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Synthesis of a Hexahydro-2*H*-imidazo[4,5-*g*]isoquinolin-2-one Derivative as an Isostere of Catecholamine-based Selective Dopamine D-1 Antagonists

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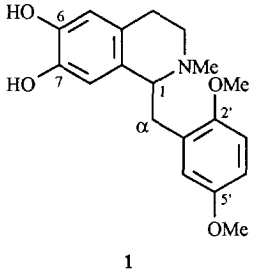
Abstract: The synthesis of the racemic hexahydro-2*H*-imidazo [4,5-*g*] isoquinolin-2-one **15** (BW2247W94), a 6,7-ureylene isostere of the 6,7-dihydroxy-tetrahydroisoquinoline **1** (BW32C73), has been achieved in ten stages from 4-nitrobenzyl cyanide **5**. The key step is a selective reduction of the nitrile **8** to the amine **9**, in the presence of nitro and carbamate functional groups.

During the course of a programme of work devoted to the development of centrally-acting dopamine antagonists as neuroleptic agents, 1-(2,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dihydroxy-2-methylisoquinoline (**1**, BW32C73) emerged as the lead compound, with selectivity for the D-1 receptor. This programme subsequently culminated in the discovery of *S*-**2** (BW737C89)[1] with a selectivity for the D-1 vs. D-2 receptor of ca. 260:1, [pK_i (D_1) = 9.5; pK_i (D_2) = 7.1]. In the search for analogues of **1**, concern was centred on the oral bioavailability and metabolic stability of **1** and in particular on the catecholamine moiety in relation to this. The literature contains several instances of the isosteric replacement of one or more catecholamine ring hydroxyls with a heterocyclic ring system. For example, indole-phenol isosteres have been exploited at α- and β-adrenoceptors[2] and dopamine receptors[3], whilst 2 (3*H*)-indolones[4] and carbostyril derivatives[5] have been investigated at dopamine receptors. In an attempt to prepare a novel metabolically stable analogue of **1**, which would preserve at least in part the hydrogen-bonding potential of the 6 and 7 hydroxyls in **1**, we considered the use of a imidazolin-2-one ring fused at positions 6 and 7 of **1**, as a replacement for the two hydroxyl groups.



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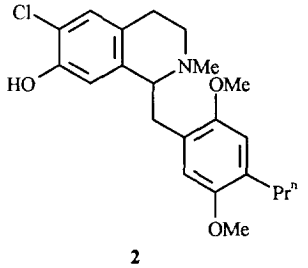

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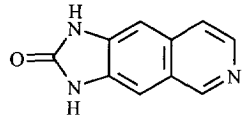
The synthesis of the racemic hexahydro-2*H*-imidazo[4,5-*g*]isoquinolin-2-one **15** (Scheme 1), the 6,7-ureylene analogue of **1**, therefore became the target for our work.



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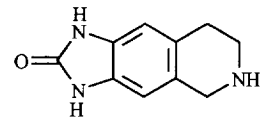

