Synthesis of 1-(2-Aminophenyl)isoquinolines and the Biological Activity of Their *cis*-Dichloro Platinum(II) Complexes

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The broad biological effects of isoquinolines prompted us to use them as chelating, nonleaving ligands in *cis*-platinum(II) antitumor complexes. The synthesis of several 1-(2-aminophenyl)-isoquinoline derivatives with different levels of hydrogenation and varying substitution of the phenyl ring is reported. These compounds constitute a new class of ligands for the synthesis of oligocyclic platinum(II) complexes. In vitro cytotoxicity tests indicate that the most basic amine ligands afford the most effective complexes. Two of the new complexes were more potent against L1210 murine leukemia cells than the well-established antitumor compound cisplatinum.

Introduction

Since the discovery of the antitumor activity of *cis*-diamminedichloroplatinum(II) by Rosenberg et al.,[1] a tremendous number of platinum(II) complexes have been synthesized and their cytotoxicity examined. Second generation platinum(II) antitumor complexes that carry nonleaving groups other than simply ammonia are of interest for their altered affinity to tissues (carrier function, tumor specific accumulation) and their ability to modulate drug metabolism (hydrolysis) and target binding through steric and electronic effects on the substitution mechanism.[2]

Knowledge of the relationship between the ligand structure and the cytotoxicity of the complexes derived therefrom is still limited.[3] However, several rules are apparent.[4] A general assumption is, that in order to be cytotoxic, the compounds must have two *cis*-coordinated amine ligands as nonleaving groups, each carrying at least one N−H bond. However, Farrell[5] and others[6] have shown examples which do not follow this structure-activity relationship. Apparently, polar substituents or charged compounds also diminish the biological activity.[7] The substitution of NH_3 in cisplatinum by chelate ligands such as *trans*-1,2-diaminocyclohexane,[8] 3-aminohexahydroazepines,[9] or aminomethylpiperidines[10,11] yields bicyclic chelate platinum(II) complexes with an altered spectrum of biological activity including cases with reduced cross resistance. Thus far, only few platinum(II) complexes with amine ligands of different basicity have been reported, e.g., complexes with a mixed aromatic-aliphatic amine environment around the metal. A recent case is *cis*-ammine-dichloro-picoline-platinum(II).[12] In addition, Bierbach[13] and Farrell[14] have prepared *trans*-platinum complexes with isoquinoline and related ligands. However, these compounds have not yet been used for chelate complexes.

In this paper we report on the synthesis and biological evaluation of several new platinum(II) complexes with 1-(2-aminophenyl)isoquinoline ligands.

Chemistry

Synthesis of the Ligands. Since imines of *ortho*-donor-substituted benzaldehydes are weak electrophiles and may not be cyclized under classical Pictet−Spengler conditions,[15] all 1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinolines were synthesized on a highly efficient modified route. The dihydroisoquinolines[16] were obtained by Bischler−Napieralski reactions.

Condensation of 2-(trifluoroacetylamino)benzaldehydes **2** with homoveratrylamine (**1**) afforded the imines **3** (Scheme 1). As indicated by the NH signal at 14.7 ppm and the X-ray crystal structure, compounds **3** are stabilized by a strong intramolecular hydrogen bond. The Pictet−Spengler cyclization could therefore only be achieved in a pressure tube with pure trifluoroacetic acid anhydride (TFAA). Under less vigorous reaction conditions, hydrolytic cleavage of the imines **3** was observed. The resulting tetrahydroisoquinolines **4** were then deprotected either with sodium borohydride[17] or concentrated hydrobromic acid to yield the ligands **5** or **6**.

Dihydroisoquinolines **9** and **10** were synthesized by Bischler−Napieralski cyclization of the nitro compounds **7** followed by selective reduction[18] of the nitro group with stannous chloride in ethyl acetate (Scheme 2).

Dehydration of the dihydroisoquinoline **8a** yielded the isoquinoline ligand precursor **11a** (Scheme 3).

Synthesis of the Platinum(II) Complexes. The platinum(II) complexes **12**−**15** (Chart 1) were prepared by titration of the isoquinoline ligands in the presence of equimolar amounts of K_2PtCl_4 in 0.05 M HCl (pH 2) with 0.1 M NaOH to pH 6 at 60 °C. The complexes were characterized by elemental analyses, IR, and NMR techniques. Due to slow chloro-ligand-DMSO exchange,[19]

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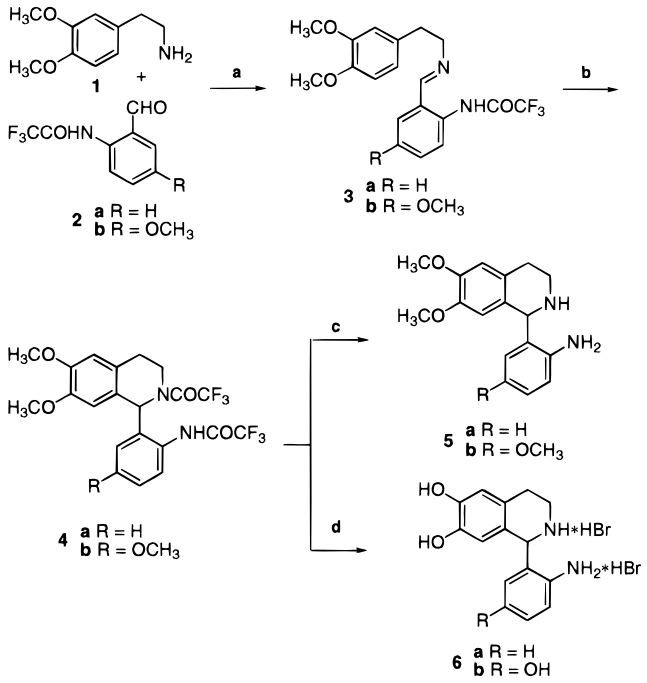
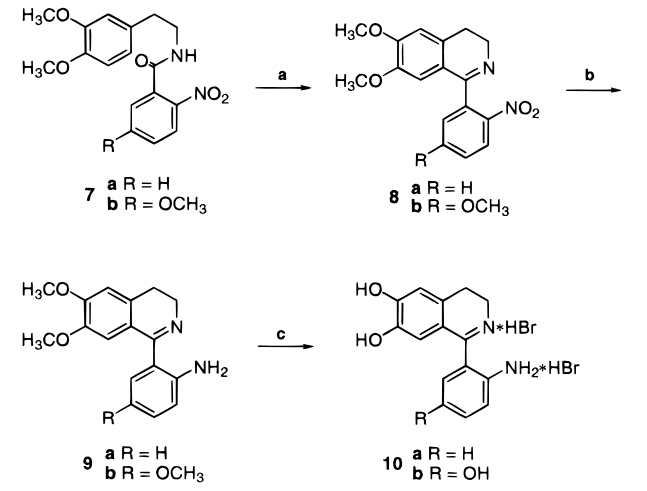
Scheme 1. Pictet–Spengler Route to 1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinolines[a]



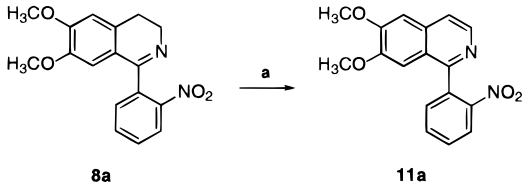
[a] Reagents: (a) pyridine, 145 °C {>95%}; (b) TFAA, pressure tube, 80 °C {72–86%}; (c) $NaBH_4$, MeOH {71–89%}; (d) 48% HBr, 145 °C {71–73%}.

Scheme 2. Bischler–Napieralski Route to 1-(2-Aminophenyl)-3,4-dihydroisoquinolines[a]



[a] Reagents: (a) $POCl_3$, CH_3CN, 80 °C {84–96%}; (b) $SnCl_2 \cdot 2H_2O$, EtOAc, 80 °C, 5–18 h {74–88%}; (c) 48% HBr, 145 °C {67–91%}.

Scheme 3. Dehydration of 1-(2-Aminophenyl)-3,4-dihydroisoquinoline **8a**[a]



[a] Reagents: (a) activated MnO_2, PhH, 80 °C, 8–10 h {84–88%}.

all ^1H NMR spectra, taken in (D_6)DMSO, showed multiple sets of signals. This exchange was observed also in the ^{13}C NMR spectra.

