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Original article

Synthesis and antitumor activity of *cis*-dichloroplatinum(II) complexes of 1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinolines

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Abstract

Fifteen *cis*-dichloroplatinum complexes (**5a**–**5o**) were synthesized by treatment of 1-(2-aminophenyl)-1,2,3,4-THIQs (**4a**–**4o**) with K_2PtCl_4. The antitumor activity of these compounds was examined against four different human tumor cell lines. Their structure–activity relationships for antitumor activity are reported. All of these compounds exhibited activity against MCF-7 cell line and showed good activity against WiDr cell line except **5c** and **5f**. On the other hand, compounds **5j** and **5o** are more active than the other compounds against Hepa59T/VGH cell line. The electron-donating group at the 6-position of isoquinoline ring seems to decrease the antitumor activity and the chloro substituent at the C-4 position of the aniline ring shown the highest potency. The "trans influence" dominates the control of the stability of [1-(2-aminophenyl)-1,2,3,4-THIQ]dichloroplatinums(II).

Keywords: Isoquinoline; Antitumor activity; Trans influence

1. Introduction

Cisplatin (*cis*-diamminedichloroplatinum, *cis*-DDP, *cis*-[$PtCl_2(NH_3)_2$]) has been known since 1845 [1], but not until 1970 was its antitumor activity established [2,3]. That is used to treat many kinds of malignancies, including ovarian [4], cervical [5–7], head [4], nonsmall cell lung cancer [4] and so on. It is a very useful antitumor agent for the treatment of testicular and ovarian cancers [8,9], while its geometric isomer transplatin (*trans*-DDP), *trans*-[$PtCl_2{\cdot}(NH_3)_2$], was found to be therapeutically inactive. Since the antitumor activity of cisplatin was reported, various platinum complexes have been synthesized and tested for the antitumor activity [10], however, the relationship between the ligand structure and the cytotoxicity of the complexes is still unclear [11]. Although the relationship between the ligand structure and the cytotoxicity of the complexes is still not clear, several rules are apparent [12]. Typically, the compounds must have two *cis*-coordinated amine ligands as nonleaving groups, each carrying at least one N–H bond in order to be cytotoxic. Apparently, *trans*-coordinated amine ligands always showed inactive. The synthesis of several new platinum(II) complexes with 1-(2-aminophenyl) isoquinoline ligands is reported by Nussbaum et al. [13]. Two of the new complexes, the isoquinoline backbone appears in these compounds, were more potent against L1210 murine leukemia cells than the well-established antitumor compound cisplatinum. On the other hand, isoquinolines, a kind of alkaloids, are widespread occurrence in nature and most of them exhibit bioactivity [14,15]. Berberrubine, a protoberberine alkaloid, presents antitumor activity in animal models [16], 6-alkyl-12-formyl-5,6-dihydroindolo[2,1-*a*]isoquinolines have been shown to inhibit the growth of human mammary cells [17] and 2,3-dihydroimidazo[2,1-*a*]isoquinolines which contain isoquinoline skeleton showed antitumor activity also [18]. Considering this background, we attempted to synthesize *cis*-dichloroplatinum(II) complexes of 1-(2-aminophenyl)-1,2,3,4-

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tetrahydroisoquinolines (APTHIQs) and evaluate their structure–activity relationships as antitumor agents.

2. Results and discussions

2.1. Chemistry

Three different types of isoquinoline skeleton cisplatinum complexes have been synthesized by Nussbaum et al. [13], two 1,2,3,4-THIQ dichloroplatinums(II) which have a twisted structure showed more potent against L1210 murine leukemia cells than cisplatin. In order to understand the relationship between the structure of ligands of the complexes and the biological activity further, we synthesized five series of 1-(2-aminophenyl-1,2,3,4-THIQ)dichloroplatinums(II) (APTHIQDPs) differentiated at 1-substitution level: (a) 1-(2-aminophenyl-1,2,3,4-THIQ) dichloroplatinums(II) (APTHIQDP) (b) 5-chloro-1-(2-aminophenyl-1,2,3,4-THIQ)dichloroplatinums(II) (5-Cl-APTHIQDPs) (c) 5-methoxy -1-(2-aminophenyl-1,2,3,4-THIQ)dichloroplatinums(II) (5-MeO-APTHIQDPs) (d) 5-Methyl-1-(2-aminophenyl-1,2,3,4-THIQ) dichloroplatinums(II) (5-Me-APTHIQD Ps) (e) 4-chloro-1-(2-aminophenyl-1,2,3,4-THIQ) dichloroplatinums(II) (4-Cl-AP THIQDPs).

2.1.1. Synthesis of the 1-(2-aminophenyl)-1,2,3,4-THIQs

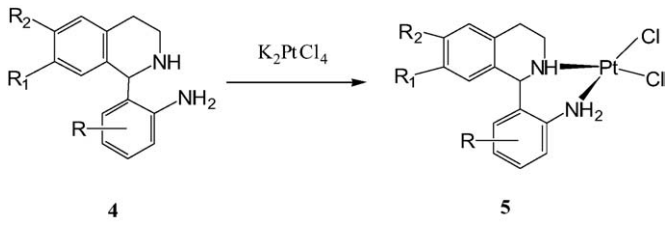
The synthesis of 1-(2-aminophenyl)-1,2,3,4-THIQs is shown in Scheme 1.

The corresponding acid chlorides, prepared by the reaction of benzoic acids with thionyl chloride, were condensed with phenylethylamines under Schotten–Baumann [19,20] conditions to give the expected *N*-phenylethylamides (**1a**–**1o**) [21]. The *N*-phenylethylamides were converted into the 1-(2-nitrophenyl)-3,4-DHIQs (**2a**–**2o**) [21] by Bischler-Napieralski [22–24] reaction conditions, respectively. Compounds **2a**–**o** were then treated with $SnCl_2{\cdot}2H_2O$ in ethyl acetate to give 1-(2-aminophenyl)-3,4-DHIQs (APDHIQ) (**3a**–**3o**) and 5,6-dihydroindazolo[3,2-*a*]isoquinoines [21]. Treatment of APDHIQs (**3a**–**3o**) with sodium borohydride in methanol gave 1-(2-aminophenyl)-1,2,3,4-THIQs (**4a**–**4o**) in good yields.

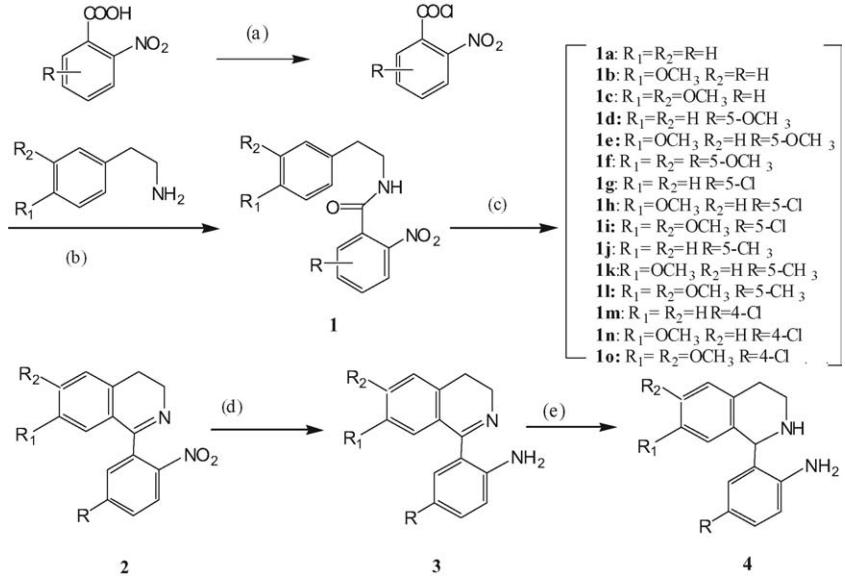
2.1.2. The synthesis of [1-(2-aminophenyl)-1,2,3,4-THIQ] dichloroplatinums(II)

The 1-(2-aminophenyl)-1,2,3,4-THIQs and equimolar amounts of K_2PtCl_4 were dissolved in 0.1 M HCl at 60–65 °C. To this stirring solution was added with 0.1 N NaOH to neutrality at 60–65 °C. [1-(2-Aminophenyl)-1,2,3,4-THIQ]dichloroplatinums(II) (**5a**–**5o**) were obtained in good yields (Scheme 2).

The structures of compounds (**1**–**3)** have been determined in our previously reported [21] and compounds (**4a**–**4o)** were determined on the basis of their ^{1}H NMR, ^{13}C NMR spectral data, mass spectroscopic and elemental analysis. The ^{1}H NMR spectroscopic data of compound **4** shows the presence of the downfield signals at δ 6.30–7.20 suggested the presence of aromatic protons, and the singlet signal at δ 5.10 (1H) suggested the C-1 position proton (CH). These compounds have a twisted structure showed multiple signals at δ 2.60–3.43 for both methylene (CH_2) group. ^{13}C NMR spectra indicated that these molecules contain 12 sp^2 carbons signals at δ 110–130, imine (C=N) signal at δ 148 no more present and C-1 position carbon signal present at δ 61. In addition, the mass spectra in-



Scheme 2. Synthetic route for compound **5**.