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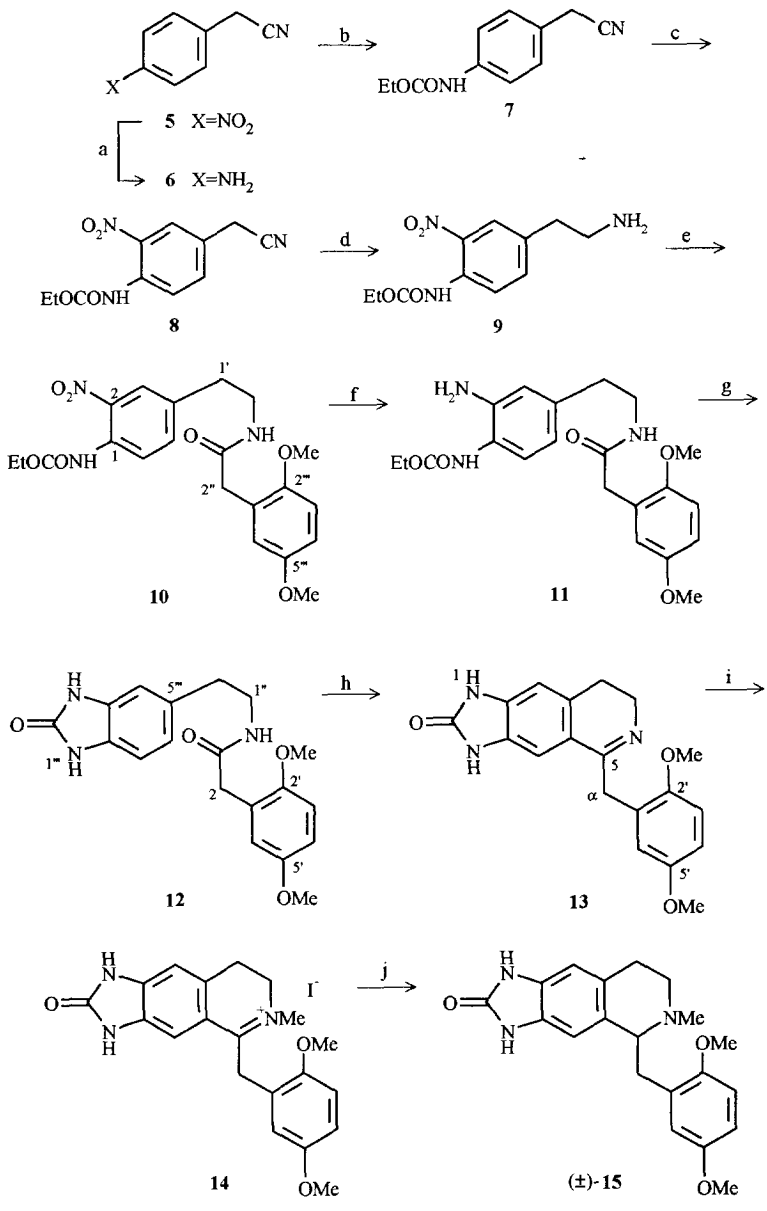
Although there is an extensive literature on imidazole, benzimidazoles and their 2-oxo-derivatives[6,7], as well as on isoquinolines[8,9], there appears to be no literature reference to the synthesis of 1,3-dihydro-2*H*-imidazo [4,5-*g*]isoquinolin-2-one **3** and 1,3,5,6,7,8-hexahydro-2*H*-imidazo[4,5-*g*]isoquinolin-2-one **4** or their derivatives[10,11]. The route which was finally evolved to **15** is shown in Scheme 1. 4-Nitrobenzyl cyanide (**5**)[12] was hydrogenated catalytically to 4-aminobenzyl cyanide (**6**)[13-15], which was acylated on the amino-group with ethyl chloroformate to give the carbamate **7**[16]. The carbamate was then nitrated in the 2-position to afford the nitro-carbamate **8**[17]. Initially, it had been planned to construct the imidazolin-2-one ring early on in the synthesis (Scheme 2). Thus, the nitro-group of carbamate **8** was hydrogenated catalytically to give the amino-carbamate **17**[15] which underwent as anticipated ring closure in refluxing acetic acid[18,19], to afford the 1,3-dihydro-2*H*-benzimidazol-2-one **18**. However, this latter compound proved to be extremely insoluble in the usual organic solvents (with the exception of DMF and DMSO). Although compound **18** was readily obtained and fully characterised by spectral and analytical data, it was not converted to an identifiable compound on reduction with Raney nickel in methanolic ammonia[20].

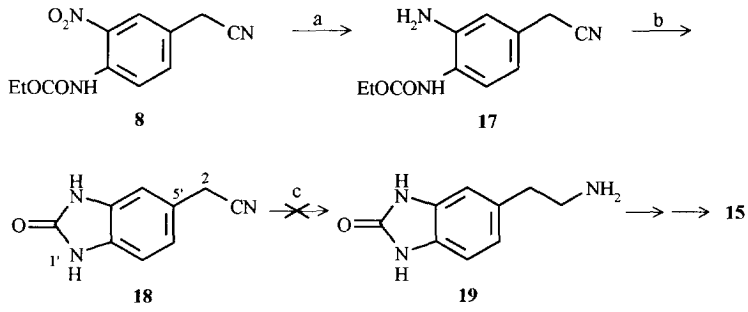
Instead of trying alternative means of reduction to give **19**, it was felt desirable to modify the synthesis at this stage, so as to keep the intermediates less polar and hence more soluble in organic solvents. It was therefore decided to proceed as in Scheme 1 in which the imidazolin-2-one ring is introduced after the introduction of the 2,5-dimethoxyphenylacetyl moiety. To this end, nitro-carbamate **8** was converted to the nitro-amine **9**. This required the selective reduction of the cyano-group in the presence of nitro and carbamate functional groups, and was achieved by the use of sodium (trifluoroacetoxy) borohydride prepared *in situ* in THF from sodium borohydride and trifluoroacetic acid[21]. The resultant amine **9** was then coupled with 2,5-dimethoxyphenylacetyl chloride[22,23] to yield the amide **10**[24]. Reduction of the nitro-group in **10** afforded the corresponding amino-carbamate **11**[15]. This underwent imidazolin-2-one ring formation in refluxing acetic acid to give the 1,3-dihydro-2*H*-benzimidazol-2-one[18,19] **12**. It remained to complete the synthesis of the 1,3,7,8-tetrahydro-2*H*-imidazo[4,5-*g*]isoquinolin-2-one ring system of compound **13** and this was achieved when amide **12** was subjected to a Bischler-Napieralski cyclisation in phosphoryl chloride at reflux[24,25]. Quaternisation of the base **13** with iodomethane in butanone then gave the dihydro-isoquinolinium iodide **14**[25], which was reduced with sodium borohydride in aqueous solution to the target 6,7-ureylene-tetrahydroisoquinoline **15**[25]. The latter was purified as its hydrochloride salt. The synthesis of **15** according to Scheme 1 thus constitutes a route to a dialkyl derivative of the 1,3,5,6,7,8-hexahydro-2*H*-imidazo[4,5-*g*]isoquinolin-2-one system in ten stages from **5**.