Chart 1. Platinum(II) Complexes of 1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinolines, 1-(2-Aminophenyl)-3,4-dihydroisoquinolines, and 1-(2-Aminophenyl)isoquinolines

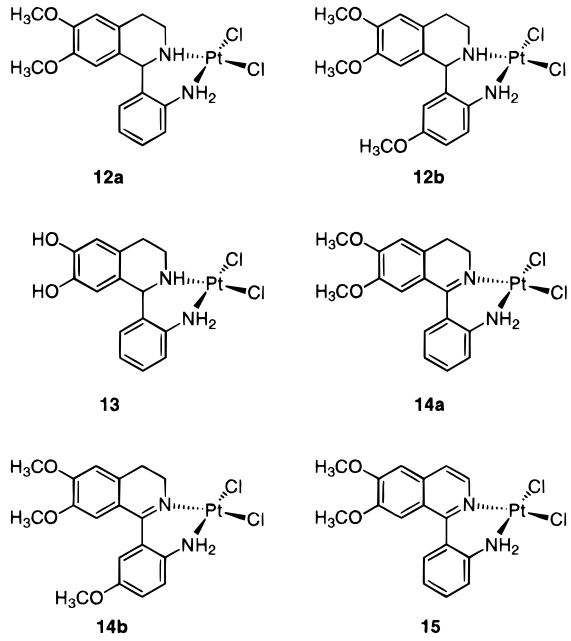


Table 1. IC_{50} of Platinum(II) Complexes and Free Ligands **5** (Growth Inhibition during 48 h)

compound	solvent[a]	$IC_{50} \pm SD$ (μM)
12a	DMSO	0.88 ± 0.08
12b	DMSO	0.95 ± 0.16
cisplatinum	H_2O	1.4 ± 0.2
15	DMSO	9.7 ± 0.6
5a	H_2O	141 ± 14
5b	H_2O	97 ± 9
cisplatinum	DMSO	>100

[a] "DMSO" indicates that the compound has been dissolved in DMSO and then diluted with water to a final DMSO concentration of 0.5%.

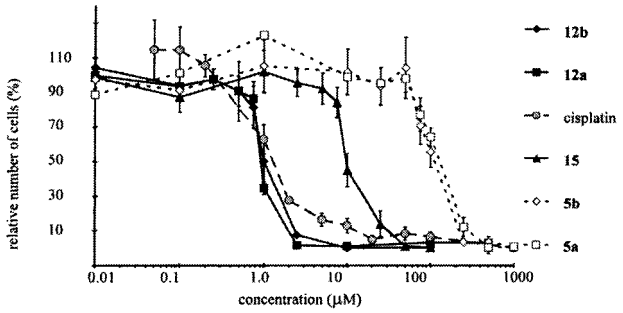


Figure 1. Growth inhibition by different platinum(II) complexes and the free ligands **5**.

Biology

In Vitro Cytotoxicity. The cytotoxicities of the complexes and ligands were studied with L1210 cells. The cytotoxicity of some complexes could not be tested due to precipitation on dilution of the stock solutions with water. The results are shown in Figure 1 as a log-linear plot of concentration-inhibition. Table 1 summarizes the L1210 data for the compounds assayed. The complexes **12a** and **12b** may have a similar mode of action, due to their close structural relationship. Both species are roughly 2 times more effective than cisplatinum. In contrast, the complex **15** shows a significantly

Table 2. IC_{50} of Platinum(II) Complexes and Free Ligands **5** (Inhibition of DNA Synthesis during 48 h)

compound	solvent[a]	$IC_{50} \pm SD$ (μM)
12a	DMSO	1.4 ± 0.6
12b	DMSO	1.4 ± 0.5
cisplatinum	H_2O	1.7 ± 0.2
15	DMSO	20 ± 0.6
5a	H_2O	90 ± 10
5b	H_2O	100 ± 10
cisplatinum	DMSO	>100

[a] "DMSO" indicates that the compound has been dissolved in DMSO and then diluted with water to a final DMSO concentration of 0.5%.

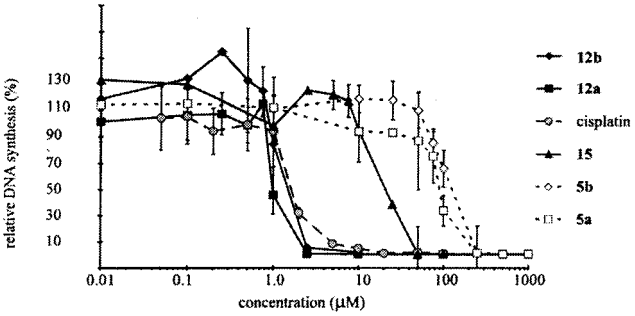


Figure 2. Inhibition of DNA synthesis by different platinum(II) complexes and the free ligands **5**.

reduced cytotoxicity, which was found to be about 10 times lower than that of cisplatinum. The free ligands **5** are about 100 times less cytotoxic than the corresponding platinum(II) complexes **12a** and **12b**.

Inhibition of DNA Synthesis. L1210 cells were incubated with the platinum complexes for 48 h. During the last 6 h, [6-^{3}H]thymidine was added to examine DNA synthesis. IC_{50} values were derived from log-linear plots of concentration effects (Table 2, Figure 2). We found a good correlation between the IC_{50} values derived from the cytotoxicity tests and those from the inhibition of DNA synthesis.

Discussion

Differences in structure, leaving groups, oxidation state, or ligands are important for the development of alternatives for cisplatinum. Carboplatinum, the second clinically administered platinum complex, leads to the formation of identical platinum-DNA adducts,[7] since both compounds differ only in their leaving groups.

Our 1-(2-aminophenyl)isoquinolines represent a novel class of platinum(II) ligands, which combine an aniline with an isoquinoline unit. The basicity of the isoquinoline nitrogen depends significantly on the hydrogenation state of the pyridine ring, whereas the basicity of the aniline nitrogen differs only slightly due to substituent effects. Three different types of isoquinoline substructures were synthesized: aromatic isoquinolines, 3,4-dihydroisoquinolines, and 1,2,3,4-tetrahydroisoquinolines. The aromatic isoquinolines are probably planar due to the intramolecular NH−N hydrogen bond. In contrast, the tetrahydroisoquinolines **5**−**6** and dihydroisoquinolines **9**−**10** have a twisted structure. For example, in the crystal structure of tetrahydroisoquinoline **4b** the interplanar angle between the isoquinoline ring and the aniline moiety is 85°, whereas it is only 52° in dihydroisoquinoline **9b** due to the formation of an intramolecular hydrogen bond (Figure 3).[20]

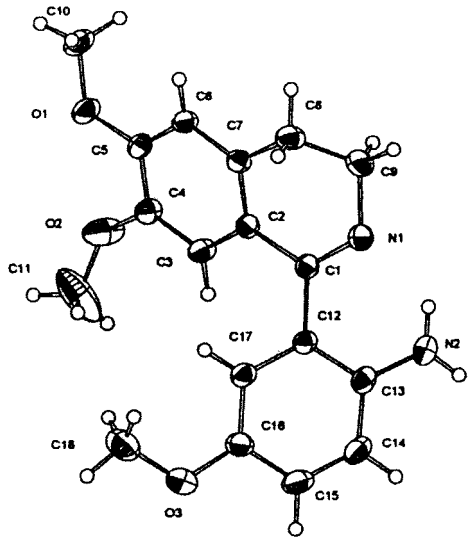


Figure 3. Structure analysis of the dihydroisoquinoline **9b** in the crystal.

All our platinum(II) complexes are soluble in DMSO. A critical factor for the solubility of the complexes is the exchange[21] of one chloride ligand by a DMSO molecule inducing a positive charge at the metal atom. In the biological testing, the DMSO solutions were therefore kept for 30 min at 40 °C to allow for the ligand exchange before water was added. This procedure revealed different degrees of solubility. The highest solubility was observed for the methoxy substituted tetrahydroisoquinoline complexes **12a** and **12b**, whereas the complexes **14**−**15** showed a reduced solubility. Obviously, ligands with stronger basicity, e.g., tetrahydroisoquinolines **5**, favor the displacement of chloride by DMSO.[22] Surprisingly, the phenolic complex **13** showed only a low solubility.

In clinically administered cisplatinum, the chloride is displaced by water giving an activated aqua form of the drug,[23] whereas substitution of a chloride by DMSO results in severely reduced cytotoxicity.[24] Despite the chloride-DMSO exchange, our compounds display a 2 times higher biological activity, in terms of cytotoxicity and inhibition of DNA synthesis, than cisplatinum dissolved in water,[25] and they are 2 orders of magnitude more active than cisplatinum dissolved in DMSO. The new diamine ligands form a rigid system enclosing the six-membered metallacycle. The most basic ligands **5** afford the biologically most potent complexes **12**.