Scheme 1. Synthetic route for compounds **1**–**4**. Reagents: (a) $SOCl_2$, benzene (b) pyridine (c) $POCl_3$, CH_3CN (d) $SnCl_2{\cdot}2H_2O$, EtOAc (e) $NaBH_4$, methanol.

dicated that the molecular weights of compounds (**4a**–**4o**) were equal to the value of prediction, and elemental analysis showed that the molecule formula of compounds (**4a**–**4o**) satisfied our expectation also. The crystal structure of compound **4o** is shown in Fig. 1. Due to Cl-DMSO ligand exchange [25], the target products (**5a**–**5o**) showed multiple sets of signals in ^{1}H NMR and ^{13}C NMR spectra, taken in DMSO(d6) that made assignment more difficult. The ^{1}H NMR spectroscopic data of compound **5** shows the presence of multiple sets singlet signals at δ 5.30–5.90 suggested the methine (CH) group at the 1-position, and ^{13}C NMR spectra indicated that C-1 position carbon present of multiple sets singlet signals at δ 61–62 also. Elemental analysis confirmed the structure of the target products further.

2.2. Biological activities

The cytotoxicities of the series of *cis*-dichloroplatinum complexes (**5a**–**5o**) of 1-(2-aminophenyl)-1,2,3,4-THIQs (**4a**–**4o**) were examined with Hepa59T/VGH, WiDr, HeLa and MCF-7 cell lines. The results are summarized in Table 1.

As shown in Table 1, all these compounds exhibited good activity against MCF-7 cell lines, except compound **5f**. Most of these compounds showed good activity against WiDr cell lines, except **5c** and **5f**. Compounds **5j** and **5o** showed more active than other compounds against Hepa59T/VGH cell lines. Compounds **5j**–**o** showed good activity against HeLa cell lines than other compounds.

2.3. Structure–activity relationships

Concerning the relationship between structure and cytotoxicity of these compounds against human tumor cell lines, the following conclusion can be made: (a) Compounds **5c**, **5f**, **5i** and **5l** bearing an electron-donating group (MeO) at the C-6 position of isoquinoline ring seems to decrease the antitumor activity. (b) Compounds **5m**–**o** containing chloro substituent at the C-4 position of aniline ring, will improve their activity. (c) Compounds **5d**–**f** with electron-donating group (MeO) at the C-5 position of aniline ring seems to decrease the antitumor activity. This finding is in contrast to the report by Steglich. Previously, Steglich indicated that the cytotoxicity is related to the basicity of the amine ligands. Compounds **5c**, **5f** and **5i** bearing two methoxy groups at 6- and 7-positions are considered to have most basic amine in the isoquinoline ligands and show less effective in the series of complexes. We found that the antitumor activity of these platinum complexes have some relevant to the trans effect of these substituents since the trans influence [26,27] controls the stability of [1-(2-aminophenyl)-1,2,3,4-THIQ]dichloroplatinums(II). The approximate order of trans influence (resonance) is 6,7-DiMeO < 7-MeO < H (isoquinoline ring) and 5-MeO < 5-Cl < 5-Me < H < 4-Cl (aniline ring). This effect concludes why compounds **5m**–**o** are more active than the other compounds and compounds **5c**, **5f** and **5i** are less active. The 6-position methoxy group makes the amino group in the isoquinoline ring more negative and Pt–N was broken more rapidly than other THIQ dichloroplatinums (II) without methoxy group at the 6-position. Similarly, The C-5 position substituted groups with nonbonding electron pair make the amino group in the aniline ring more negative, so the Pt–N bond was broken more rapidly than other THIQ dichloroplatinums(II) (Fig. 2).

Table 1
Cytotoxicity of compounds **5a**–**o** against human tumor cells (ED_{50} ± S.D., μg/ml)

Compounds	Hepa59T/VGH[a]	WiDr[b]	HeLa[c]	MCF-7[d]
5a	10.42 ± 0.67	5.32 ± 0.61	15.84 ± 0.60	5.94 ± 0.83
5b	19.77 ± 1.20	7.12 ± 0.31	(–)	9.66 ± 0.73
5c	(–)[e]	17.39 ± 1.07	(–)	6.95 ± 0.90
5d	8.74 ± 0.29	4.88 ± 0.63	11.34 ± 0.56	4.37 ± 0.63
5e	13.67 ± 0.57	7.39 ± 0.46	14.27 ± 0.63	6.97 ± 0.19
5f	(–)	14.21 ± 0.61	(–)	(–)
5g	12.68 ± 0.56	8.49 ± 0.45	14.06 ± 0.51	2.37 ± 0.20
5h	6.45 ± 0.49	2.32 ± 0.17	11.89 ± 0.48	4.41 ± 0.39
5i	15.70 ± 0.29	9.40 ± 0.37	19.65 ± 0.35	4.77 ± 0.24
5j	1.49 ± 0.08	2.80 ± 0.21	4.03 ± 0.34	3.18 ± 0.16
5k	4.65 ± 0.28	1.40 ± 0.07	1.90 ± 0.13	4.40 ± 0.32
5l	7.73 ± 0.35	3.57 ± 0.39	2.32 ± 0.38	5.66 ± 0.38
5m	3.68 ± 0.17	4.35 ± 0.16	1.49 ± 0.02	4.30 ± 0.20
5n	3.80 ± 0.20	3.88 ± 0.16	1.22 ± 0.08	4.71 ± 0.13
5o	1.46 ± 0.04	3.61 ± 0.12	4.16 ± 0.12	3.43 ± 0.15
Cisplatin	1.06 ± 0.09	4.91 ± 0.25	4.02 ± 0.17	4.75 ± 0.21

(–): ED_{50} > 20 μg/ml.
[a] Human liver carcinoma.
[b] Human colon adenocarcinoma.
[c] Human cervical epitheloid carcinoma.
[d] Human breast adenocarcinoma.

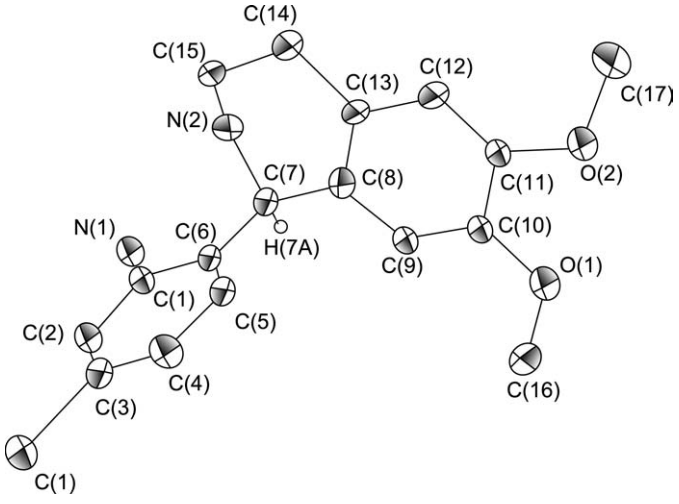


Fig. 1. Structure analysis of the 6,7-dimethoxy-1-(4-chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline **4o** in the crystal.

Although cisplatin is highly effective in the treatment of many malignancies [28] but some tumors such as colorectal and nonsmall cell lung cancers have intrinsic resistance to cisplatin [29]. However, most of our synthesized compounds are effective in the treatment of human colon adenocarcinoma, and compound **5h** is the most effective one. The 6-position methoxy group such as **5c**, **5f** and **5i** make less effective in the treatment of human colon adenocarcinoma as shown in Table 1. Similarly, compounds **5c**, **5f** and **5i** that contain methoxy group

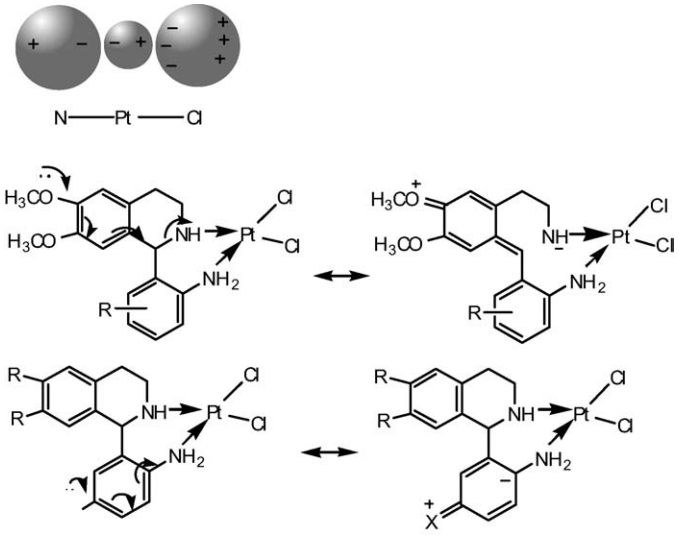


Fig. 2. Trans influence of amino group in both isoquinolines and anilines ring.