Pharmacological examination of compound **15** was carried out in the dopamine D-1 and D-2 receptor binding assays. Whilst the compound is somewhat less active than **2**, it is nevertheless a selective D-1 antagonist [pK_i (D_1) = 5.78, pK_i (D_2) = 3.30; D_1/D_2 selectivity = ca. 290:1].



Reagents: (a) H_2, Pd-C, MeOH; (b) EtOCOCl, Et_3N, $CHCl_3$; (c) fuming HNO_3, Ac_2O; (d) $NaBH_3(OCOCF_3)$, THF; (e) 2,5-$(MeO)_2C_6H_3COCl$ (**16**), Et_3N, $CHCl_3$; (f) H_2, Pd-C, MeOH; (g) HOAc, reflux; (h) $POCl_3$, reflux; (i) MeI, butanone; (j) $NaBH_4$, H_2O

Scheme 1



Reagents: (a) H_2, Pd-C, MeOH; (b) HOAc, reflux; (c) H_2, Ra-Ni, MeOH-NH_3

Scheme 2

EXPERIMENTAL

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. ^{1}H-NMR spectra were run on Bruker AC 200 (200MHz) and AMX 360 (360MHz) spectrometers. Chemical shifts are stated in ppm downfield from TMS (δ = o). IR spectra were obtained on films or KBr discs between NaCl plates on a Perkin-Elmer 157G spectrometer. Low resolution mass spectra were recorded on a Concept IS instrument operating at 70 eV; accurate mass measurements were obtained on the same instrument at 10,000 resolution with perfluorokerosine as a reference standard. Tlc was carried out on Merck pre-coated plates, 0.25 mm thick, 20 cm x 5 cm (silica gel 60 F_{254}, Art.5714 and aluminium oxide 60 F_{254}, Art.5731). Plates were run over 10 cm and spots visualised by UV at 254 nm. Column chromatography was performed on Merck silica gel 60 (70-230 mesh, Art.7734) and Merck aluminium oxide 90 active neutral (70-230 mesh, Art.1077). Solvents were evaporated at water-pump vacuum using a Büchi evaporator at ≤30°C unless otherwise stated. Solid samples were routinely dried at 0.2-0.5 mmHg, whilst analytical samples were dried *in vacuo* at 60-80°C as appropriate. Chloroform was dried by distillation from phosphorus pentoxide. THF was pre-dried over sodium wire and then distilled from LAH. Benzene was dried over sodium wire.

4-Aminobenzyl cyanide (6)

4-Nitrobenzyl cyanide (71.8 g; 0.438 mol) in methanol (1.1 L) was hydrogenated in the presence of 10% Pd-C catalyst (7.1 g) at 50-100 atm H_2, at rt with stirring. The mixture was filtered through Hyflo and evaporated *in vacuo* to give a brown oil which was further purified by column chromatography on silica (column 50 cm x 7 cm) with methanol-benzene (1:9) as the eluent. Removal of the solvent from the appropriate fractions gave **6** as an off-white crystalline solid. Yield 44.5 g (76.0%). M.p. 43-44°C (lit.[13] m.p. 46°C). R_f 0.58 (silica; MeOH:PhH = 1:9). ^{1}H NMR ($CDCl_3$, 200MHz) δ : 3.62 (2H, s, CH_2CN), 3.72 (2H, br.s, NH_2), 6.67 (2H, m, H-3, H-5) and 7.09 (2H, m, H-2, H-6). IR (KBr) : 3446, 3360, 2954, 2246, 1628, 1515, 1280 cm^{-1}. MS m/z 132 (M).

Ethyl *N*-(4-cyanomethyl)carbamate (7)

Ethyl chloroformate (36.3 g; 0.335 mol) in dry chloroform (200 ml) was added at 0-5°C with vigorous stirring to a solution of 4-aminobenzyl cyanide (**6**) (45.0 g; 0.340 mol) and triethylamine (34.0 g; 0.336 mol) in the same solvent (700 ml) under dry N_2, over 20 min with cooling. After 1h further, the mixture was warmed to rt and left overnight to give an homogenous mixture. The solution was then washed with 2N H_2SO_4 (400 ml), water (100 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a yellow solid (48.3 g), which was purified further by chromatography on silica (column 60 cm x 6 cm) with chloroform as the eluent. Yield 41.6 g (59.8%). M.p. 82-83°C. R_f 0.29 (silica; EtOAc:$CHCl_3$ = 1:20) ^{1}HNMR ($CDCl_3$, 200MHz) δ:1.30 (3H, t, J = 7.0Hz, CH_3CH_2O), 3.69 (2H, s, CH_2CN), 4.22 (2H, q, J = 7.0Hz, CH_3CH_2O), 6.84 (1H, br.s, N*H*CO), 7.18-7.28 (2H, m, H-3, H-5) and 7.35-7.45 (2H, m, H-2, H-6). IR (KBr) : 3300, 2979, 2248, 1708, 1596, 1529, 1411, 1314, 1227 cm^{-1}. MS m/z : 204 (M). Anal. $C_{11}H_{12}N_2O_2$ requires C, 64.69; H, 5.92; N, 13.72. Found C, 64.71; H, 5.78; N, 13.75.