Experimental Section

Silica gel 60 230−400 mesh (Merck, Germany) was used for chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 600, ARX 300, WH-90, and JEOL EX-400 instruments. ^{1}H and ^{13}C chemical shifts are given with respect to TMS or the solvent as internal standard. ^{13}C NMR signals for the solvolysis products of the platinum complexes **12**−**15** are also given, if there was no certain assignment possible. The symbols #, †, and ‡ indicate an interchangeable assignment of NMR signals. IR spectra were measured on a Nicolet 520 FT-IR. An interchangeable assignment of IR absorption is indicated by an asterisk (*). C, H, N, Br analyses were performed by the microanalytical laboratories of our institutes. X-ray structure analyses [measured with Enraf Nonius CAD4 MACH3; solution and refinement with SHELXS-86 and SHELXL-93] are shown as ORTEP plots. The full data of the X-ray crystal structures have been deposited at the Cambridge

Crystallographic Data Centre. Mass spectra were measured with a Finnigan MAT 95Q sector mass spectrometer using EI at 70 eV.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-2-(trifluoroacetylamino)benzylidenimine (3a).** A mixture of 2-(trifluoroacetylamino)benzaldehyde (**2a**)[26] (2.17 g, 10.0 mmol), homoveratrylamine (**1**) (1.81 g, 10.0 mmol), molecular sieve 4 Å (1.0 g), and pyridine (15 mL) was refluxed for 36 h. After filtration, the filtrate was concentrated under reduced pressure and the resulting residue subjected to flash chromatography (SiO_2; EtOAc/hexanes, 2:3) to yield imine **3a** (3.65 g, 96%) as a yellow solid. Recrystallization from EtOH afforded 3.00 g (78%) of yellow needles: mp 116.5 °C; IR (KBr) 2940 (m), 2850 (m), 1720 (s), 1650 (s), 1620 (s), 1600 (s), 1560 (s), 1520 (s), 1480 (s), 1430 (w), 1350 (w), 1300 (m), 1270 (m), 1240 (m), 1150 (m), 880 (w) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.97 (t, J = 7.1 Hz, 2H, $ArCH_2$), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.85 (td, J = 7.1, 1.1 Hz, 2H, CH_2N), 6.66 (d, J = 1.9 Hz, 1H, 2′-H), 6.70 (dd, J = 8.1, 1.9 Hz, 1H, 6′-H), 6.76 (d, J = 8.1 Hz, 1H, 5′-H), 7.19 (ddd, J = 8.2, 7.4, 1.1 Hz, 1H, 5-H), 7.30 (dd, J = 7.7, 1.7 Hz, 1H, 6-H), 7.43 (ddd, J = 8.2, 7.7, 1.9 Hz, 1H, 4-H), 8.16 (s, 1H, CH=N), 8.63 (d, J = 8.4 Hz, 1H, 3-H), 14.35 (s, 1H, $NHCOCF_3$); ^{13}C NMR (76 MHz, $CDCl_3$) δ 36.65 ($ArCH_2$), 55.68 (OCH_3), 55.84 (OCH_3), 62.45 (CH_2N), 111.31, 112.09, 116.01 (q, $^1J_{CF}$ = 288.9 Hz, CF_3), 120.25, 120.68, 121.52, 124.58, 131.56, 131.64, 132.91, 137.75, 147.56, 148.80, 155.68 (q, $^2J_{CF}$ = 37.6 Hz, $COCF_3$), 164.20 (C=N); FAB-MS m/z (%) = 381 (100) [M^+ + H], 380 (50), 289 (14). Anal. ($C_{19}H_{19}F_3N_2O_3$) C, H, N.

5-Methoxy-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(trifluoroacetylamino)benzylidenimine (3b). Imine **3b** was prepared from 5-methoxy-2-(trifluoroacetylamino)benzaldehyde (**2b**) (1.49 g, 6.03 mmol) according to the procedure described for **3a**. Flash chromatography (SiO_2; EtOAc/hexanes, 1:2) afforded imine **3b** (2.36 g, 95%) as a yellow solid: mp 115−115.5 °C; IR (KBr) 3450 (m), 1715 (s, C=O), 1641 (m), 1554 (s), 1519 (s), 1468 (m), 1456 (m), 1283 (s), 1260 (s), 1239 (s), 1163 (s), 1148 (s), 1123 (m), 804 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.98 (t, J = 7.0 Hz, 2H, $ArCH_2$), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.86 (t, J = 6.8 Hz, 2H, CH_2N), 6.67 (d, $J \approx$ 1.3 Hz, 1H, 2′-H), 6.71 (dd, J = 8.3, 1.7 Hz, 1H, 6′-H), 6.78 (d, J = 7.9 Hz, 1H, 5′-H), 6.82 (d, J = 2.9 Hz, 1H, 6-H), 6.96 (dd, J = 9.1, 2.9 Hz, 1H, 4-H), 8.12 (s, 1H, CH=N), 8.58 (d, J = 9.2 Hz, 1H, 3-H), 14.07 (s, 1H, $NHCOCF_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.57 ($ArCH_2$), 55.48 (OCH_3), 55.63 (OCH_3), 55.80 (OCH_3), 62.45 (CH_2N), 111.25, 112.04, 116.18 (q, $^1J_{CF}$ = 289.0 Hz, CF_3), 116.30, 118.18, 120.63, 121.64, 122.66, 131.03, 131.50, 147.51, 148.76, 155.01 (q, $^2J_{CF}$ = 37.2 Hz, $COCF_3$), 156.19, 163.91 (CH=N); EI-MS m/z (%) = 410 (43) [M^+], 341 (31) [$M^+ - CF_3$], 259 (24), 232 (7), 165 (20), 151 (100), 146 (12); HR-EI-MS calcd for $C_{20}H_{21}F_3N_2O_4$ 410.1453, found 410.1453. Anal. ($C_{20}H_{21}F_3N_2O_4$) C, H, N.

6,7-Dimethoxy-2-(trifluoroacetyl)-1-[2-(trifluoroacetylamino)phenyl]-1,2,3,4-tetrahydroisoquinoline (4a). A mixture of benzylidenimine **3a** (1.0 g, 2.63 mmol) and trifluoroacetic anhydride (3.0 mL, 21.4 mmol) was heated to 80 °C for 24 h. After removal of the volatiles in vacuo, flash chromatography (SiO_2; EtOAc/hexanes, 1:2) yielded **4a** (900 mg, 72%) as a yellow solid: mp 74.5 °C; IR ($CHCl_3$) 3250 (s.br), 1740 (s), 1680 (s), 1615 (m), 1520 (s), 1460 (m), 1280 (m), 1260 (s), 1200 (s), 1160 (s), 1125 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.91 (dd, J = 16.6, 3.0 Hz, 1H, 4-$H^{\alpha\#}$), 3.13 (ddd, J = 17.6, 12.3, 5.3 Hz, 1H, 4-$H^{\beta\#}$), 3.69 (s, 3H, OCH_3), 3.69 (td, J = 13.5, 3.3 Hz, 1H, 3-$H^{\beta\dagger}$), 3.89 (s, 3H, OCH_3), 4.08 (dd, J = 14.3, 4.7 Hz, 1H, 3-$H^{\alpha\dagger}$), 6.21 (s, 1H, 1-$H^{\ddagger}$), 6.52 (s, 1H, 5-$H^{\ddagger}$), 6.66 (s, 1H, 8-$H^{\ddagger}$), 7.03 (d, J = 7.6 Hz, 1H), 7.17 (t, J = 7.7 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.99 (d, J = 8.3 Hz, 1H), 10.74 (s, 1H, $NHCOCF_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.46 (C-4), 39.59 (C-3), 52.98 (C-1), 55.92 (OCH_3), 56.12 (OCH_3), 110.63 (2C, C-5, C-8), 116.08 (q, $^1J_{CF}$ = 288.0 Hz, CF_3), 116.34 (q, $^1J_{CF}$ = 287.6 Hz, CF_3), 124.68 (C-4$^{\alpha\#}$), 124.79 (CH), 125.03 (C-8$^{\alpha\#}$), 126.54 (CH), 129.52 (CH), 130.74 (CH), 132.02 (C), 133.90 (C), 148.62 (C-7†), 148.80 (C-6†), 156.43 (q, $^2J_{CF}$ = 37.8 Hz, $COCF_3$), 157.36 (q, $^2J_{CF}$ = 36.8 Hz, $COCF_3$); EI-MS m/z (%) = 476 (33) [M^+], 380 (15), 379 (73), 365 (20), 364 (100), 288 (10); HR-EI-MS calcd for $C_{22}H_{20}F_6N_2O_5$ 476.1171, found 476.1182. Anal. ($C_{21}H_{18}F_6N_2O_4$) C, H, N.