at the 6-position are poor in against other human tumor cells in our report. Smith et al. [30] have reported that compounds with substituent at the 6-position of the tetrahydroquinoline ring were promoted their ability to cause expression of a reporter gene downstream of an ecdysone response element in a mammalian cell line engineered to express the ecdysone receptor from *Aedes aegypti*. Cortes [20] have reported that an alkoxy group at the C-6 position of 1-substituted-3,4-dihydro isoquinoline were relevant for cytotoxicity in vitro against the leukemia L1210 cell line. Contrastively, in our results, compounds containing electron-donating group at the 6-position of isoquinoline ring were less active than others. On the other hand, compounds **5m**–**o** containing chloro substituent at the C-4 position of aniline ring, were more potent than cisplatin against MCF-7 cell lines and HeLa cell lines. This is because the lowest trans effect and the chelating effect [31–33] make their DNA adducts more stable than other APTHIQdichloroplatinums(II)-DNA adducts and cisplatin-DNA adducts. Application of the Student's *t*-test indicates that the chloro substituent at the C-4 position and the CH_3 at the C-5 position of values are not statistically different ($P = 0.6972$). The CH_3 at the C-5 position and the chloro substituent at the C-4 position show a similar activity. The exact reason is not clear, it may due to the lower trans influence and moderate electron-donating effect make the DNA adducts of **5j**–**l** have a similar stability as **5m**–**o**.

3. Conclusion

We have synthesized a series of cisplatinum complexes with THIQs. Where we found that a compound containing the chloro substituent at the C-4 position of the aniline ring shows a good activity. However, the compounds bearing Cl or MeO group at the C-5 position at the aniline ring gave the weaker activity than others. Having an electron-donating group at the C-6 position of isoquinoline ring also reduce the antitumor activity.

4. Experimental section

4.1. Chemistry

The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. High-resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using EI at 70 eV. All reactions were monitor by analytical TLC (silica gel 60 F_{254}, Merck). The residues were purified by flash chromatography (silica gel 230–400 μm, Merck, Germany). All melting points are uncorrected.

4.2. N-Phenylethyl-2-nitrobenzamides

4.2.1. N-Phenylethyl-2-nitrobenzam ides (**1a**–**c**) [13,21,22] (general procedure A1)

To a stirred solution of phenethylamine (30 mmol) and pyridine (38 mmol) in dry benzene (80 ml) was added a solution of 2-nitrobenzoyl chloride (27.7 mmol) in dry benzene (30 ml). The mixture was continuously stirred at room temperature overnight and then poured into water (200 ml). The solution was filtered and the solid was washed with 1.0 N HCl (80 ml), 1.0 N NaOH (80 ml), and water (80 ml). The crude product was recrystallized from EtOAc/n-hexane to give **1a**–**c**. The mother layer was evaporated and the residue was recrystallized from EtOAc/n-hexane. The white crystals were combined.

4.2.2. N-Phenylethyl-2-nitrobenzamide (**1d**–**1o**) [13,21,22] (general procedure A2)

The acids (5-methoxy-2-nitro benzoic acid, 5-methyl-2-nitrobenzoic acid, 5-chloro-2-nitrobenzoic acid or 4-chloro-2-nitrobenzoic acid) were treated with thionyl chloride in dry benzene. The resulting solution was stirred at 70–75 °C for 12 h. The excess thionyl chloride was removed under reduced pressure. The resulting acid chloride was dissolved in dry benzene, and added dropwise to a stirred solution of phenethylamine and pyridine in dry benzene. The mixture was continuously stirred at room temperature overnight and then poured into water (200 ml). The solution was filtered and the solid was washed with 1.0 N HCl (100 ml), 1.0 N NaOH (100 ml), and water (100 ml), the crude product was recrystallized from EtOAc/n-hexane. The mother liquid was evaporated and the residue was recrystallized from EtOAc/n-hexane. The crystals were combined.

4.3. 1-(2-Nitrophenyl)-3,4-dihydroiso quinolines (**2a**–**2o**) [13, 21,22]

4.3.1. General procedure B

To a stirred solution of *N*-phenyl ethyl-2-nitrobenzamides (12.9 mmol) in dry CH_3CN (80 ml) was added $POCl_3$ (32 mmol) dropwise, and the stirring was continued for 1 h at room temperature. The resulting mixture was heated to reflux and stirred for approximately 5–12 h. After removal of the sol-

vent in vacuo, $CHCl_3$ (50 ml) and H_2O (50 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 $NaHCO_3$ (3 × 100 ml), dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. Recrystallization of the crude product from EtOAc/n-hexane, afforded crystals **2a**–**2o**.

4.4. 1-(2-Aminophenyl)-3,4-dihydroiso quinolines (**3a**–**3o**) [13,21,22]

4.4.1. General procedure C

The 1-(2-nitrophenyl)-3,4-dihydro- isoquinolines (4.4 mmol) and $SnCl_2{\cdot}2H_2O$ (26.4 mmol) in dry EtOAc (150 ml) were refluxed until completion of the reaction (30 h). To this mixture were added with stirring H_2O (20 ml) and 10 N NaOH (5 ml), and the resulting solution was carefully poured into saturated aqueous $NaHCO_3$ (100 ml). After extraction with EtOAc (3 × 50 ml), the combined organic layers were dried over $MgSO_4$ (3 h), and evaporated in vacuo. Pure product was obtained by recrystallization of the crude product from EtOAc/n-hexane.

4.5. 1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinolines

4.5.1. General procedure D

To a solution of 1-(2-aminophenyl)-3,4-dihydroisoquinolines (4.2 mmol) in methanol (80 ml) and $NaBH_4$ (21 mmol) was added in portions, the mixture was continuously stirred at room temperature for approximately 2 hours. After removal of the solvent in vacuo, CH_2Cl_2 (50 ml) and H_2O (50 ml) were added. The aqueous phase was extracted with CH_2Cl_2 (20 ml × 2), and the combined organic layers were washed with water (30 ml × 2) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo and the crude product was recrystallized from acetone/n-hexane.

4.5.2. 1-(2-Aminophenyl)-1,2,3,4-tetra hydroisoquinoline (**4a**)

The title compound was obtained as a white powders in 75% yield from 1-(2-aminophenyl)-3,4-dihydroisoquinoline following procedures D; m.p. 106–108 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10–7.20 (4H, m, H-5,6,7,8), 7.01 (1H, d, J = 7.6, H-6′), 6.84 (1H, J = 7.6, H-3′), 6.73 (1H, ddd, J = 7.6, 1.2, 0.8 Hz, H-4′), 6.65 (1H, dd, J = 8.0, 0.8 Hz, H-5′), 5.12 (1H, s, H-1), 3.26–3.32 (1H, m, H-3e), 3.04–3.14 (2H, m, H-3a, H-4e), 2.79–2.86 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.0 (C-NH_2), 137.3 (C-1′), 135.0 (C-4a), 131.0 (C-8a), 128.9 (CH-6) 128.4 (CH-7), 127.0 (CH-8), 126.8 (CH-5), 126.4 (CH-4′), 125.9 (CH-6′), 117.3 (CH-5′), 116.7 (CH-3′), 61.8 (C-1), 42.9 (CH_2N), 29.6 (CH_2CH_2N). EI-MS m/z (%) = 224 (66) [M^+], 223 (53) [M^+ – H], 206 (100) [M^+ – NH_2–2H], Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.01; H, 7.22; N, 12.32.

4.5.3. 7-Methoxy-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4b**)

The title compound was obtained as a white powders in 70% yield in a similar procedure for the preparation of **4a**; m.p. 100–101 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, ddd, J = 7.6, 7.6, 1.2 Hz, H-4′), 7.06 (1H, d, J = 8.4, H-6′), 6.97 (1H, dd, J = 7.6, 1.2 Hz, H-3′), 6.74 (1H, dd, J = 8.4, 2.8 Hz, H-6), 6.69 (1H, ddd, J = 7.6, 7.6, 1.2 Hz, H-5′), 6.64 (1H, dd, J = 8.0, 1.8 Hz, H-5′), 6.37 (1H,d, J = 2.8 Hz , H-8), 5.08 (1H, s, H-1), 3.64 (3H, s, OCH_3), 3.22–3.27 (1H, m, H-3e), 2.93–3.09 (2H, m, H-3a, H-4e), 2.71–2.77 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (C-7), 146.0 (C-NH_2), 138.3 (C-1′), 131.0 (C-4a), 130.0 (C-8a), 128.5 (CH-5) 127.2 (CH-4′), 117.5 (CH-5′), 116.8 (CH-3′), 112.6 (CH-6), 111.8 (CH-8), 61.6 (C-1), 55.1 (OCH_3), 42.9 (CH_2N), 28.8 (CH_2CH_2N). EI-MS m/z (%) = EI-MS m/z (%) = 254 (100) [M^+], 253 (49) [M^+ – H], 236 (50) [M^+ – NH_2–2H], Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.67; H, 6.91; N, 11.15.