Ethyl *N*-(4-cyanomethyl-2-nitrophenyl)carbamate (8)

Fuming nitric acid (19.3 g; 0.306 mol) was added dropwise to acetic anhydride (37.2 g; 0.364 mol) at ca. 10°C with stirring. To this mixture was added ethyl *N*-(4-cyanomethylphenyl)carbamate (**7**) (36.4 g; 0.178 mol) as a dry powder at 5°C. The mixture was then stirred at 5-10°C for 2h, allowed to warm to rt and poured into ice-water (1 kg). The mixture was extracted with dichloromethane (3 x 300 ml) and the combined organic extracts washed with water (2 x 600 ml), sodium bicarbonate solution (10%; 400 ml), dried (Na_2SO_4) and evaporated *in vacuo*. The resultant solid (43.1 g) was purified further by chromatography on silica (column 60 cm x 7 cm) with chloroform as the eluent to give **8** as a bright yellow solid. Yield 30.4 g (68.4%). M.p. 80-81°C. R_f 0.40 (silica; EtOAc:$CHCl_3$ = 1:20). ^{1}HNMR ($CDCl_3$, 200MHz) δ:1.36 (3H, t, J = 7.1Hz, CH_3CH_2O), 3.79 (2H, s, CH_2CN), 4.29 (2H, q, J = 7.1Hz, CH_3CH_2O), 7.61 (1H, dd, J = 8.8Hz, J = 2.3Hz, H-5), 8.20 (1H, d, J = 2.3Hz, H-3), 8.65 (1H, d, J = 8.8Hz, H-6), 9.81 (1H, br.s, N*H*CO). IR (KBr) : 3346, 2970, 2244, 1772, 1625, 1579, 1511, 1440, 1344 cm^{-1}. MS m/z 249 (M). Anal. $C_{11}H_{11}N_3O_4$ requires C, 53.01; H, 4.45; N, 16.86. Found C, 52.91; H, 4.50; N, 16.91.

Ethyl *N*-[4-(2-aminoethyl)-2-nitrophenyl]carbamate (9)

To a stirred suspension of sodium borohydride (9.50 g; 0.251 mol) in dry THF (150 ml) at 20°C was added dropwise a solution of trifluoroacetic acid (28.5 g; 0.250 ml) in the same solvent (30 ml) over 1h, with external cooling. At the end of this period, the mixture consisted of a white solid suspended on a colourless liquid. Ethyl *N*-(4-cyanomethyl-2-nitrophenyl)carbamate (**8**) (12.5 g; 50.1 mmol) in dry THF (30 ml) was then added with stirring at 20°C over 30 min. The mixture was stirred at rt for 4h to give a deep yellow-brown mixture, which was *cautiously* decomposed by the addition of water (300 ml) at 10°C. The mixture was transferred to a 1 L flask and evaporated *in vacuo* (37°C) to one phase which was partitioned between dichloromethane (3 x 300 ml) and water (300 ml). The combined organic phase was washed with sodium chloride solution (sat., 200 ml), dried (Na_2SO_4) and evaporated to yield the amine **9** as a thick dark-brown oil which was used without further purification. Yield: 9.32 g (73.4%). R_f 0.26 (alumina, MeOH-CH_2Cl_2, 2:3) . ^{1}HNMR ($CDCl_3$, 200MHz) δ:1.34 (3H, t, J = 7.1Hz, CH_3CH_2O), 2.15 (2H, br.s, $CH_2CH_2NH_2$), 2.80 (2H, t, J = 7.0Hz, $CH_2CH_2NH_2$), 3.02 (2H, t, J = 7.0Hz, $CH_2CH_2NH_2$), 4.26 (2H, q, J = 7.1Hz, CH_3CH_2O), 7.48 (1H,

dd, J = 1.9Hz, J = 8.7Hz, H-5), 8.0 (1H, d, J = 1.9Hz, H-3), 8.46 (1H, d, J = 8.7Hz, H-6), 9.70 (1H, br.s, N*H*COO). IR (film) : 3370, 2936, 1736, 1628, 1578, 1519, 1450, 1340 cm^{-1}. MS m/z : 253 (M). Accurate MS on M : 253.1074; $C_{11}H_{15}N_3O_4$ requires 253.1063. The compound was analysed as the hydrochloride. The free base **9** (3.74 g) was purified further by flash chromatography on alumina (column 20 cm x 6 cm) with dichloromethane-methanol (97.5 : 2.5) as eluent. Purified base in dichloromethane was treated with hydrogen chloride in diethyl ether, the solvent removed *in vacuo* and the residue crystallised from ethanol-diisopropyl ether (1:1) to give the hydrochloride of **9** as a light-yellow powder. M.p. 200-203°C (sinters >185°C). R_f 0.74 (silica; Bu^nOH:EtOAc:HOAc:H_2O = 1:1:1:1). Anal. $C_{11}H_{15}N_3O_4$.HCl requires C, 45.60; H, 5.57; N, 14.50. Found C, 45.17; H, 5.56; N, 14.30.