6,7-Dimethoxy-1-[5-methoxy-2-(trifluoroacetylamino)-phenyl]-2-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (4b). Isoquinoline **4b** was prepared from benzylidenimine **3b** (1.80 g, 4.45 mmol) according to the procedure described for **4a**. Flash chromatography (SiO_2; EtOAc/hexanes, 1:1) gave **4b** (1.94 g, 86%) as a yellow solid: mp 156 °C; IR (KBr) 3441 (s br), 1726 (s), 1700 (m), 1676 (s), 1521 (s), 1465 (m), 1368 (m), 1281 (m), 1255 (s), 1219 (s), 1179 (m), 1154 (s), 1121 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.89 (dd, J = 16.3, 2.4 Hz, 1H, 4-H^{α}), 3.10 (ddd, J = 17.1, 12.4, 5.3 Hz, 1H, 4-H^{β}), 3.71 (ddd, 1H, 3-H^{α}), 3.70 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.08 (dd, J = 14.8, 4.5 Hz, 1H, 3-H^{β}), 6.22 (s, 1H, 5-$H^{\#}$), 6.46 (s, 1H, 1-H), 6.54 (d, J = 3.2 Hz, 1H, 6′-H), 6.64 (s, 1H, 8-$H^{\#}$), 6.94 (dd, J = 8.8, 3.0 Hz, 1H, 4′-H), 7.85 (d, J = 8.8 Hz, 1H, 3-H), 10.47 (s, 1H, $NHCOCF_3$); ^{13}C NMR (151 MHz, $CDCl_3$) δ 28.48 (C-4), 39.74 (C-3), 53.01 (C-1), 55.53 (OCH_3), 55.98 (OCH_3), 56.16 (OCH_3), 110.72 (C-8$^{\#}$), 110.74 (C-5$^{\#}$), 113.34 (CH), 116.23 (q, $^1J_{CF}$ = 288.3 Hz, CF_3), 116.38 (q, $^1J_{CF}$ = 287.5 Hz, CF_3), 117.35 (CH), 124.57 (C), 124.98 (C), 126.53 (CH), 126.69 (C), 134.25 (C-2′), 148.75 (C-7†), 148.90 (C-6†), 156.51 (q, $^2J_{CF}$ = 37.0 Hz, $COCF_3$), 157.29 (q, $^2J_{CF}$ = 37.1 Hz, $COCF_3$), 157.79 (C-5′); EI-MS m/z (%) = 506 (24) [M^+], 409 (50) [$M^+ - CF_3 - CO$], 394 (100) [$M^+ - NHCOCF_3$], 288 (6); HR-EI-MS calcd for $C_{22}H_{20}F_6N_2O_5$ 506.1276, found 506.1270. Anal. ($C_{22}H_{20}F_6N_2O_5$) C, H, N.

1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a).[27] To a stirred solution of **4a** (2.38 g, 5.00 mmol) in dry EtOH (25 mL) $NaBH_4$ (1.15 g, 40.0 mmol) was added in portions.[17] After the gas evolution had ceased, the mixture was stirred for another hour. The white precipitate was filtered off under Ar, washed with H_2O and dried in vacuo (0.95 g of **5a**, 67%, colorless solid). After the addition of acetone (30 mL) and H_2O (30 mL), the filtrate was partitioned between H_2O (150 mL) and EtOAc (150 mL). The aqueous phase was extracted with EtOAc (2 × 150 mL), and the combined organic layers were washed with brine (100 mL) and dried ($MgSO_4$). The solvent was evaporated in vacuo and the residue recrystallized from MeOH to yield **5a** as yellow crystals (0.31 g, 22%); all-over yield of **5a** was 1.26 g, 89%: mp 157 °C; IR (KBr) 3406 (s), 3324 (m), 3003 (w), 2948 (m), 2934 (m), 2832 (w), 1612 (s), 1580 (w), 1514 (s), 1494 (s), 1458 (s), 1406 (w), 1360 (m), 1325 (w), 1312 (m), 1260 (s), 1233 (s), 1215 (s), 1170 (w), 1154 (w), 1115 (s), 1100 (s), 1065 (w), 1032 (m), 1013 (m), 940 (w), 903 (w), 874 (w), 858 (m), 835 (m), 797 (s), 771 (s), 759 (s), 723 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.71 (dt, J = 15.7, 4.4 Hz, 1H, 4-H^{α}), 2.89−3.09 (m, 2H, 4-H^{β}, 3-H^{α}), 3.22 (dt, J = 11.9, 5.2 Hz, 1H, 3-H^{β}), 3.64 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.54 (br, 2H, NH_2), 5.06 (s, 1H, 1-H), 6.32 (s, 1H, 5-$H^{\#}$), 6.62−6.71 (m, 3H, 8-$H^{\#}$, 2 ArH), 6.94 (dd, J = 7.4, 1.4 Hz, 1H), 7.10 (dt, J = 7.6, ∼0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 29.22 (C-4), 42.52 (C-3), 55.80 (2C, 2 OCH_3), 60.76 (C-1), 109.95 (C-5$^{\#}$), 111.51 (C-8$^{\#}$), 116.65 (CH), 117.42 (CH), 127.23 (C-4$^{\alpha\dagger}$), 127.37 (C-8$^{\alpha\dagger}$), 128.41 (CH), 129.22 (C-1′), 130.75 (CH), 146.18 (C-2′‡), 147.28 (C-6‡), 147.70 (C-7‡); EI-MS m/z (%) = 284 (100) [M^+], 283 (48) [$M^+ - H$], 269 (41) [$M^+ - CH_3$], 267 (45) [$M^+ - NH_3$], 253 (16) [$M^+ - CH_3O$], 192 (36) [$M^+ - C_6H_4NH_2$]. Anal. ($C_{17}H_{20}N_2O_2$) C, H, N.

1-(2-Amino-5-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5b). Tetrahydroisoquinoline **4b** (240 mg, 0.474 mmol) was deprotected with $NaBH_4$ as described above to yield **5b** (106 mg, 71%) as a yellow solid: mp 163 °C; IR (KBr) 3443 (s br, NH_2), 2960 (m), 2925 (s), 2853 (m, OCH_3), 1635 (s.br), 1578 (s), 1559 (m), 1504 (s), 1463 (m), 1283 (m), 1214 (m), 1121 (m), 1036 (m), 1025 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (m, 1H, 4-$H^{\alpha\#}$), 2.86−2.94 (m, 1H, 4-$H^{\beta\#}$), 3.00−3.06 (m, 1H, 3-$H^{\alpha\dagger}$), 3.14−3.20 (m, 1H, 3-$H^{\beta\dagger}$), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.07 (s, 1H, 1-H), 6.33 (s, 1H, 8-$H^{\ddagger}$), 6.52 (d, J = 2.0 Hz, 1H, 6′-H), 6.59−6.61 (m, 2H, 5-$H^{\ddagger}$, 3′-H), 6.68 (dd, J = 8.4, 2.4 Hz, 4′-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.87 (C-4), 41.93 (C-3),

55.73 (OCH_3), 55.78 (OCH_3), 55.83 (OCH_3), 59.90 (C-1), 109.97 (CH), 111.46 (CH), 113.27, 117.18, 127.08, 128.45, 128.91, 139.60, 147.30 (C), 147.78 (C), 147.78 (C), 152.01 (C); EI-MS *m*/*z* (%) = 314 (56) [M^+], 313 (41) [$M^+ - H$], 299 (38) [$M^+ - CH_3$], 297 (44) [$M^+ - NH_3$], 283 (23) [$M^+ - CH_3O$], 266 (30), 192 (36) [$M^+ - CH_3O(C_6H_3)NH_2$]. Anal. ($C_{18}H_{22}N_2O_3$) C, N; H: calcd, 7.05; found, 6.46.

General Procedure A. A suspension of the 6,7-dimethoxyisoquinoline **4** or **9** (10 mmol) in 48% aqueous hydrobromic acid (3 mL) was refluxed until TLC showed no starting material (approximately 4−8 h). The reaction mixture was slowly cooled to 5 °C and stirred at this temperature for additional 12 h. The resulting yellow precipitate was filtered under Ar, immediately washed with Et_2O (3 × 5 mL) and then dried in vacuo.