4.5.4. 6,7-Dimethoxy-1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4c**)

The title compound was obtained as a yellow powders in 78% yield in a similar procedure for the preparation of **4a**; m.p. 144–145 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (1H, ddd, J = 7.6, 1.6, 1.2 Hz, H-4′) 6.93 (1H, dd, J = 7.6, 1.2 Hz, H-6′) 6.81 (1H, s, H-5) 6.68 (1H, ddd, J = 7.2, 1.2, 1.2 Hz, H-5′), 6.64 (1H, dd, J = 8.0, 1.2 Hz, H-3′) 6.63 (1H,s, H-8) 6.32 (1H, s, H-1) 3.86 (3H, s, OCH_3) 3.64 (3H, s, OCH_3) 3.18-3.24 (1H, m, H-3e) 3.01–3.09 (1H, m, H-3a) 2.91–2.98 (1H, m, H-4e) 2.68-2.75 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (C-7), 147.3 (C-6), 146.2 (C-NH_2), 130.8 (C-1′), 139.1 (C-4a), 128.5 (C-8a), 127.3 (CH) 127.2 (CH), 117.5 (CH-8), 116.7 (CH-5), 111.5 (CH-5′), 110.0 (CH-3′), 60.6 (C-1), 55.8 (2OCH_3), 42.4 (CH_2N), 29.1 (CH_2CH_2N). EI-MS m/z (%) = 284 (93) [M^+], 283 (51) [M^+ – H], 269 (55) [M^+ – CH_3], 268 (15) [M^+ – NH_2], 253 (20) [M^+ – OCH_3], Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.83; H, 7.04; N, 9.86. Found: C, 71.60; H, 7.09; N, 9.82.

4.5.5. 1-(5-Methoxy-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4d**)

The title compound was obtained in 65% yield in a similar procedure for the preparation of **4a**; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.14–7.18 (2H, m, H-7,8), 7.05–7.10 (1H, ddd, J = 7.6, 7.6, 2.4 Hz, H-6), 6.85 (1H, d, J = 7.6 Hz, H-5), 6.71 (1H, dd, J = 8.8, 2.8 Hz, H-3′), 6.62 (2H, m, H-4′,6′), 5.10 (1H, s, H-1), 3.73 (3H, s, OCH_3), 3.23–3.30 (1H, m, H-3e), 3.01–3.12 (2H, m, H-3a, H-4e), 2.78–2.85 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (C-5′), 139.5 (C-NH_2), 136.9 (C-1′), 134.9 (C-4a), 129.0 (C-8a), 128.8 (CH-6) 126.9 (CH-7), 126.5 (CH-8), 125.9 (CH-5), 117.7 (CH-3′), 117.4 (CH-4′), 113.3 (CH-6′), 61.2 (C-1), 55.7 (OCH_3), 42.6 (CH_2N), 29.4 (CH_2CH_2N). EI-MS m/z (%) = 254 (100) [M^+], 253 (47) [M^+ – 1], Anal. Calcd for $C_{16}H_{18}N_2O{\cdot}1/8\ CHCl_3$: C, 71.93; H, 6.79; N, 10.04. Found: C, 71.88; H, 6.89; N, 9.94.

*4.5.6. 7-Methoxy-1-(5-methoxy-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4e**)*

The title compound was obtained as a white powders in 68% yield in a similar procedure for the preparation of **4a**; m.p. 96–98 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05(1H, d, J = 8.4, H-5), 6.72 (1H, dd, J = 8.4, 2.8 Hz, H-6), 6.69 (1H, d, J = 2.8 Hz, H-8), 6.60 (1H, d, J = 8.4, 2.8 Hz, H-4′), 6.60 (1H, d, J = 8.4 Hz, H-3′), 6.39 (1H, d, J = 2.8 Hz, H-6′), 5.09 (1H, s, H-1), 3.72 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.20–3.40 (3H, br, NH, NH_2), 3.20–3.25 (1H, m, H-3e) 3.02–3.08 (1H, m, H-3a) 2.93–2.99 (1H, m, H-4e) 2.73–2.78 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7 (C-5′), 152.1 (C-7), 139.5 (C-NH_2), 137.7 (C-1′), 130.0 (C-4a), 128.6 (C-8a), 127,0 (C-5), 117.9 (CH-4′) 117.3 (CH-3′), 113.4 (CH-6′), 112.8 (CH-8), 111.9 (CH-5), 61.0 (C-1), 55.7 (OCH_3), 55.1 (OCH_3), 42.5 (C-3), 28.5 (C-4). EI-MS m/z (%) = 284 (100) [M^+], 283 (41) [$M^+ - 1$], Anal. Calcd for $C_{17}H_{20}N_2O$·1/4 EtOAc: C, 70.56; H, 7.24; N, 9.14. Found: C, 71.82; H, 7.34; N, 9.18.

*4.5.7. 6,7-Dimethoxy-1-(5-methoxy-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4f**)*

The title compound was obtained as a white powders in 75% yield in a similar procedure for the preparation of **4a**; m.p. 98–100 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, dd, J = 8.4, 2.8 Hz, H-4′), 6.61 (1H, d, J = 8.4 Hz, H-3′), 6.61 (1H, s, H-5), 6.52 (1H, d, J = 2.8 Hz, H-3′), 6.33 (1H, s, H-8), 5.10 (1H, s, H-1), 3.86 (3H, s, OCH_3), 3.70 (3H, s, OCH_3) , 3.66 (3H, s, OCH_3), 3.15–3.21 (1H, m, H-3e) 3.01–3.07 (1H, m, H-3a) 2.88–2.95 (1H, m, H-4e) 2.71–2.76 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1 (C-7), 147.4 (C-6), 147.3 (C-5′), 139.5 (C-NH_2), 128.9 (C-1′), 128.3 (C-4a), 127.0 (C-8a), 117.8 (CH-4′) 117.2 (CH-3′), 113.3 (CH-6′), 111.5 (CH-8), 110.0 (CH-5), 59.7 ($COCH_3$), 55.9 (OCH_3), 55.8 (OCH_3), 55.7 (C-NH_2), 41.9 (CH_2N), 28.8 (CH_2CH_2N). EI-MS m/z (%) = 314 () [M^+], Anal. Calcd for $C_{18}H_{22}N_2O_3$·1/2 EtOAc: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10; H, 7.21; N, 7.55.

*4.5.8. 1-(5-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4g**)*

The title compound was obtained as a white powders in 70% yield in a similar procedure for the preparation of **4a**; m.p 108–110 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.20 (2H, m, H-6,7), 7.05–7.10 (2H, m, H-5,8), 6.95 (1H, d, J = 6.4 Hz, H-6′), 6.83 (1H, d, J = 8.0 Hz, H-3′), 6.56 (1H, d, J = 8.0, Hz, H-4′), 5.07 (1H, s, H-1), 3.22–3.28 (1H, m, H-3e), 3.05–3.12 (2H, m, H-3a, H-4e), 2.78–2.85 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7 (C-NH_2), 136.4 (C-1′), 135.0 (C-4a), 130.5 (C-8a), 129.1 (CH-6) 128.6 (CH-7), 128.2 (CH-8), 126.8 (CH-5), 126.7 (CH-4′), 126.0 (CH-6′), 121.9 (CH-5′), 117.8 (CH-3′), 61.1 (C-1), 42.6 (CH_2N), 29.4 (CH_2CH_2N). EI-MS m/z (%) = 260 (29) [$M^+ + 2$], 258 (92) [M^+], 241 (100) [$M^+ - NH_2 - H$], Anal. Calcd for $C_{15}H_{15}N_2Cl$: C, 69.63; H, 5.84; N, 10.83. Found: C, 69.73; H, 5.98; N, 10.29.