Ethyl *N*-[4-[2-(2,5-dimethoxyphenylacetamido)ethyl]-2-nitrophenyl]carbamate (10)

A solution of (2,5-dimethoxyphenyl)acetyl chloride (**16**) (6.25 g; 29.1 mmol) in dry chloroform (25 ml) was added with stirring to a solution of ethyl *N*-[4-(2-aminoethyl)-2-nitrophenyl]carbamate (**9**) (7.40 g; 29.2 mmol) and triethylamine (3.40 g; 33.6 mmol) in the same solvent (50 ml) over 20 min at -10°C. The mixture was kept at rt for 0.5h and at -20°C overnight. It was then diluted with more chloroform (100 ml), washed with water (4 x 100 ml), dried (Na_2SO_4) and evaporated *in vacuo* to give a brown sticky solid (11.76 g) which was purified by trituration with ethyl acetate and chromatography on silica (column 30 cm x 7 cm) with ethyl acetate-chloroform (1:1) as the eluent to afford the carbamate **10** as a bright yellow solid. Yield 6.08 g (48.2%). M.p. 143-146.5°C. R_f 0.62 (silica, EtOAc). ^{1}HNMR ($CDCl_3$, 200MHz) δ:1.36 (3H, t, J = 7.2Hz, C*H*$_3$CH$_2$O), 2.75 (2H, t, J = 6.5Hz, C*H*$_2$CH$_2$NH), 3.46 (2H, q, J = 6.5Hz, CH$_2$C*H*$_2$NH), 3.48 (2H, s, C*H*$_2$CONH), 3.72 (3H, s, MeO), 3.74 (3H, s, MeO), 4.28 (2H, q, J = 7.2Hz, CH$_3$C*H*$_2$O), 5.82 (1H, br.t, N*H*COCH$_2$), 6.76 (3H, m, H-3‴, H-4‴, H-6‴), 7.29 (1H, dd, J = 2.1Hz, J = 8.7Hz, H-5), 7.87 (1H, d, J = 2.1Hz, H-3), 8.41 (1H, d, J = 8.7Hz, H-6), 9.71 (1H, br.s, N*H*COO). IR (KBr) : 3367, 3300, 3068, 2918, 1727, 1646, 1580, 1528 cm^{-1}. MS m/z : 431 (M). Anal. $C_{21}H_{25}N_3O_7$ requires C, 58.46; H, 5.84; N, 9.74. Found C, 58.68; H, 5.97; N, 10.04.

Ethyl *N*-[2-amino-4-[2-(2,5-dimethoxyphenylacetamido)ethyl]phenyl]carbamate (11)

Ethyl *N*-[4-[2-(2,5-dimethoxyphenylacetamido)ethyl]-2-nitrophenyl]-carbamate (**10**) (6.20 g; 14.4 mmol) in ethanol (120 ml) was hydrogenated at ca 13 atm pressure in the presence of 10% Pd-C catalyst (0.24 g) at rt for 12h. The mixture was filtered through Hyflo and evaporated *in vacuo* (40°C) to give the amino-carbamate **11** as a yellow solid. Yield 5.72 g (99.2%). M.p. 154-157°C. R_f 0.31 (silica; EtOAc). ^{1}HNMR ($CDCl_3$, 200MHz) δ:1.31 (3H, t, J = 7.1Hz, C*H*$_3$CH$_2$O), 2.60 (2H, t, J = 6.5Hz, C*H*$_2$CH$_2$NH), 3.41 (2H, q, J = 6.5Hz, CH$_2$C*H*$_2$NH), 3.49 (2H, s, C*H*$_2$CONH), 3.67 (3H, s, MeO), 3.69 (2H, br.s, N*H*$_2$), 3.76 (3H, s, MeO), 4.22 (2H, q, J = 7.1Hz, CH$_3$C*H*$_2$O), 5.86 (1H, br.t, CH$_2$CH$_2$N*H*), 6.26 (1H br.s, OCON*H*), 6.43 (1H, d, J = 2.0Hz, H-3), 6.45 (1H, dd, J = 2.0Hz, J = 7.8Hz, H-5), 6.79 (3H, m, H-3‴, H-4‴, H-6‴), 7.11 (1H, d, J = 7.8Hz, H-6). IR (KBr) : 3436, 3363, 3304, 1687, 1648, 1537, 1505, 1259, 1224 cm^{-1}. MS m/z : 401 (M). Anal. $C_{21}H_{27}N_3O_5$ requires C, 62.82; H, 6.78; N, 10.47. Found C, 62.47; H, 6.52; N, 10.05.