1-(2-Aminophenyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Dihydrobromide (6a). The title compound (3.09 g, 73%) was prepared from tetrahydroisoquinoline **4a** (4.84 g, 10.2 mmol) according to the general procedure A: mp 274 °C (dec); IR (KBr) 3435 (s br), 1618 (s), 1495 (s), 1457 (s), 1274 (s), 754 (m) cm^{-1}; UV/vis (H_2O): λ_{max} (lg ϵ) = 227 (sh, 4.03), 287 nm (3.64); ^1H NMR (600 MHz, CD_3OD) δ 3.09 (dt, *J* = 17.4, 4.8 Hz, 1H, 4-H^{α}), 3.25−3.31 (m, 1H, 4-H^{β}), 3.62−3.65 (m, 2H, 3-H^{α}, 3-H^{β}), 5.95 (s, 1H, 1-H), 6.21, 6.77 (2 s, each 1H, 5-H, 8-H), 7.39 (dd, *J* = 7.9, 1.0 Hz, 1H, 6′-H), 7.54−7.57 (m, 2H, 3′-H, 5′-H$^{\#}$), 7.67 (ddd, *J* = 7.3, 7.1, 1.3 Hz, 1H, 4′-H$^{\#}$); ^{13}C NMR (151 MHz, CD_3OD) δ 25.68 (C-4), 42.80 (C-3), 55.71 (C-1), 115.67 (CH), 116.33 (CH), 122.61 (C), 125.18 (C), 125.35 (CH), 130.33 (CH), 131.45 (C), 133.11 (CH), 133.37 (CH), 134.00 (br, C), 146.41 (C-6$^{\#}$), 147.81 (C-7$^{\#}$); FAB-MS *m*/*z* (%) = 257 (7) [$M^+ + H$]; HR-FAB-MS calcd for $C_{15}H_{17}N_2O_2$ 257.1290, found 257.1283. Anal. ($C_{15}H_{18}Br_2N_2O_2$) C, H, N, Br.

1-(2-Amino-5-hydroxyphenyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline Dihydrobromide (6b). The title compound (612 mg, 71%) was prepared from tetrahydroisoquinoline **4b** (1.00 g, 1.98 mmol) following the general procedure A: mp 247 °C (dec); IR (KBr) 3388 (s br), 1608 (m), 1506 (m), 1451 (m), 1366 (m), 1275 (m), 1193 (m), 1105 (m), 868 (m) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.95 (dt, *J* = 17.4, 5.7 Hz, 1H, 4-$H^{\alpha\#}$), 3.05−3.15 (m, 1H, 4-$H^{\beta\#}$), 3.37−3.46 (m, 1H, 3-$H^{\alpha\dagger}$), 3.54 (dt, *J* = 12.7, 6.1 Hz, 1H, 3-$H^{\beta\dagger}$), 5.66 (s, 1H, 1-H), 6.18 (s, 1H, 5-H‡), 6.61 (d, *J* = 2.9 Hz, 1H, 6′-H), 6.74 (s, 1H, 8-H‡), 6.97 (dd, *J* = 8.8, 2.7 Hz, 1H, 4′-H), 7.33 (d, *J* = 8.7 Hz, 1H, 3′-H); ^{13}C NMR (75 MHz, D_2O) δ 25.03 (C-4), 41.58 (C-3), 54.56 (C-1), 116.06 (C-8), 116.87 (C-5), 119.43 (C-4′$^{\#}$), 119.93 (C-6′$^{\#}$), 122.85 (2C, C-4$^{\alpha\dagger}$, C-2′), 126.13 (C-8$^{\alpha\dagger}$), 127.53 (C-3′), 132.54 (C-1′), 144.45 (C-7‡), 145.96 (C-6‡), 158.03 (C-5′); EI-MS *m*/*z* (%) = 272 (1) [M^+], 269 (4) [$M^+ - 3$ H], 153 (12), 124 (49), 82 (96) [$H^{81}Br^+$], 81 (32) [$^{81}Br^+$], 80 (100) [$H^{79}Br^+$], 79 (31) [$^{79}Br^+$]; HR-EI-MS calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1160. Anal. ($C_{15}H_{18}Br_2N_2O_3 \cdot 1^1/_2H_2O$) C, H, N.

General Procedure B. $POCl_3$ (128 mL) was added dropwise to a stirred solution of *N*-phenylethyl-2-nitrobenzamide **7** (200 mmol) in dry CH_3CN (800 mL), and the stirring was continued for 1 h at room temperature. The resulting mixture was refluxed for approximately 5 h until all starting material had been consumed (TLC monitoring). After removal of the solvent in vacuo, $CHCl_3$ (400 mL) and H_2O (400 mL) were added, and the aqueous phase was adjusted with aqueous 10 N NaOH to pH 12. The organic layer was washed with saturated aqueous $NaHCO_3$ (4 × 100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The isoquinolines **13** precipitate on addition of Et_2O.

6,7-Dimethoxy-1-(2-nitrophenyl)-3,4-dihydroisoquinoline (8a).[28] The title compound was prepared from amide **7a**[29] (66.1 g, 200 mmol) according to general procedure B. Recrystallization of the crude product from acetone/hexanes yielded **8a** as a yellow solid (60.2 g, 96%): mp 117−118 °C; IR (KBr) 3000 (w), 1618 (m), 1575 (s), 1540 (s), 1470 (m), 1360 (s), 1330 (m), 1290 (s), 1275 (s), 1240 (w), 1210 (s), 1130 (s), 1090 (w), 1030 (m), 995 (w), 720 (w), 702 (w), 693 (w), 616 (w) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.79 (t, *J* = 7.8 Hz, 2H), 3.62 (s, 3H, OCH_3), 3.83 (t, *J* = 7.8 Hz, 2H), 3.88 (s, 3H, OCH_3), 6.33 (s, 1H), 6.77 (s, 1H), 7.43−7.83 (m, 3H), 7.97−8.17 (m, 1H); ^{13}C NMR (23 MHz, $CDCl_3$) δ 25.5 (C-4), 47.7 (C-3), 56.1 (OCH_3), 56.2 (OCH_3), 109.6 (CH), 110.7 (CH), 121.5 (C), 124.5 (CH), 129.8 (CH), 131.2 (CH), 131.7 (C), 133.5 (CH), 134.7 (C), 147.7 (C), 148.7 (C), 151.7 (C), 164.6 (C).

6,7-Dimethoxy-1-(5-methoxy-2-nitrophenyl)-3,4-dihydroisoquinoline (8b).[16] The title compound was prepared from amide **7b**[16] (64.0 g, 178 mmol) according to the general procedure B. Recrystallization of the crude product from acetone/hexanes/MeOH yielded a yellow powder (56.9 g, 93%): mp 138−139 °C; IR (KBr) 3035 (w), 1605 (m), 1588 (s), 1570 (m), 1515 (s), 1405 (m), 1335 (s), 1295 (m), 1265 (m), 1242 (s), 1122 (m), 1080 (s), 1000 (w), 752 (w) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.83 (t, *J* = 6.6 Hz, 2H), 3.58 (s, 3H, OCH_3), 3.82 (t, *J* = 6.6 Hz, 2H), 3.87 (s, 6H, OCH_3), 6.32 (s, 1H), 6.77 (s, 1H), 6.91−7.11 (m, 2H), 8.08 (d, *J* = 9.6 Hz, 1H); ^{13}C NMR (23 MHz, $CDCl_3$) δ 25.5 (C-4), 46.8 (C-3), 56.2 (OCH_3), 56.3 (2C, OCH_3), 109.5 (CH), 110.7 (CH), 115.5 (CH), 115.7 (CH), 121.2 (C), 127.2 (CH), 131.9 (C), 136.2 (C), 141.1 (C), 147.8 (C), 152.3 (C), 163.9 (C), 165.8 (C); EI-MS *m*/*z* (%) = 342 (100) [M^+], 312 (26), 299 (26), 281 (30), 269 (21). Anal. ($C_{18}H_{18}N_2O_5$) C, H, N.

General Procedure C. A suspension of the (nitrophenyl)-isoquinoline **8** or **11** (20.0 mmol) and $SnCl_2 \cdot 2H_2O$ (120 mmol) in dry EtOAc (250 mL)[18] was refluxed until completion of the reaction was indicated by TLC (18−36 h). To this mixture were added with stirring H_2O (60 mL) and 10 N NaOH (18 mL), and the resulting solution was cautiously poured into saturated aqueous $NaHCO_3$ (500 mL). After extraction with EtOAc (3 × 200 mL), the combined organic layers were filtered, dried over $MgSO_4$, and evaporated in vacuo.