*4.5.9. 7-Methoxy-1-(5-chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4h**)*

The title compound was obtained as a white powders in 76% yield in a similar procedure for the preparation of **4a**; m.p. 165–166 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 8.4 Hz, H-3′) 7.04 (1H, dd, J = 8.4 , 2.4 Hz, H-4′) 6.92 (1H, d, J = 2.4 Hz, H-6′) 6.75 (1H, dd, J = 8.4 , 2.8 Hz, H-6) 6.55 (1H, d, J = 8.4 Hz, H-5), 6.37 (1H, d, 2.8 Hz, H-8), 5.03 (1H, s, H-1), 3.67 (3H, s, OCH_3) 3.19–3.24 (1H, m, H-3e) 3.01–3.08 (1H, m, H-3a) 2.91–2.98 (1H, m, H-4e) 2.71–2.77 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7 (C-7), 144.7 (C-NH_2), 137.4 (C-Cl), 130.4 (C-1′), 130.0 (C-4a), 128.5 (C-8a), 128.2 (CH-4′), 127.2 (CH-5), 122.0 (CH-6′), 117.8 (CH-3′), 112.8 (CH-6), 111.9 (CH-8), 61.1 (C-1), 55.2 (OCH_3), 42.6 (CH_2N), 28.6 (CH_2CH_2N). EI-MS m/z (%) = 290 (35) [$M^+ + 2$], 288 (100) [M^+], Anal. Calcd for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.41; H, 5.90; N, 9.61.

*4.5.10. 6,7-Dimethoxy-1-(5-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4i**)*

The title compound was obtained as a white powders in 81% yield in a similar procedure for the preparation of **4a**; m.p. 164–166 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, dd, J = 8.4, 2.8 Hz, H-4′) 6.87 (1H, d, J = 2.4 Hz, H-6′) 6.63 (1H, s, H-5) 6.58 (1H, d, J = 8.8 Hz, H-3′), 6.31 (1H, s, H-8), 5.08 (1H, s, H-1), 3.87 (3H, s, OCH_3) 3.69 (3H, s, OCH_3) 3.15–3.21 (1H, m, H-3e) 3.02–3.08 (1H, m, H-3a) 2.89–2.98 (1H, m, H-4e) 2.71–2.78 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9 (C-7), 147.4 (C-6), 144.7 (C-NH_2), 130.3 (C-1′), 128.5 (C-4a), 128.3 (C-8a), 127.6 (CH-5′) 127.0 (CH), 122.2 (CH), 117.9 (CH-8), 111.5 (CH-5), 109.8 (CH-3′), 59.5 (C-1), 55.9 (OCH_3), 55.8 (OCH_3), 41.8 (CH_2N), 28.6 (CH_2CH_2N). EI-MS m/z (%) = 320 (32) [$M^+ + 2$], 318 (100) [M^+], Anal. Calcd for $C_{17}H_{19}N_2O_2Cl$: C, 64.05; H, 6.01; N, 8.79. Found: C, 64.00; H, 5.99; N, 8.70.

*4.5.11. 1-(5-Methyl-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4j**)*

The title compound was obtained as white powders in 72% yield in a similar procedure for the preparation of **4a**; m.p. 90–92 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.17 (2H, m, H-5,8), 7.06 (1H, ddd, J = 7.6, 7.6, 2.8 Hz, H-6), 6.93 (1H, ddd, J = 7.6, 3.2, 0.8 Hz, H-7), 6.83–6.85 (2H, m, H-4′,6′), 6.56 (1H, J = 8.0 Hz, H-3′), 5.08 (1H, s, H-1), 3.27–3.33 (1H, m, H-3e), 3.25 (2H, br, NH_2), 3.04–3.14 (2H, m, H-3a, H-4e), 2.78-2.85 (1H, m, H-4a), 2.25 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4 (C-NH_2), 137.4 (C-5′), 134.9 (C-1′), 131.6 (C-4a), 129.0 (C-8a), 128.9 (CH-6) 127.2 (CH-7), 126.8 (CH-8), 126.6 (CH-5), 126.4 (CH-4′), 125.9 (CH-6′), 116.9 (CH-3′), 61.8 (C-1), 43.1 (CH_2N), 29.6 (CH_2CH_2N), 20.4 (OCH_3). EI-MS m/z (%) = 238 (78) [M^+], 237 (75) [$M^+ - H$], 220 (100) [$M^+ - NH_2 - 2H$], Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.23; H, 7.71; N, 11.63.

*4.5.12. 7-Methoxy-1-(5-methyl-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4k**)*

The title compound was obtained as white powders in 77% yield in a similar procedure for the preparation of **4a**; m.p. 115–117 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (1H, d, J = 8.4, H-5), 6.91 (1H, d, J = 8.0, 2.0 Hz, H-4′), 6.80 (1H, d, J = 2.0 Hz, H-6′), 6.73 (1H, dd, J = 8.4, 2.8 Hz, H-6), 6.56 (1H, d, J = 8.4 Hz, H-3′), 6.38 (1H, d, J = 2.8 Hz, H-8), 5.09 (1H, s, H-1), 3.65 (3H, s, OCH_3), 3.24–3.29 (1H, m, H-3e) 3.05–3.08 (1H, m, H-3a) 2.97–3.03 (1H, m, H-4e) 2.72–2.77 (1H, m, H-4a), 2.23 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6(C-7), 143.3 (C-NH_2), 138.4 (C-5′), 131.5 (C-1′), 129.8 (C-4a), 129.0 (C-8a), 127.2 (CH-5), 126.7 (CH-4′) 117.0 (CH-3′), 112.4 (CH-6), 112.1 (CH-8), 61.6 (CH-1), 55.1 (OCH_3), 43.0 (C-3), 28.8 (C-4), 20.5 (CH_3). EI-MS *m*/*z* (%) = 268 (100) [M^+], 267 (67) [M^+ – H], Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.24; H, 7.50; N, 10.31.

*4.5.13. 6,7-Dimethoxy-1-(5-methyl-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4l**)*

The title compound was obtained as a yellow crystals in 80% yield in a similar procedure for the preparation of **4a**; m.p. 132–134 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, d, J = 8.0, 2.0 Hz, H-4′), 6.75 (1H, d, J = 2.0 Hz, H-6′), 6.63 (1H, s, H-5), 6.56 (1H, d, J = 8.4 Hz, H-3′), 6.34 (1H, s, J = 2.8 Hz, H-8), 5.03 (1H, s, H-1), 3.86 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.18–3.24 (1H, m, H-3e) 3.01–3.07 (1H, m, H-3a) 2.90–2.97 (1H, m, H-4e) 2.68–2.74 (1H, m, H-4a), 2.22 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6(C-7), 147.2 (C-6), 143.4 (C-NH_2), 131.5 (C-5′), 129.8 (C-4a), 129.0 (C-8a), 127.5 (C-1′), 127.2 (CH-6′), 126.6 (CH-4′) 116.7 (CH-3′), 111.4 (CH-5), 110.0 (CH-8), 60.5 (CH-1), 55.9 (OCH_3), 55.8 (OCH_3), 42.5 (C-3), 29.2 (C-4), 20.5 (CH_3). EI-MS *m*/*z* (%) = 298 (100) [M^+], 297 (60) [M^+ – H].

*4.5.14. 1-(4-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4m**)*

The title compound was obtained as a white powders in 60% yield in a similar procedure for the preparation of **4a**; m.p. 108–110 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14–7.20 (2H, m, H-7,8), 7.07 (1H, ddd, J = 7.6, 7.6, 2.0 Hz, H-6), 6.88 (1H, d, J = 8.0 Hz, H-6′), 6.82 (1H, d, J = 7.6 Hz, H-5), 6.66 (1H, d, J = 8.0, 2.0 Hz, H-5′), 6.61 (1H, J = 8.0, 2.0 Hz, H-3′), 5.09 (1H, s, H-1), 3.23-3.29 (1H, m, H-3e), 3.05–3.12 (2H, m, H-3a, H-4e), 2.78–2.85 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3 (C-NH_2), 136.7 (C-1′), 135.0 (C-4a), 133.9 (C-8a), EI-MS *m*/*z* (%) = 260 () [], 258 () [M^+], 241 () [M^+ – NH_2–H], Anal. Calcd for $C_{15}H_{15}N_2Cl{\cdot}1/3\ CHCl_3$: C, 61.69; H, 5.18; N, 9.38. Found: C, 61.21; H, 5.28; N, 9.22.

*4.5.15. 7-Methoxy-1-(4-chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4n**)*

The title compound was obtained as a colorless needles in 83% yield in a similar procedure for the preparation of **4a**; m.p. 140–142 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (1H, d, J = 8.4 Hz, H-6′) 6.87 (1H, d, J = 8.0 Hz, H-5), 6.75 (1H, dd, J = 8.4 , 2.8 Hz, H-5′), 6.64 (1H, dd, J = 8.0, 2.0 Hz, H-6), 6.61 (1H, d, J = 2.0 Hz, H-3′), 6.35 (1H, d, 2.0 Hz , H-8), 5.04 (1H, s, H-1), 4.20–4.80 (1H, br, NH), 3.66 (3H, s, OCH_3), 3.20–3.25 (1H, m, H-3e) 3.01–3.08 (1H, m, H-3a) 2.91–2.99 (1H, m, H-4e) 2.71–2.77 (1H, m, H-4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6 (C-7), 147.3 (C-NH_2), 137.8 (C-Cl), 133.9 (C-1′), 131.9 (C-4a), 129.9 (C-8a), 127.1 (CH-5′), 125.3 (CH-5), 117.1 (CH-6′), 116.2 (CH-3′), 112.7 (CH-6), 111.7 (CH-8), 61.1 (C-1), 55.1 (OCH_3), 42.7 (CH_2N), 28.6 (CH_2CH_2N). EI-MS *m*/*z* (%) = 290 () [M^++2], 288 () [M^+], Anal. Calcd for $C_{16}H_{17}N_2OCl$: C, 66.55; H, 5.93; N, 9.70. Found: C, 66.53; H, 5.97; N, 9.66.