N-[2-(1,3-dihydro-2-oxo-2*H*-benzimidazol-5-yl)ethyl]-1-(2,5-dimethoxyphenyl)acetamide (12)

Ethyl *N*-[2-amino-4-[2-(2,5-dimethoxyphenylacetamido)ethyl]phenyl]-carbamate (**11**) (12.0 g : 29.9 mmol) was dissolved in acetic acid (1.2 L) and heated under reflux for 9h; the process was repeated with a further batch (12.0 g) of the starting material. Both reaction mixtures were then combined, the solvent removed *in vacuo* (Büchi, 40°C) and the residue washed in turn with ethanol (2 x 200 ml) and diethyl ether (2 x 200 ml). The resultant pink solid was crystallised from hot ethanol (100ml) to give an off-white solid (24.1 g), which was further purified by recrystallisation from ethanol-diisopropyl ether (150 ml, 2:1) to give the amide **12** (11.1 g), m.p. 195-196°C. A further amount of the product (3.54 g), m.p. 197-198°C, was obtained from the mother liquors by chromatography on silica (column 60 cm x 6 cm) with ethanol-chloroform (1:9) as eluent, followed by recrystallisation from ethanol-diisopropyl ether (110ml, 5:6). Total yield 14.7 g (69.2%). R_f 0.36 (silica; MeOH:$CHCl_3$ = 1:9). ^{1}HNMR (DMSO-d_6, 200MHz) δ:2.67 (2H, t, J = 7.5Hz, C*H*$_2$CH$_2$NH), 3.25 (2H, m, CH$_2$C*H*$_2$NH), 3.34 (2H, s, C*H*$_2$CONH), 3.67 (3H, s, MeO), 3.68 (3H, s, MeO), 6.70-6.78 (4H, m, H-4', H-6', H-4''', H-6'''), 6.81 (1H, d, J = 7.8Hz, H-7'''), 6.86 (1H, m, H-3'), 7.66 (1H, t, J = 5.4Hz, CH$_2$CH$_2$N*H*), 10.40 (1H, br.s, N*H*CONH), 10.43 (1H, br.s, NHCON*H*). IR (KBr) : 3600-2560, 1702, 1648, 1500, 1279, 1227, 1045, 1022 cm^{-1}. MS m/z : 355 (M). Anal. $C_{19}H_{21}N_3O_4$ requires C, 64.14; H, 5.96; N, 11.82. Found C, 64.17; H, 6.02; N, 11.73.

5-(2,5-Dimethoxybenzyl)-1,3,7,8-tetrahydro-2-oxo-2*H*-imidazo[4,5-*g*]isoquinolin-2-one (13)

A mixture of *N*-[2-(1,3-dihydro-2-oxo-2*H*-benzimidazol-5-yl)ethyl]-1-(2,5-dimethoxyphenyl)acetamide (**12**) (1.68 g; 4.73 mmol) and phosphoryl chloride (400 ml) was heated quickly to 70°C with exclusion of moisture (silica guard tube). After keeping at 70°C for 40 min with vigorous swirling, the initial solid formed a brown oil which subsequently formed a solid suspended in the liquid. The reaction mixture was then evaporated (Büchi, 40°C) and the residue dried *in vacuo* to give a yellow solid. This was added to ice-cold water (200 ml) with additional external cooling and the mixture basified to pH 12 with 0.880 ammonia solution (ca 15 ml). The solid which precipitated was filtered off and dried *in vacuo* (0.01 mmHg) over phosphorus pentoxide to give the dihydro-isoquinoline **13**. Yield 1.50 g (94.0%). M.p. >134°C contracts; 172°C decomposes. R_f 0.71 (silica; Bu^{n}OH:EtOAc:HOAc:H_2O = 1:1:1:1). ^{1}HNMR (DMSO-d_6, 200MHz) δ: 2.61 (2H, m ≃ t, J = 7.5Hz, C*H*$_2$CH$_2$N), 3.52 (2H, m ≃ t, J = 7.5Hz, CH$_2$C*H*$_2$N), 3.60 (3H, s, MeO), 3.79(3H, s, MeO), 3.85 and 3.88 (2H, 2s in ratio 1:2, α-C*H*$_2$), 6.62 (1H, d, J = 3.1Hz, H-6'), 6.72 (1H, dd, J = 3.1Hz, J = 8.8Hz, H-4'), 6.77 (1H, s, H-9), 6.90 (1H, d, J = 8.8Hz, H-3'), 7.01 (1H, s, H-4), 10.56 (1H, br.s, N*H*CONH), 10.69 (1H br.s, NHCON*H*). IR (KBr). 3700-2500, 1704, 1629, 1590, 1497, 1297, 1224 cm^{-1}. MS m/z : 337 (M). Accurate MS on M : 337.1406; $C_{19}H_{19}N_3O_3$ requires 337.1426. The compound was analysed as the hydrochloride. The free base **13** was dissolved in chloroform-ethanol (10:1) and treated with a solution of hydrogen chloride in diethyl ether. The crude hydrochloride was purified by recrystallisation from methanol-diisopropyl ether (2:5) to give the hydrochloride of **13** as a yellow solid. M.p. 314°C (decomp.). R_f 0.71 (silica; Bu^{n}OH:EtOAc:HOAc:H_2O = 1:1:1:1). Anal. $C_{19}H_{19}N_3O_3$. 1.2HCl requires C, 59.88; H, 5.34; N, 11.02. Found C, 60.14; H, 5.32; N, 10.82.