1-(2-Aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (9a).[28] The title compound was prepared from dihydroisoquinoline **8a** (6.3 g, 20.0 mmol) according to the general procedure C. The foamy crude product (4.95 g, 88%) was recrystallized from EtOAc, providing yellow crystals: mp 129 °C; IR (KBr) 3423 (s), 2942 (m), 2927 (m), 2832 (w), 1613 (s), 1573 (m), 1557 (s), 1513 (s), 1491 (m), 1454 (m), 1358 (s), 1320 (m), 1298 (m), 1278 (s), 1256 (m), 1234 (w), 1208 (s), 1162 (w), 1111 (s) cm^{-1}; UV/vis (CH_3OH) λ_{max} (lg ϵ) = 232 (4.48), 284 (3.92), 311 nm (3.93); ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (t, *J* = 7.3 Hz, 2H, $ArCH_2$), 3.73 (s, 3H, OCH_3), 3.81 (t, *J* = 7.3 Hz, 2H, CH_2N), 3.95 (s, 3H, OCH_3), 5.12 (br, 2H, NH_2), 6.67−6.78 (m, 2H), 6.75 (s, 1H), 6.82 (s, 1H), 7.15 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.17 (dd, *J* = 6.4, 1.5 Hz, 1H); ^{13}C NMR (76 MHz, $CDCl_3$) δ 25.90 (C-4), 47.14 (C-3), 56.01 (OCH_3), 56.13 (OCH_3), 110.13 (CH), 111.85 (CH), 116.64 (CH), 116.80 (CH), 121.61 (C), 121.99 (C), 129.83 (CH), 131.02 (CH), 132.61 (C), 146.99 (C), 147.00 (C), 150.78 (C), 166.93 (C-1); GC/EI-MS *m*/*z* (%) = 282 (31) [M^+], 281 (100) [$M^+ - H$], 266 (12) [$M^+ - NH_2$], 251 (36) [$M^+ - CH_3O$]; FAB-MS *m*/*z* (%) = 283 (100) [$M^+ + H$]; HR-EI-MS calcd for $C_{17}H_{18}N_2O_2$ 282.1368, found 282.1329. Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

1-(2-Amino-5-methoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (9b). The title compound (5.12 g, 94%) was prepared from dihydroisoquinoline **8b** (6.0 g, 17.5 mmol) according to the general procedure C. Flash chromatography (SiO_2; $CHCl_3$/MeOH, 10:1) of the crude product afforded **9b** (4.03 g, 74%) as an orange solid, which yielded yellow crystals on recrystallization from EtOAc: mp 108 °C; UV/vis (MeOH) λ_{max} (lg ϵ) = 233 (4.48), 286 (3.86), 314 nm (3.94); IR (KBr) 3402 (br), 2999 (w), 2931 (m), 2832 (w), 1602 (s), 1557 (s), 1511 (s), 1498 (s), 1467 (m), 1414 (w), 1357 (s), 1319 (m), 1280 (s), 1229 (s), 1206 (s), 1166 (m), 1110 (s), 1043 (m), 1003 (w), 956 (w), 870 (m), 820 (w), 802 (w), 756 (w), 676 (w), 643 (w) 622 (w), cm^{-1}; ^1H NMR (300 MHz, [D_6]DMSO) δ 2.63 (t, *J* = 7.3 Hz, 2H, $ArCH_2$), 3.58 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.68 (t, *J* = 7.1 Hz, 2H, CH_2N), 3.82 (s, 3H, OCH_3), 5.33 (s, 2H, NH_2), 6.63−6.79 (m, 4H), 6.95 (s, 1H); ^{13}C NMR (75 MHz, [D_6]-DMSO) δ 25.28 (C-4), 46.90 (C-3), 55.60 (OCH_3), 55.89 (OCH_3), 55.90 (OCH_3), 111.10 (C-5$^{\#}$), 111.57 (C-8$^{\#}$), 114.75, 116.95, 117.46 (3 × 1C, C-3′, C-4′, C-6′), 121.15 (C), 121.30 (C), 132.46 (C), 141.89 (C), 146.79 (C), 149.72 (C), 150.87 (C), 165.62 (C-1); GC/EI-MS *m*/*z* (%) = 312 (43) [M^+], 311 (100) [$M^+ - H$], 296 (12) [$M^+ - NH_2$], 281 (28) [$M^+ - OCH_3$], 267 (8), 238 (3);

HR-EI-MS calcd for $C_{18}H_{20}N_2O_3$ 282.1368, found 282.1329. Anal. ($C_{18}H_{20}N_2O_3$) C, H, N.

General Procedure D. To a refluxing solution of the dihydroisoquinoline **8** (10.0 mmol) in dry benzene was added every 30−50 min a portion of activated MnO_2 (1.0 g) (Dean−Stark apparatus). After TLC indicated the completion of the reaction (8−10 h), the hot reaction mixture was filtered, and the filter cake was washed with hot $CHCl_3$ (5 × 100 mL). The combined filtrates were dried (Na_2SO_4) and the remaining particles of MnO_2 removed by filtration over Celite. Evaporation of the solvent yielded the isoquinolines **11** as yellow oils that crystallized on addition of Et_2O.

6,7-Dimethoxy-1-(2-nitrophenyl)isoquinoline (11a). The title compound was prepared from isoquinoline **7a** (50 g, 160 mmol) by the general procedure D. Recrystallization of the crude product from Et_2O/acetone/hexanes provided **11a** (43.87 g, 88%) as a colorless solid: mp 170−171 °C; IR (KBr) 3050 (w), 2980 (w), 2870 (w), 1635 (m), 1575 (s), 1540 (s), 1518 (s), 1503 (m), 1490 (s), 1443 (s), 1430 (s), 1375 (s), 1360 (m), 1300 (m), 1265 (s), 1243 (s), 1230 (s), 1145 (s), 870 (s), 753 (s) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 6.86 (s, 1H), 7.12 (s, 1H), 7.42−7.85 (m, 4H), 8.00−8.25 (m, 1H), 8.40 (d, J = 6.0 Hz, 1H); ^{13}C NMR (23 MHz, $CDCl_3$) δ 55.9 (OCH_3), 56.2 (OCH_3), 103.8 (CH), 105.4 (CH), 119.6 (CH), 122.8 (C), 124.7 (CH), 129.5 (CH), 132.2 (CH), 133.1 (CH), 133.4 (C), 135.1 (C), 141.4 (CH), 149.4 (C), 150.7 (C), 153.1 (C), 154.7 (C); EI-MS m/z (%) = 311 (19) [M^+ + 1], 310 (100) [M^+], 279 (6), 264 (15), 249 (31), 220 (14), 191 (8); HR-EI-MS calcd for $C_{17}H_{14}N_2O_4$ 310.0954, found 310.0927. Anal. ($C_{17}H_{14}N_2O_4$) C, H, N.

1-(2-Aminophenyl)-6,7-dimethoxyisoquinoline (Ligand of 15). The title compound was prepared from isoquinoline **11a** (6.51 g, 21.0 mmol) according to the general procedure C. Flash chromatography (SiO_2; $CHCl_3$/MeOH, 20:1) of the crude product yielded 1-(2-aminophenyl)-6,7-dimethoxyisoquinoline (3.25 g, 55%) as a colorless solid: mp 163−167 °C; IR (KBr) 3468 (m), 1620 (s), 1558 (m), 1508 (s), 1496 (s), 1433 (m), 1417 (m), 1350 (w), 1313 (w), 1255 (s), 1235 (s), 1120 (m), 1034 (w), 1008 (w), 865 (m), 749 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.23 (s br, 2H, NH_2), 7.00−7.05 (m, 2H), 7.02 (s, 1H), 7.17 (ddd, J = 8.0, 7.2, 1.3 Hz, 1H), 7.22 (s, 1H), 7.25 (dd, J = 7.9, 1.6 Hz, 1H), 7.41 (d, J = 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.64 (OCH_3), 55.83 (OCH_3), 104.72, 105.54, 116.60, 117.56, 118.53, 122.96, 123.86, 129.27, 130.81, 133.95, 140.77, 145.11, 149.75, 152.59, 156.83; EI-MS m/z (%) = 280 (54) [M^+], 279 (100) [M^+ − H], 264 (12), 249 (9), 246 (11), 234 (16). Anal. ($C_{17}H_{16}N_2O_2 \cdot {}^1/_4CH_3OH$) C, H, N.