*4.5.16. 6,7-Dimethoxy-1-(4-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline (**4o**)*

The title compound was obtained as a yellow crystals in 80% yield in a similar procedure for the preparation of **4a**; m.p. 135–136 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, d, J = 8.0 Hz, H-3′), 6.63 (1H, d, J = 2.0 Hz, H-5′), 6.62 (1H, d, J = 8.0 Hz, H-4′), 6.61 (1H, s, H-5), 6.29 (1H, s, H-8), 5.02 (1H, s, H-1), 4.20–4.80 (2H, br, NH_2), 3.85 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.15–3.21 (1H, m, H-3e) 3.00–3.06 (1H, m, H-3a) 2.88–2.96 (1H, m, H-4e) 2.68–2.74 (1H, m, H-4a), 1.50–2.20 (1H, br, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8 (C-7), 147.8 (C-6), 147.3 (C-NH_2), 133.4 (C-Cl), 131.7 (C-1′), 128.4 (C-4a), 127.1 (C-8a), 125.6 (CH-5′), 117.1 (CH-6′), 116.2 (CH-3′), 111.4 (CH-5), 109.6 (CH-8), 60.1 (C-1), 55.8 (OCH_3), 55.7 (OCH_3), 42.3 (CH_2N), 29.0 (CH_2CH_2N). EI-MS *m*/*z* (%) = 320 () [M^+ + 2], 318 () [M^+], Anal. Calcd for $C_{17}H_{19}N_2O_2Cl$: C, 64.05; H, 6.01; N, 8.79. Found: C, 64.08; H, 5.92; N, 8.60.

4.6. [1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinoline] dichloroplatinums(II)

4.6.1. General procedure E

The THIQs were dissolved at 60–65 °C in 0.05 M HCl (50 ml). After addition of the equimolar amount of K_2PtCl_4, the mixture was neutralized slowly with 0.1 M NaOH to pH 6. The complexes precipitated out, were washed with H_2O and with EtOH and were dried.

*4.6.2. [1-(2-Aminophenyl)-1,2,3,4-tetrahydroisoquinoline] dichloroplatinum(II) (**5a**)*

The title compound was obtained as a yellowish powders in 70% yield from **4a** following procedures E; m.p. 294–296 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.50–8.50 (3H, NH, NH_2), 7.21–7.42 (6H, m, H-6,7,3′,4′,5′,6′), 6.97–7.13 (1H, m, H-5), 6.33–6.82 (1H, m, H-8), 5.53 5.87 5.92 5.96 (1H, 4s, H-1), 3.38–3.43 (1H, m, H-3β), 2.97–3.12 (1H, m, H-3α), 2.72–2.78 (1H, m, H-4β), 2.45–2.54 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) δ 137.1 (C-2′), 133.0 (C-1′), 132.5 132.2 (4a), 130.8 (C-8a), 129.4 129.2 129.0 (C-8), 128.2 (C-

5), 127.8 (C-6), 127.5 (C-4′), 126.1 (C-6′), 125.6 (C-5′), 121.9 (C-3′), 58.4 (C-1), 44.1 (C-3), 27.6 (C-4), Anal. Calcd for $C_{15}H_{16}N_2PtCl_2·0.5H_2O$: C, 36.08; H, 3.43; N, 5.61. Found: C, 36.13; H, 3.41; N, 5.55.

*4.6.3. [1-(2-Aminophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5b**)*

The title compound was obtained as a yellowish powders in 68% yield from **4b** following procedures E; m.p. 290–292 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.50–8.70 (3H, NH, NH$_2$), 7.13–7.40 (4H, m, H-3′,4′,5′,6′), 6.90–7.01 (1H, m, H-5), 6.29–6.50 (2H, m, H-6,8), 5.50 5.62 5.82 (1H, 3s, H-1), 3.35–3.40 (1H, m, H-3β), 2.83–2.97 (1H, m, H-3α), 2.66–2.71 (1H, m, H-4β), 2.44–2.50 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) δ 157.6 (C-7), 134.0 (C-2′), 131.1 (C-1′), 130.7 (C-4a), 130.4 (8a), 129.8 (C-4′), 126.2 (C-6′), 125.8 (C-3′), 125.2 (C-4′), 115.0 (C-5), 114.2 (C-6), 112.4 (C-8), 58.9 (C-1), 55.4 55.3 55.2 (OCH$_3$), 44.6 (C-3), 27.1 (C-4), Anal. Calcd for $C_{16}H_{18}N_2OPtCl_2·0.5H_2O$: C, 36.31; H, 3.62; N, 5.29. Found: C, 36.36; H, 3.68; N, 5.26.

*4.6.4. [1-(2-Aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5c**)*

The title compound was obtained as a yellowish powders in 67% yield from **4c** following procedures E; m.p. 298–300 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.47–9.50 (3H, NH, NH$_2$), 7.28–7.40 (1H, m, H-6′), 7.06–7.16 (1H, m, H-4′), 6.70–6.84 (2H, m, H-3′,5′), 6.25–6.56 (2H, m, H-5, 8), 5.42 5.78 5.85 5.84 (1H, 4s, H-1), 3.79 3.78 3.68 3.63 3.54 (OCH$_3$), 3.24–3.40 (1H, m, H-3β), 2.88-2.97 (1H, m, H-3α), 2.63–2.66 (1H, m, H-4β), 2.43–2.50 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) δ 148.9 (C-7), 147.4 (C-6), 137.2 (C-2′), 132.3 (C-1′), 130.9 130.5 (C-4a), 129.7 129.4 (8a), 126.1 125.7 (C-4′), 125.1 124.9 (C-6′), 124.1 (C-3′), 121.8 (C-4′), 111.8 111.3 (C-5), 110.3 (C-8), 58.2 (C-1), 55.6 55.5 55.4 (OCH$_3$), 44.2 (C-3), 27.3 (C-4), Anal. Calcd for $C_{17}H_{20}N_2O_2PtCl_2·H_2O$: C, 35.93; H, 3.90; N, 4.93. Found: C, 36.89; H, 4.01; N, 5.01.

*4.6.5. [1-(5-Methoxy-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5d**)*

The title compound was obtained as a yellowish powders in 58% yield from **4d** following procedures E; m.p. 280–282 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.60–8.50 (3H, NH, NH$_2$), 7.15–7.48 (4H, m, H-5,6,7,8), 6.79–7.00 (3H, m, H-3′,4′,6′), 5.50 5.76 5.77 5.85 (1H, 4s, H-1), 3.57 3.61 (OCH$_3$), 3.36–3.43 (1H, m, H-3β), 2.89–3.03 (1H, m, H-3α), 2.76–2.80 (1H, m, H-4β), 2.47–2.56 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) 156.8 (C-5′), 134.6 134.1 (C-2′), 133.9 133.8 (C-1′), 133.3 (C-4a), 132.6 (8a), 129.7 129.3 129.2 129.1(C-6,7), 126.3 (C-5), 125.9 (C-8), 123.2 (C-3′), 118.4 118.3 118.2 (C-4′), 112.9 (C-6′), 58.7 (C-1), 55.4 55.3 55.2 (OCH$_3$), 44.5 (C-3), 27.6 (C-4), Anal. Calcd for $C_{16}H_{18}N_2OPtCl_2$: C, 36.93; H, 3.49; N, 5.38. Found: C, 36.63; H, 3.55; N, 5.32.

*4.6.6. [1-(5-Methoxy-2-aminophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5e**)*

The title compound was obtained as a yellowish powders in 61% yield from **4e** following procedures E; m.p. 280–282 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.55–8.50 (3H, NH, NH$_2$), 7.11–7.48 (2H, m, H-5,3′), 6.89–7.02 (3H, m, H-6,8,4′), 6.40–6.49 (1H, m, 6′), 5.45 5.73 5.78 5.83 (1H, 4s, H-1), 3.73 3.69 3.67 (OCH$_3$), 3.64 3.63 3.59 (OCH$_3$), 3.32–3.43 (1H, m, H-3β), 2.81–2.93 (1H, m, H-3α), 2.68–2.72 (1H, m, H-4β), 2.47–2.51 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) 157.4 (C-7), 156.8 156.2 (C-5′), 134.4 (C-2′), 133.6 (C-1′), 130.5 (C-4a), 130.3 130.2 (8a), 125.9 125.6 125.0 (C-5), 123.1 (C-3′), 118.3 118.2 (C-4′), 114.9 114.4 114.0 (C-6), 112.9 (C-6′), 112.3 112.1 (C-8), 58.8 (C-1), 55.4 55.3 55.2 55.1 55.0 (2OCH$_3$), 44.6 (C-3), 26.9 (C-4), Anal. Calcd for $C_{17}H_{20}N_2O_2PtCl_2$: C, 37.10; H, 3.66; N, 5.09. Found: C, 37.11; H, 3.73; N, 5.03.

