 (aromatic *C*-C), 120.3 (aromatic C-H), 113.1 (aromatic C-H), 76.9 (aminal C), 42.2 (benzylic C), 27.2 (NCO*C*H_3), 20.7 (OCO*C*H_3). *m/z* (EI) 355.0137 (M^+, 15%. $C_{14}H_{11}{}^{35}Cl_2N_3O_4$ requires 355.0127), 312 (45), 270 (100), 242 (45), 43 (78). (Anal. found C, 47.51; H, 3.30; N, 11.33. $C_{14}H_{11}Cl_2N_3O_4$ requires C, 47.21; H, 3.11; N, 11.80).

Equilibration of 3 with 10: A sample of compound **3** (10 μL of a 0.1 mg mL^{-1} solution in DMSO diluted into 1 mL pH 7.4 phosphate buffer, giving a final concentration of 1 μg mL^{-1}, equivalent to the assay conditions), was incubated at 37 ºC and analyzed by HPLC over the course of 1 week. It was found that under these conditions 3-hydroxyanagrelide **3** had a half-life of approximately 40 hours (Figure 3) converting mainly to RL 603 **2** and giving only at most a very low, steady state-like concentration (ca. 0.1 μg mL^{-1}) of isomer **10**. A similar experiment was performed with isomer **10**.

X-Ray Crystallography. *Crystal data for* **10**: $C_{10}H_7Cl_2N_3O_2$ .C_2H_6OS, *M* = 350.2, orthorhombic, space group *Cmca*, *a* = 6.9482(19), *b* = 22.751(6), *c* = 18.326(5) Å, *V* = 2897.0(13) $Å^3$, *Z* = 8, *T* = 120 K; 11009

reflections measured, 1138 unique (R_{int} = 0.065), 141 parameters, R (F, $F^2 > 2\sigma$) = 0.143, R_w (F^2, all data) = 0.316, difference map features within ±0.90 e Å^{-3}. *Crystal data for* **11**: $C_{14}H_{11}Cl_2N_3O_4$, M = 356.2, monoclinic, space group $P2_1/c$, a = 7.6520(5), b = 22.443(2), c = 9.1383(5) Å, β = 107.087(4)°, V = 1500.08(18) Å^3, Z = 4, T = 150 K; 35724 reflections measured, 3417 unique (R_{int} = 0.034), 211 parameters, R (F, $F^2 > 2\sigma$) = 0.034, R_w (F^2, all data) = 0.094, difference map features within ±0.56 e Å^{-3}. Data were collected on Bruker SMART and Nonius KappaCCD diffractometers with synchrotron (λ = 0.6898 Å) and Mo *K*α radiation (λ = 0.71073 Å) for **10** and **11**, respectively. Standard programs (Bruker SMART and SAINT, Nonius COLLECT and EVALCCD, Bruker SADABS and SHELXTL) were used for data collection and processing, absorption corrections, structure solution and refinement. Whole-molecule disorder was resolved and refined for **10**, with the major component itself disordered across a crystallographic mirror plane and the minor components lying on each side of this plane; it is possible that this model is an approximation to an incommensurate structure, adequate for confirmation of the identity of the material. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre with numbers CCDC 689073 and 689074. Copies of data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (deposit@ccdc.com.ac.uk).

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