1-(2-Aminophenyl)-6,7-dihydroxy-3,4-dihydroisoquinoline Dihydrobromide (10a). The title compound (1.38 g, 91%) was prepared from dihydroisoquinoline **9a** (1.0 g, 3.54 mmol) according to general procedure A: mp 212−220 °C; UV/vis (H_2O) λ_{max} = 236 (4.01), 313 (3.80), 368 nm (3.80); IR (KBr) 3457 (s.br), 2851 (s), 2571 (m), 1634 (m), 1615 (m), 1574 (s), 1538 (m), 1494 (m), 1473 (m), 1453 (m), 1387 (w), 1333 (s), 1307 (s), 1252 (m), 1230 (m), 1198 (m), 1154 (m), 915 (m), 618 (m), 451 (m), 424 (w) cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 2.98 (t, J = 6.5 Hz, 2 H, 4-H$^\alpha$, 4-H$^\beta$), 3.80 (t, J = 6.5 Hz, 2H, 3-H$^\alpha$, 3-H$^\beta$), 6.66 (s, 1H, 5-H), 6.81 (s, 1H, 8-H), 7.05 (d, J = 8.5 Hz, 1H, 3′-H$^\#$), 7.08 (t, J = 7.4 Hz, 1H, 5′-H†), 7.26 (d, J = 7.8 Hz, 1H, 6′-H$^\#$), 7.47 (t, J = 8.2 Hz, 1H, 4′-H†); ^{13}C NMR (75 MHz, D_2O/CD_3OD [25:1]) δ 25.54 (C-4), 42.62 (C-3), 117.11 (CH), 117.83 (C), 120.46 (C), 120.74 (CH), 121.61 (CH), 123.99 (CH), 132.02 (CH), 135.44 (CH), 136.14 (C), 140.50 (C), 145.17 (C), 156.00 (C), 172.91 (C-1); FAB-MS m/z (%) = 255 (34) [M^+ + H]; HR-FAB-MS calcd for $C_{15}H_{15}N_2O_2$ 255.1134, found 255.1153. Anal. ($C_{15}H_{16}Br_2N_2O_2 \cdot H_2O$) C, H, N, Br.

1-(2-Amino-5-hydroxyphenyl)-6,7-dihydroxy-3,4-dihydroisoquinoline Dihydrobromide (10b). The title compound (191 mg, 67%) was prepared from dihydroisoquinoline **9b** (205 mg, 0.656 mmol) according to general procedure A: mp >272 °C (dec); IR (KBr) 3428 (s br), 3120 (m br), 3040 (w), 2576 (w), 1628 (m), 1603 (m), 1615 (m), 1571 (s), 1503 (m), 1470 (m), 1435 (m), 1387 (w), 1342 (m), 1328 (m), 1305 (s), 1220 (m), 1197 (m), 1156 (m), 1113 (m), 914 (w), 879 (m) cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.29 (m, 2H, 4-H$^\alpha$, 4-H$^\beta$), 4.08−4.13 (m, 2H, 3-H$^\alpha$, 3-H$^\beta$), 6.73 (s, 1H, 5-H), 7.00 (s, 1H, 8-H), 7.14 (d, J = 2.8 Hz, 1H, 6′-H), 7.28 (dd, J = 8.8, 2.8 Hz, 1H, 4′-H), 7.54 (d, J = 8.8 Hz, 1H, 3′-H); ^{13}C NMR (75 MHz, [D_6]-DMSO) δ 25.89 (C-4), 43.52 (C-3), 117.39 (CH), 117.96 (C), 119.32 (CH), 120.19 (CH), 121.12 (C), 121.75 (CH), 128.02 (C), 128.23 (C), 136.35 (C), 147.17 (C), 158.73 (C), 159.81 (C), 170.75 (C-1); EI-MS m/z (%) = 270 (28) [M^+], 269 (100) [M^+ − H], 253 (15) [M^+ − NH_3]; HR-EI-MS calcd for $C_{15}H_{14}N_2O_3$ 270.1004, found 270.0996.

General Procedure E. The amines used as ligands were dissolved at 60 °C in 0.05 M HCl (5 mL). Hydrobromide **6a** was used directly as H_2O solution. After addition of the equimolar amount of K_2PtCl_4, the mixture was neutralized slowly with 1 M NaOH to pH 6. The complexes precipitated out, were washed twice with H_2O and once with EtOH, and were dried.

[1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (12a). The title compound (148 mg, 68%) was prepared from tetrahydroisoquinoline **5a** (100 mg, 0.396 mmol), 1 M HCl (0.80 mL), K_2PtCl_4 (168 mg, 0.396 mmol), and 1 M NaOH (0.80 mL) according to the general procedure E: mp > 200 °C (dec); IR (KBr) 3477 (br, υ-NH_2), 3228 (m), 3197 (m), 3158 (m), 3107 (m), 3072 (sh), 2963 (m), 2932 (m), 2835 (m, OCH_3), 1613 (s), 1516 (s, NH), 1498 (m), 1458 (s), 1365 (m), 1323 (m), 1260 (s), 1237 (s), 1221 (m), 1119 (m), 1010 (m), 877 (m, ρ-NH_2), 813 (m), 779 (sh), 768 (m), 748 (sh), 328 (m, υ-Pt−Cl) cm^{-1}; ^1H NMR (400 MHz, [D_6]-DMSO) δ 2.60 (m, 1H, 4-H$^\alpha$), 2.84−2.89 (m, 1H, 4-H$^\beta$), 3.53−3.68 (m, 2H, 3-H$^\alpha$, 3-H$^\beta$), 3.77 (s, 6H, 2 OCH_3), 5.42 (s, 1H, 1-H), 6.10 (d, J = 6.8 Hz, 1H, 5-H$^\#$), 6.26−6.35 (m, 2H, NH_2), 6.82 (s, 2H, ArH), 7.31 (t, J = 7.2 Hz, 2H, ArH), 7.50 (d, J = 7.6 Hz, 1H, ArH); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 27.97 (C-4), 44.87 (C-3), 56.04 (2C, OCH_3), 58.85 (C-1), 110.98 (C-5$^\#$), 112.59 (C-8$^\#$), 122.35 (C), 124.72 (C), 125.86 (CH), 126.76 (CH), 129.70 (C), 130.13 (CH), 131.57 (CH), 147.89 (C-2‡), 148.99 (C-6‡), 149.50 (C-7‡). Anal. ($C_{17}H_{20}Cl_2N_2O_2Pt$) C, H, N.

[1-(2-Amino-5-methoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (12b). The title compound (144 mg, 78%) was prepared from tetrahydroisoquinoline **5b** (100 mg, 0.318 mmol), 1 M HCl (0.64 mL), K_2PtCl_4 (132 mg, 0.318 mmol), and 1 M NaOH (0.64 mL) according to the general procedure E: mp > 200 °C (dec); IR (KBr) 3466 (s br, υ-NH_2), 3205 (s), 3131 (s), 3006 (s), 2934 (s), 2835 (s, OCH_3), 1610 (s), 1516 (s, δ-NH_2), 1503 (s), 1463 (s), 1434 (s), 1366 (m), 1288 (s), 1267 (s), 1260 (s), 1234 (s), 1216 (s), 1187 (s), 1165 (s), 1031 (s), 1009 (s), 862 (m, ρ-NH_2), 825 (m), 780 (s), 335 (m, υ-Pt-Cl*), 325 (sh, υ-Pt-N*) cm^{-1}; ^1H NMR (400 MHz, [D_6]DMSO) δ 2.60−2.53 (m, 1H, 4-H$^\alpha$), 2.85−2.65 (m, 1H, 4-H$^\beta$), 3.50−3.75 (m, 2H, 3-H$^\alpha$, 3-H$^\beta$), 3.76 (s, 6H, 2 OCH_3), 5.36 (s, 1H, 1-H), 6.0−5.8 (m, 1H, NH), 6.4−6.1 (m, 1H, NH), 8.4−6.6 (m, CH), 10.2−9.2 (m, 1H, NH); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 28.00 (C-4), 44.95 (C-3), 56.08 (OCH_3), 56.09 (OCH_3), 56.18 (OCH_3), 58.95 (C-1), 110.94, 111.62, 112.01, 112.60, 113.40, 116.46, 118.83, 123.63, 124.62, 125.70, 125.82, 126.39, 130.25, 134.50, 147.58, 147.91, 148.05, 149.04, 149.15, 149.53, 149.58, 157.25, 157.44. Anal. ($C_{18}H_{22}Cl_2N_2O_3Pt$) C, H, N.