*4.6.7. [1-(5-Methoxy-2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5f**)*

The title compound was obtained as a yellowish powders in 75% yield from **4f** following procedures E; m.p. 306–309 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.59–9.30 (3H, NH, NH$_2$), 7.37–7.49 (1H, m, H-3′), 6.81–7.09 (3H, m, H-8,4′,6′), 6.24 6.37 6.42 6.45 (1H, 4s, 5), 5.37 5.72 5.80 5.88 (1H, 4s, H-1), 3.81 3.78 3.77 3.73 (OCH$_3$), 3.68 3.64 (OCH$_3$), 3.60 3.57 3.55 3.53 (OCH$_3$), 3.31–3.42 (1H, m, H-3β), 2.84–2.94 (1H, m, H-3α), 2.65–2.70 (1H, m, H-4β), 2.45–2.51 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) 156.9 (C-7),149.1 (C-6) 147.3 (C-5′), 133.9 (C-2′), 129.7 (C-1′), 125.2 (8a), 124.0 (C-4a), 123.1 (C-3′), 118.4 118.3 (C-4′), 112.8 (C-6′), 112.0 (C-8), 110.3 (C-5), 58.4 (C-1), 55.7 55.6 55.5 55.4 55.3 (3OCH$_3$), 44.5 (C-3), 27.3 (C-4), Anal. Calcd for $C_{18}H_{22}N_2O_3PtCl_2$: C, 37.25; H, 3.82; N, 4.83. Found: C, 37.05; H, 3.92; N, 4.73.

*4.6.8. [1-(5-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5g**)*

The title compound was obtained as a yellowish powders in 65% yield from **4g** following procedures E; m.p. 305–308 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.54–8.90 (3H, br, NH, NH$_2$), 7.22–7.56 (6H, m, H-5,6,7,8,4′,6′), 6.70–7.02 (H, m, H-3′), 5.54 5.75 5.89 6.16 (1H, 4s, H-1), 3.30–3.43 (1H, m, H-3β), 2.85–3.07 (1H, m, H-3α), 2.79–2.84 (1H, m, H-4β), 2.49–2.57 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) δ 146.9 (C-2′), 133.9 (C-4′), 133.5 (C-1′), 132.2 131.9 (4a), 130.5 (C-8a), 129.8 129.5 (C-8), 129.2 (C-5), 128.8 (C-6), 128.2 (C-4′), 126.7 (C-6′), 123.5 (C-5′), 122.5 (C-3′), 58.7 (C-1), 44.8 (C-3), 27.8 (C-4), Anal. Calcd for $C_{15}H_{15}N_2PtCl_3$: C, 34.33; H, 2.88; N, 5.34. Found: C, 34.58; H, 2.96; N, 5.32.

*4.6.9. [1-(5-Chloro-2-aminophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5h**)*

The title compound was obtained as a yellowish powders in 66% yield from **4h** following procedures E; m.p. 292–294 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.56–9.00 (3H, br, NH,

NH_2), 7.21–7.58 (2H, m, H-4′,6′), 6.81–7.20 (2H, m, H-3′,5), 6.20–6.52 (2H, m, 6,8), 5.52 5.77 5.87 (1H, 3s, H-1), 3.73 3.69 3.62 (OCH_3), 3.29–3.42 (1H, m, H-3β), 2.81–3.01 (1H, m, H-3α), 2.71–2.80 (1H, m, H-4β), 2.49–2.51 (1H, m, H-4α); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 157.8 157.4 157.3 (C-7), 146.7 (C-5′), 135.3 (C-2′), 133.2 132.8 (C-1′), 130.7 130.4 (C-4a), 130.2 130.1 (8a), 129.6 129.5 129.3 129.2 (6′), 125.9 125.6 125.0 124.8 (C-5), 122.2 (C-3′), 117.8 (C-4′), 115.0 114.3 113.9 (C-6), 112.5 112.3 112.2 (C-8), 58.7 (C-1), 55.3 55.1 55.1 (OCH_3), 44.6 (C-3), 26.8 26.4 (C-4), Anal. Calcd for $C_{16}H_{17}N_2OPtCl_3 \cdot H_2O$: C, 33.55; H, 3.34; N, 4.89. Found: C, 33.93; H, 3.32; N, 4.88.

*4.6.10. [1-(5-Chloro-2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5i**)*

The title compound was obtained as a yellowish powders in 73% yield from **4i** following procedures E; m.p. 284–286 °C, ^1H NMR (400 MHz, $[D]_6$DMSO) δ 7.55–9.10 (3H, br, NH, NH_2), 7.41–7.50 (1H, m, H-6′), 6.81–7.20 (2H, m, H-3′,6′), 6.24–6.48 (2H, m, 5,8), 5.45 5.72 5.82 (1H, 3s, H-1), 3.79 3.78 3.78 3.78 3.69 3.54 ($3OCH_3$), 3.25–3.41 (1H, m, H-3β), 2.84–3.00 (1H, m, H-3α), 2.68–2.72 (1H, m, H-4β), 2.49–2.51 (1H, m, H-4α); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 149.1 148.6 147.6 147.4 147.1 (C-6 ,7), 146.9 (C-5′), 135.6 (C-2′), 130.4 (C-1′), 129.7 129.6 (C-4a), 129.4 129.2 (8a), 126.9 125.9 125.3 (6′), 123.7 123.2 121.7 (C-3′), 119.4 117.8 (C-4′), 112.111.6 (C-5), 110.5 110.4 (C-8), 58.2 (C-1), 55.7 55.6 55.6 55.5 55.4 (OCH_3), 44.5 (C-3), 27.3 26.9 24.3 (C-4), Anal. Calcd for $C_{17}H_{19}N_2O_2PtCl_3$: C, 34.92; H, 3.27; N, 4.79. Found: C, 35.13; H, 3.57; N, 4.74.

*4.6.11. [1-(5-Methyl-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5j**)*

The title compound was obtained as a yellowish powders in 72% yield from **4j** following procedures E; m.p. 292–294 °C,^1H NMR (400 MHz, $[D]_6$ DMSO) δ 7.40–8.50 (3H, NH, NH_2), 7.15–7.48 (6H, m, H-5,6,7,8,4′,6′), 5.90–6.15 (1H, m, H-3′), 5.50 5.62 5.89 (1H, 3s, H-1), 3.29–3.45 (1H, m, H-3β), 2.92–3.02 (1H, m, H-3α), 2.76–2.81 (1H, m, H-4β), 2.49–2.55 (1H, m, H-4α), 2.08 2.09 2.12 2.13 (3H, 4s, CH_3); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 134.1 (C-5′), 133.8 133.3 (C-2′), 133.0 132.8 (C-1′), 131.3 (C-4a), 130.0 (8a), 129.5 129.4 129.1 128.3 128.0(C-6,7), 127.9 (C-5), 127.7 (C-8), 126.3 126.2 (C-3′), 121.7 (C-4′), 120.4 (C-6′), 58.6 (C-1), 44.3 (C-3), 27.5 27.3 (C-4), 20.7 20.6 (CH_3), Anal. Calcd for $C_{16}H_{18}N_2PtCl_2$: C, 38.11; H, 3.60; N, 5.55. Found: C, 38.11; H, 3.69; N, 5.55.

*4.6.12. [1-(5-Methyl-2-aminophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline] dichloroplatinum(II) (**5k**)*

The title compound was obtained as a yellowish powders in 68% yield from **4k** following procedures E; m.p. 286–289 °C, ^1H NMR (400 MHz, $[D]_6$ DMSO) δ 7.40–8.50 (3H, NH, NH_2), 7.15–7.48 (3H, m, H-3′, 4′,6′), 6.90–7.00 (2H, m, 5,6), 6.09–6.46 (1H,m, H-8), 5.45 5.58 5.81 5.85 (1H, 4s, H-1), 3.72 3.69 3.68 3.67 (OCH_3), 3.30–3.49 (1H, m, H-3β), 2.92–3.00 (1H, m, H-3α), 2.61–2.81 (1H, m, H-4β), 2.44–2.55 (1H, m, H-4α), 2.07 2.13 2.16 2.18 (3H, 4s, CH_3); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 157.4 157.1(C-7),135.2 134.7 (C-5′), 134.1 (C-2′), 133.7 (C-1′), 132.8 132.1 131.2 (C-4a), 130.6 130.2 130.0 129.5 (8a), 125.9 125.6 125.5 (C-5), 125.0 (C-3′), 121.9 (C-4′), 120.3 (C-6), 114.9 114.0 (C-6′), 112.3 (C-8), 58.8 (C-1), 55.3 55.2 55.1 (OCH_3), 44.5 (C-3), 26.9 26.5 (C-4), 20.7 20.6 (CH_3), Anal. Calcd for $C_{17}H_{20}N_2OPtCl_2$: C, 38.21; H, 3.77; N, 5.24. Found: C, 38.24; H, 3.85; N, 5.22.