5-(2,5-Dimethoxybenzyl)-1,3,7,8-tetrahydro-6-methyl-2-oxo-2*H*-imidazo[4,5-*g*]-isoquinolinium iodide (14)

A mixture of 5-(2,5-dimethoxybenzyl)-1,3,7,8-tetrahydro-2*H*-imidazo[4,5-*g*]-isoquinolin-2-one (**13**) (0.310 g; 0.919 mmol) and iodomethane (1.0 ml ≡ 1.53 g, 10.8 mmol) was heated in butanone (5 ml) under reflux at 50°C for 1.5h. Solid material was scraped down and heating continued for a further 2h. The mixture was cooled, evaporated *in vacuo* and the residue treated with diethyl ether to give a yellow solid which was recrystallised from methanol-diisopropyl ether (40 ml, 3:5) to yield the dihydroisoquinolinium iodide **14**. Yield 0.27 g (58.0%). M.p. 232-234°C. R_f 0.62 (silica, Bu^{n}OH:EtOAc:HOAc:H_2O = 1:1:1:1). ^{1}HNMR (DMSO-d_6, 200MHz) δ: 3.11 (2H, t, J = 7.5Hz, $CH_2CH_2N^+Me$), 3.68 and 3.73 (3H, s and 6H, s, 2 x MeO, MeN), 4.05 (2H, t, J = 1.5Hz, $CH_2CH_2N^+Me$), 4.48 (2H, s, α-CH_2), 6.78 (1H, d, J = 3.0Hz, H-6'), 6.83 (1H, dd, J = 3.0Hz, J = 8.8Hz, H-4'), 6.96 (1H, d, J = 8.8Hz, H-3'), 7.00 (1H, s, H-9), 7.40 (1H, s, H-4), 10.99 (1H, br.s, N*H*CONH), 11.38 (NHCON*H*). IR (KBr) : 3610, 3488, 3300-2500, 1704, 1630, 1600, 1507, 1435 cm^{-1}. MS m/z : 352 (M). Accurate MS on M 352.1619. $C_{20}H_{22}N_3O_3$ requires 352.1661. Anal. $C_{20}H_{22}N_3O_3I$. 1.5H_2O requires C, 47.44; H, 4.97; N, 8.29. Found C, 47.52; H, 4.75; N, 8.21.

5-(2,5-Dimethoxybenzyl)-1,3,5,6,7,8-hexahydro-6-methyl-2*H*-imidazo[4,5-*g*]-isoquinolin-2-one (15)

5-(2,5-dimethoxybenzyl)-1,3,7,8-tetrahydro-6-methyl-2-oxo-2*H*-imidazo[4,5-*g*]isoquinolinium iodide (**14**) (0.198 g; 0.391 mmol) was dissolved in water (10 ml) with warming. Sodium borohydride (0.100 g; 2.64 mmol) in water (5 ml) was then added to the solution at rt. The yellow colour of the dihydroisoquinolinium salt immediately disappeared and an off-white solid precipitated. After 2h, the solid was filtered off and dried *in vacuo* to give the tetrahydroisoquinoline **15**. Yield 0.107 g (77.4%). M.p. 126-128°C (sinters 115-120°C). R_f 0.65 (silica; Bu^{n}OH:EtOAc:HOAc:H_2O = 1:1:1:1). ^{1}HNMR ($CDCl_3$, 360MHz) δ: 2.50 (3H, s, NMe), 2.68-2.81 (2H, m, H-7 and H-8), 2.78 (1H, dd, J = 13.5Hz, J = 7.1Hz, α-C*H*), 2.92-3.01 (1H, m, H-7 or H-8), 3.13 (1H, dd, J = 13.5Hz, J = 5.8Hz, α-C*H*), 3.21-3.29 (1H, m, H-8 or H-7), 3.69 (3H, s, MeO), 3.73 (3H, s, MeO), 3.86 (1H, t, J = 6.5Hz, H-5), 6.26 (1H, s, H-4), 6.58 (1H, d, J = 3.0Hz, H-6'), 6.71 (1H, dd, J = 3.0Hz, J = 8.8Hz, H-4'), 6.72 (1H, s, H-9), 6.77 (1H, d, J = 8.8Hz, H-3'), 7.44 (1H, br.s, N*H*CONH), 7.65 (1H, br.s, NHCON*H*). IR (KBr) : 3660-2220, 1697, 1490, 1221 cm^{-1}. MS m/z : 353 (M). Accurate MS on M : 353.1704; $C_{20}H_{23}N_3O_3$ requires 353.1739. The compound was analysed as the hydrochloride. The free base was dissolved in chloroform, the solution filtered, treated with hydrogen chloride in diethyl ether and the white precipatate filtered off; it was recrystallised from ethanol-diisopropyl ether (1:2) to give the hydrochloride of **15**. M.p. 258-260°C (>190°decomp.). R_f 0.65 (silica; Bu^{n}OH:EtOAc:HOAc:H_2O = 1:1:1:1). Anal. $C_{20}H_{23}N_3O_3$. HCl. 1.5H_2O requires C, 57.61; H, 6.52; N, 10.08. Found C, 57.97; H, 6.34; N, 9.75.