[1-(2-Aminophenyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (13). The title compound (76 mg, 61%) was prepared from tetrahydroisoquinoline dihydrobromide **6a** (100 mg, 0.239 mmol), K_2PtCl_4 (100 mg, 0.239 mmol), and 1 M NaOH (0.44 mL) according to the general procedure E: IR (KBr) 3637 (m, OH), 3467 (sh, OH), 3434 (s, υ-NH_2), 3252 (s), 3172 (s), 3111 (s), 2957 (s), 2888 (sh), 2844 sh), 1620 (s), 1604 (s), 1592 (sh), 1521 (s, δ-NH), 1498 (s), 1461 (s), 1448 (s), 1360 (s), 1286 (s), 1274 (s), 1236 (s), 1225 (s), 1189 (s), 1169 (s), 1151 (s), 1114 (m), 1090 (m), 1038 (m), 869 (m, ρ-NH_2), 857 (m), 818 (m), 787 (m), 763 (m), 328 (m.br, υ-Pt-Cl) cm^{-1}; ^1H NMR (400 MHz, [D_6]DMSO) δ 2.14 (m, 1H, 4-H$^\alpha$), 2.39 (m, 1H, 4-H$^\beta$), 2.77 (m, 2H, 3-H), 5.29 (s, 1H, 1-H), 6.64−6.20 (m, 3H, NH), 7.01−7.79 (m, 6H), 8.86−9.14 (m, 2H, OH); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 27.72 (C-4), 44.93 (C-

3), 58.71 (C-1), 114.84 (CH), 116.12 (2C, C-5, C-8), 122.22 (C), 123.18 (C), 123.91 (CH), 124.95 (CH), 130.14 (CH), 131.72 (C), 144.56 (C-2′‡), 145.76 (C-6‡), 146.67 (C-7‡). Anal. ($C_{15}H_{16}Cl_2N_2O_2Pt \cdot 2H_2O$) C, N; H: calcd, 3.04; found, 3.61.

[1-(2-Aminophenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline]dichloroplatinum(II) (14a). The title compound (124 mg, 64%) was prepared from dihydroisoquinoline **9a** (100 mg, 0.354 mmol), 1 M HCl (0.387 mL), K_2PtCl_4 (161 mg, 0.354 mmol), and 1 M NaOH (0.387 mL) according to the general procedure E: mp > 200 °C (dec); IR (KBr) 3580 (sh), 3481 (s), 3452 (s, υ-NH_2), 3284 (m), 3159 (m), 3089 (s), 3030 (s), 2963 (s), 2912 s), 2834 (m, OCH_3), 1604 (s, C═N), 1579 (sh), 1541 (s, δ-NH), 1517 (s), 1496 (m), 1463 (s), 1453 (s), 1368 (s), 1327 (s), 1285 (s), 1273 (sh), 1215 (s), 1176 (m), 1136 (s), 1092 (m), 1040 (m), 1022 (m), 991 (m), 970 (m), 876 (m, ρ-NH_2), 865 (sh), 803 (m), 773 (m), 483 (m), 452 (m), 332 (sh, υ-Pt-N*), 328 (m, υ-Pt-Cl*) cm^{-1}; ^1H NMR (400 MHz, [D_6]DMSO) δ 2.90−2.74 (m, 4H, 4-H, 3-H), 3.61 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 6.68 (s, 1H, CH), 7.09 (s, 1H, CH), 7.32 (t, J = 7.6 Hz, 1H, CH), 7.41 (d, J = 7.5 Hz, 1H, CH), 7.49 (d, J = 7.8 Hz, 1H, CH), 7.59 (t, J = 7.5 Hz, 1H, CH); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 26.54 (C-4), 53.14 (C-3), 56.37 (OCH_3), 56.55 (OCH_3), 111.43 (C-5#), 114.21 (C-8#), 120.31, 120.58, 125.33, 131.33, 132.47, 133.22, 133.83 (7 aromat. C), 140.65 (C-2′‡), 147.34 (C-6‡), 153.19 (C-7‡), 165.38 (C-1). Anal. ($C_{17}H_{18}Cl_2N_2O_2Pt \cdot {}^1/_2H_2O$) C, H, N.

[1-(2-Amino-5-methoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline]dichloroplatinum(II) (14b). The title compound (161 mg, 87%) was prepared from dihydroisoquinoline **9b** (100 mg, 0.320 mmol), 1 M HCl (0.6 mL), K_2PtCl_4 (132.9 mg, 0.320 mmol), and 1 M NaOH (0.6 mL) according to the general procedure E: mp >200 °C (dec); IR (KBr, PE) 3578 (s), 3484 (s, υ-NH_2), 3006 (s), 2934 (s), 2846 (s, OCH_3), 1605 (s, C═N), 1534 (s, δ-NH), 1516 (s), 1502 (s), 1464 (s), 1422 (s), 1410 (s), 1368 (s), 1326 (s), 1285 (s), 1269 (s), 1238 (s), 1214 (s), 1189 (m), 1166 (s), 1137 (m), 1096 (s), 1032 (s), 999 (m), 972 (m), 876 (m, ρ-NH_2), 848 (m), 838 (m), 804 (m), 331 (m, υ-Pt-Cl*), 303 (sh, υ-Pt-N*) cm^{-1}; ^1H NMR (400 MHz, [D_6]-DMSO) δ 3.09−2.77 (m, 4H, CH_2), 3.61 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.60−8.14 (m, 5H); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 25.57 (C-4), 53.28 (C-3), 56.37 (OCH_3), 56.55 (OCH_3), 56.70 (OCH_3), 111.42, 114.15, 117.16, 118.73, 120.42, 121.71, 132.31, 133.35 (8 aromat. C), 133.87, 147.33 (C-2′‡), 153.14 (C-6‡), 156.37 (C-7‡), 165.05 (C-1). Anal. ($C_{18}H_{18}Cl_2N_2O_3Pt \cdot {}^1/_2H_2O$) C, N; H: calcd, 4.00; found, 3.28.

[1-(2-Aminophenyl)-6,7-dimethoxyisoquinoline]dichloroplatinum(II) (15). The title compound (161 mg, 83%) was prepared from 1-(2-aminophenyl)-6,7-dimethoxyisoquinoline (100 mg, 0.357 mmol), 1 M HCl (0.40 mL), K_2PtCl_4 (148 mg, 0.357 mmol), and 1 M NaOH (0.40 mL) according to the general procedure E: IR (KBr) 3451 (s br), 3077 (s), 3011 (s), 2975 (s), 2835 (s, OCH_3), 1618 (s), 1556 (m), 1510 (s, δ-NH_2), 1499 (s), 1484 (s), 1452 (m), 1423 (s), 1312 (m), 1299 (m), 1299 (s), 1265 (s), 1243 (s), 1227 (s), 862 (m, ρ-NH_2), 761 (m), 333 (m.br, υ-Pt-Cl) cm^{-1}; ^1H NMR (400 MHz, [D_6]DMSO) δ 3.78 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.20−8.78 (m, 10H); ^{13}C NMR (100 MHz, [D_6]DMSO) δ 56.10 (OCH_3), 56.83 (OCH_3), 106.88, 120.55, 121.91, 122.58, 125.32, 131.24, 132.30, 132.89, 134.89, 140.03 (10 aromat. C), 143.64 (C-2′‡), 152.54 (C-6‡), 154.59 (C-7‡). Anal. ($C_{17}H_{16}Cl_2N_2O_2Pt$) C, H, N.

Cytotoxicity Assays. L1210 murine leukemia cells were cultured in suspension culture in Dulbeccos Modified Eagle's Medium (DMEM) supplemented with 10% fetal calf serum, 2 mM glutamine, 100 μg/mL streptomycin, and penicillin. The cells were grown in a humidified atmosphere of 5% CO_2/95% air at 37 °C. Pt(II) complexes were dissolved in DMSO and then diluted immediately to a final DMSO concentration of 0.5%. The ligand hydrochlorides were tested separately in H_2O solution. Cells in the logarithmic growth phase were resuspended at 5×10^4 cells/mL, mixed with various concentrations of Pt(II) complexes, and then maintained under growth conditions. Following a 48 h incubation, cell concentrations were measured with a Neubauer haemocytometer, and proliferation inhibition was calculated as a percentage of the nontreated control. The complex concentration causing 50% growth inhibition (IC_{50}) was derived by interpolation from a log-linear plot of concentration−inhibition outcomes. All compounds were at least tested in two independent duplicates.

Examination of Inhibition of DNA Synthesis. The effect of platinum complexes upon cellular DNA synthesis was measured as changes in thymidine incorporation. Experiments were performed with logarithmic growth phase L1210 cells as described above. After 42 h a solution of [6-^{3}H]thymidine [0.5 μCi] in 20 μL of DMEM was added. Following 6 h of further incubation, cells were harvested onto glass fiber filters and washed two times with distilled H_2O. Radioactivity on the filters was measured using a Wallac 1450 Microbeta liquid scintillation counter. All the data were derived from at least two independent triplicates.

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Supporting Information Available: X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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