*4.6.13. [1-(5-Methyl-2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5l**)*

The title compound was obtained as a yellowish powders in 70% yield from **4l** following procedures E; m.p. 296–299 °C, ^1H NMR (400 MHz, $[D]_6$ DMSO) δ 7.40–8.50 (3H, NH, NH_2), 7.04–7.47 (2H, m, H- H-3′,4′), 6.90–7.00 (1H, m, H-6′), 6.09–6.46 (2H,m, H-5,8), 5.37 5.70 (1H, 2s, H-1), 3.79 3.78 3.68 3.61 ($2OCH_3$), 3.20–3.49 (1H, m, H-3β), 2.91–3.00 (1H, m, H-3α), 2.65–2.89 (1H, m, H-4β), 2.49–2.51 (1H, m, H-4α), 2.07 2.13 2.16 2.23 (3H, 4s, CH_3); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 148.9 148.6 148.4 147.3 (C-6,7), 147.0 (C-5′), 137.2 (C-2′), 134.0 (C-1′), 132.9 (8a), 131.3 (C-4a), 129.9 129.5 (C-3′), 126.2 125.3 124.2 (C-4′), 121.7 120.2 (C-6′), 111.8 112.0 (C-8), 110.5 (C-5), 58.3 57.3 (C-1), 55.7 55.6 55.5 55.4 55.3 ($2OCH_3$), 44.3 (C-3), 27.4 27.0 (C-4), 20.7 (CH_3), Anal. Calcd for $C_{18}H_{22}N_2O_2PtCl_2$: C, 38.31; H, 3.93; N, 4.96. Found: C, 38.21; H, 3.92; N, 4.96.

*4.6.14. [1-(4-Chloro-2-aminophenyl)-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5m**)*

The title compound was obtained as a yellowish powders in 61% yield from **4m** following procedures E; m.p. 290–292 °C, ^1H NMR (400 MHz, $[D]_6$DMSO) δ 7.55–8.90 (3H, br, NH, NH_2), 7.15–7.40 (5H, m, H-5,6,7,8,6′), 6.70–7.02 (1H, m, H-4′), 6.10–6.60 (1H, m, H-3′), 5.40 5.46 5.49 (1H, 3s, H-1), 3.29–3.49 (1H, m, H-3β), 2.90–3.08 (1H, m, H-3α), 2.67–2.76 (1H, m, H-4β), 2.49–2.51 (1H, m, H-4α); ^{13}C NMR (100 MHz, $[D]_6$DMSO) δ 149.2 149.0 (C-2′), 134.4 134.2 133.8 (C-4′), 133.6 133.2 133.0 (C-1′), 132.4 132.2 (4a), 132.1 132.0 131.9 (C-8a), 129.7 129.5 129.2 (C-8), 129.0 128.8 128.4 (C-5), 128.1 128.0 (C-6), 127.8 127.6 127.0 (C-8), 126.3 126.1 125.0 (C-6′), 120.4 119.9 (C-5′), 116.1 117.0 115.1 (C-3′), 62.9 58.7 57.2 (C-1), 44.5 43.7 (C-3), 27.8 27.4 27.0 (C-4), Anal. Calcd for $C_{15}H_{15}N_2PtCl_3 \cdot 1/8C_2H_5OH$: C, 34.48; H, 3.13; N, 5.27. Found: C, 35.90; H, 3.11; N, 5.45.

*4.6.15. [1-(4-Chloro-2-aminophenyl)-7-methoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5n**)*

The title compound was obtained as a yellowish powders in 70% yield from **4n** following procedures E; m.p. 302–305 °C, ^1H NMR (400 MHz, $[D]_6$DMSO) δ 7.30–9.00 (3H, br, NH, NH_2), 7.06–7.15 (2H, m, H-5′,6′), 6.81–7.00 (2H, m, H-3′,5), 6.20–6.60 (2H, m, 6,8), 5.46 5.56 5.84 (1H, 3s, H-1), 3.72 3.71 3.67 3.62 (OCH_3), 3.30–3.40 (1H, m, H-3β), 2.85–3.02 (1H, m, H-3α), 2.65–2.70 (1H, m, H-4β), 2.49–2.57 (1H, m, H-4α); ^{13}C NMR (100 MHz, $[D]_6$DMSO) 157.8 157.4 157.2 (C-7),

149.1 (C-4′), 134.2 (C-2′), 133.6 133.4 133.2 (C-1′), 133.0 132.3 132.2 (C-4a), 130.5 130.3 130.1 (8a), 125.9 125.5 (6′), 124.9 124.8 (C-5), 120.3 118.8 (C-3′), 115.9 115.0 (C-4′), 114.9 114.3 113.9 (C-6), 112.5 112.3 112.1 (C-8), 62.8 58.7 57.9 (C-1), 55.2 55.1 55.0 (OCH_3), 44.4 (C-3), 26.9 26.5 24.0 (C-4), Anal. Calcd for $C_{16}H_{17}N_2OPtCl_3$: C, 34.64; H, 3.09; N, 5.05. Found: C, 34.84; H, 3.12; N, 5.05.

*4.6.16. [1-(4-Chloro-2-aminophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline]dichloroplatinum(II) (**5o**)*

The title compound was obtained as a yellowish powders in 75% yield from **4o** following procedures E; m.p. 272–274 °C, ^{1}H NMR (400 MHz, [D]$_6$DMSO) δ 7.35–9.10 (3H, br, NH, NH_2), 6.81–7.20 (3H, m, H-3′,5′,6′), 6.40–6.70 (2H, m, 5,8), 5.41 5.42 5.72 5.80 (1H, 4s, H-1), 3.78 3.77 3.76 3.67 3.61 3.54 (3OCH_3), 3.24–3.49 (1H, m, H-3β), 2.84–3.01 (1H, m, H-3α), 2.61–2.65 (1H, m, H-4β), 2.49–2.57 (1H, m, H-4α); ^{13}C NMR (100 MHz, [D]$_6$DMSO) 149.1 148.8 148.5 148.4 147.6 (C-6, 7), 147.2 147.0 (C-4′), 134.2 (C-2′), 133.4 (C-1′), 133.2 (C-4a), 132.4 (8a), 126.2 125.8 125.7 125.2 (6′), 124.9 124.8 123.4 (C-3′), 120.2 119.0 (C-4′), 115.8 115.0 (C-5), 111.9 111.7 111.0 110.4 (C-8), 58.4 56.8 (C-1), 55.7 55.6 55.6 55.5 55.4 (OCH_3), 44.3 (C-3), 27.3 26.9 24.4 (C-4), Anal. Calcd for $C_{17}H_{19}N_2O_2PtCl_3 \cdot 1/8\ C_2H_5OH$: C, 35.04; H, 3.49; N, 4.74. Found: C, 35.56; H, 3.53; N, 4.88.

4.7. Cytotoxicity assay [34,35]

The assay using 3-(4,5-di methylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT) against Hepa59T/VGH (human liver carcinoma), WiDr (human colon adenocarcinoma), Hela (human cervical epitheloid carcinoma) and MCF-7 (human breast adenocarcinoma) tumor cells was based on the reported methods. The tumor cells were purchased from the American Type Culture Collection (ATCC). In brief, the cells were cultured in RPMI-1640 medium supplemented with serum in 5% CO_2 incubated at 37 °C. Test samples and control drug standard were prepared at concentrations of 1, 10, 20 and 40 μg/ml. After seeding 2880 cells per well in a 96-well microplate for 4 hours, 20 μl of sample or standard agent was placed in each well and incubated at 37 °C for 3 days, and then 20 μl MTT was added for 5 h. After removing the medium and adding DMSO (200 μl per well) into the microplate with shaking for 10 min, the formazan crystals (the product of MTT reacting with dehydrogenase existing in mitochondria) were redissolved and their absorbance was measured on a model MR 7000 microtiter plate reader (Dynatech International Corporation, Edgewood, NY) at a wavelength of 550 nm. The ED_{50} was defined by comparison with the untreated cells as the concentration of test sample resulting in 50% reduction of absorbance.

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