2,5-Dimethoxyphenylacetyl chloride (16)

A mixture of (2,5-dimethoxyphenylacetic acid (49.5 g; 0.253 mol) and phosphorus pentachloride (55.0 g; 0.264 mol) was heated in dry benzene (600 ml) for 2h at 60°C until the evolution of hydrogen chloride had ceased. The mixture was filtered and the solvent removed *in vacuo* to give the acid chloride as a reddish liquid. Yield 54.2g (100%). ^{1}HNMR ($CDCl_3$, 200MHz) δ: 3.77 (3H, s, OMe), 3.79 (3H, s, OMe), 4.10 (2H, s, CH_2COCl), 6.73-6.85 (3H, m, H-3', H-4', H-6'). IR (film): 3004, 2956, 2838, 1805, 1595, 1503, 1235, 1048 cm^{-1}. MS m/z : 216 (MHz), 214 (M).

Ethyl *N*-(2-amino-4-cyanomethylphenyl)carbamate (17)

Ethyl *N*-(4-cyanomethyl-2-nitrophenyl)carbamate (**8**) (36.6 g; 0.146 mol) in ethanol (1.25 L) was hydrogenated under pressure (initially 20 atm H_2) for 4h at rt in the presence of 10% Pd-C catalyst (1.7 g) until the theoretical amount of hydrogen had been taken up. The mixture was filtered through Hyflo and the solvent removed *in vacuo* to give the amino-carbamate **17** as a yellow solid. Yield 32.2 g (100%). M.p. 74-77°C. R_f 0.86 (silica; EtOAc). ^{1}HNMR ($CDCl_3$, 200MHz) δ: 1.31 (3H, t, J = 7.0Hz, CH_3CH_2O), 3.64 (2H, s, CH_2CN), 3.82 (2H, br.s, NH_2), 4.23 (2H, q, J = 7.1Hz, CH_3CH_2O), 6.25 (1H, br.s, NHCOO), 6.71 (1H, dd, J = 8.0Hz, J = 2Hz, H-5), 6.75 (1H, d, J = 2.0Hz, H-3), 7.28 (1H, d, J = 8.0Hz, H-6). IR (KBr) : 3360, 2979, 2248, 1709, 1625, 1597, 1523, 1435, 1235 cm^{-1}. MS m/z : 219 (M). Anal. $C_{11}H_{13}N_3O_2$ requires C, 60.26; H, 5.98; N, 19.17. Found C, 60.05; H, 6.01; N, 18.93.

(1,3-Dihydro-2-oxo-2*H*-benzimidazol-5-yl)acetonitrile (18)

Ethyl *N*-(2-amino-4-cyanomethyl)carbamate (**17**) (32.2 g; 0.147 mol) in glacial acetic acid (600 ml) was heated under reflux for 1h. The mixture was then evaporated *in vacuo* (Büchi, 60°C) to give a sticky brown solid which was washed with 2N HCl (250 ml). The solid was filtered off, washed with water (3 x 50 ml) and dried *in vacuo* to yield the nitrile **18** as a light-brown solid, sparingly soluble in most organic solvents. Yield 21.0 g (82.0%). M.p. 276°C (darkens >24°C). R_f 0.73 (silica, EtOH). ^{1}HNMR (DMSO-d_6, 360MHz) δ : 3.96 (2H, s, CH_2CN), 6.86-6.95 (3H, m, H-3', H-5', H-6'), 10.58 (NHCONH), 10.59 (NHCONH). IR (KBr) : 3500-2500, 2244, 1749, 1677, 1509, 1472, 1411, 1380, 1204 cm^{-1}. MS m/z : 173 (M). Anal. $C_9H_7N_3O.0.25H_2O$ requires C, 60.83; H, 4.26; N, 23.65. Found C, 60.90; H, 4.19; N, 23.60.

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