European Journal of Medicinal Chemistry 46 (2011) 356–363

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Synthesis and cytotoxicity of *cis*-dichloroplatinum (II) complexes of (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinolines

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ARTICLE INFO

Article history:
Received 30 September 2010
Received in revised form
9 November 2010
Accepted 15 November 2010
Available online 24 November 2010

Keywords:
cis-Dichloroplatinum (II) complexes
Tetrahydroisoquinolines
Synthesis
Antitumor activity

ABSTRACT

A series of novel cisplatin-type platinum complexes with (*1S*,*3S*)-1,2,3,4-tetrahydroisoquinolines as the ligands were synthesized as potential anticancer agents in several steps starting from commercially available L-DOPA. The cytotoxicities of these compounds were tested against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549 and BGC-823 cell lines by the MTT test. Some compounds exhibited better cytotoxic activity than cisplatin. The structure–activity relationship has been revealed.

1. Introduction

Platinum (II) complexes [1–3] are widely used in cancer chemotherapy. Up to now, the most important platinum-based drugs are cisplatin (**1**), carboplatin (**2**), oxaliplatin (**3**), nedaplatin (**4**), lobaplatin (**5**), and heptaplatin (**6**) (Fig. 1). The first three platinum (II) complexes are used worldwide while the last three are used mainly in Asian countries. Cisplatin [2] is one of the most potent antitumor drugs available for the therapeutic management of solid tumors, such as germ cell tumors, ovarian, lung, head and neck, bladder cancers, etc. Despite its wide application as a chemotherapeutic agent, cisplatin exhibits two main disadvantages: intrinsic or acquired resistance and toxicity. These side effects limit the use of cisplatin in some cancers. So far, tremendous efforts have been devoted to developing cisplatin analogues with broader spectra of activity, improved clinical efficacy, and reduced toxicity [3].

More recently, efforts have been directed at the design of non-classical Pt complexes to overcome the side effects of cisplatin [3], such as orally active platinum (IV) complexes [4], sterically hindered platinum (II) complexes [5], *trans*-platinum complexes [6], multinuclear platinum complexes [7], complexes with biologically active carrier ligands [8] etc. The complexes with biologically active carrier ligands are to target the Pt coordination moiety to DNA by attaching it to a suitable carrier ligand. The examples include the attachment of a Pt moiety to bioactive carrier ligands such as DNA intercalators, doxorubicin, estrogen analogues, amino acids and sugars [1d,3d,8]. Overall, studies of Pt compounds with biologically active carrier groups have yielded interesting results, and there is still potential for varying the biological activity of these compounds through altering the structure of the carrier group [3d].

1,2,3,4-Tetrahydroisosoquinoline scaffold existed in both natural products and synthetic molecules that possess various bioactivities [9]. A series of cisplatinum complexes with 1-(2-aminophenyl)-1,2,3,4-tetrahydroisoquinolines have been reported [8e,10]. Several of these new complexes showed better *in vitro* cytotoxicity against some human tumor cell lines than cisplatin. In this paper, we designed and synthesized a series of novel cisplatin analogues (compound **8a**–**r**) with (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinolines as the ligands, in which an aniline group is covalently connected with a tetrahydroisoquinoline unit at the C-3 position. All complexes were evaluated for their *in vitro* cytotoxicity against a panel of human tumor cell lines from solid tumors including HCT-8, BEL-7402, A2780, MCF-7, Hela, A549 and BGC-823 cell lines.

2. Chemistry

In order to investigate the influence of different substituents at the C-4 position of phenyl group of the 1,2,3,4-tetrahydroisoquinoline ring (R_1) and the C-4 position of aniline ring (R_2), we have designed and synthesized a series of novel cisplatin-type

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doi:10.1016/j.ejmech.2010.11.025

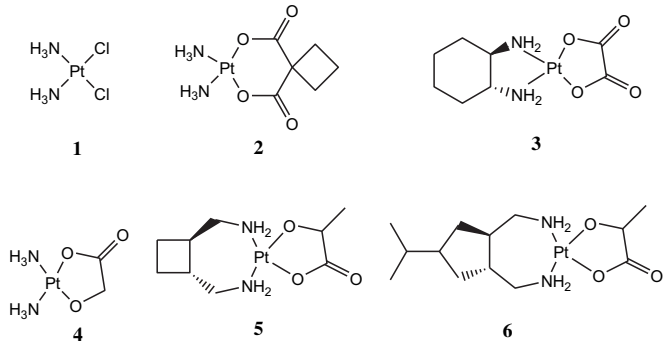
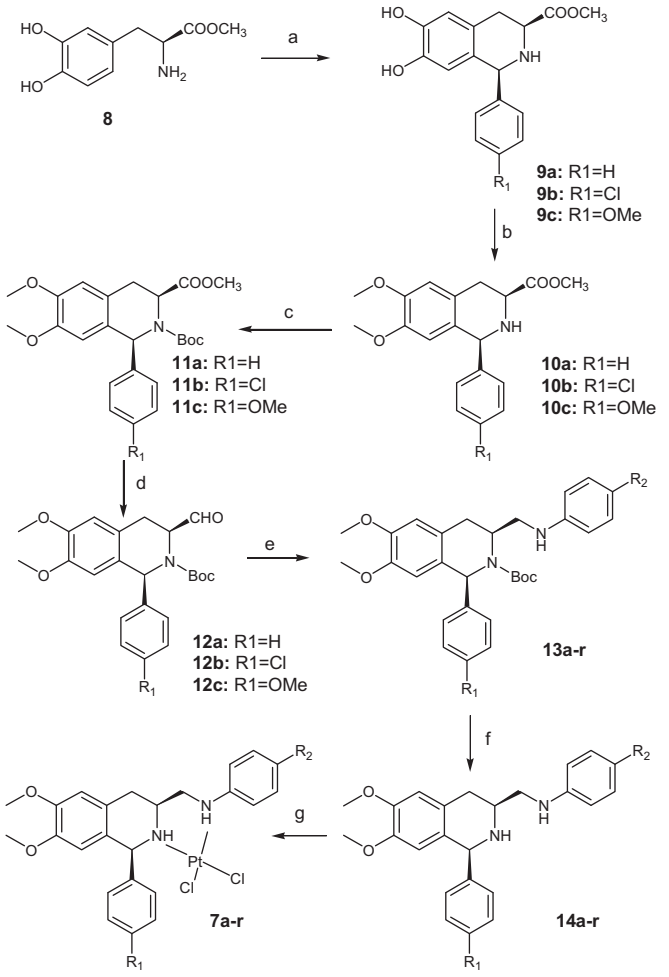


Fig. 1. Structures of the known platinum (II) complexes used in clinics.

platinum complexes with (1*S*,3*S*)-1,2,3,4-tetrahydroisoquinolines as the ligands (**7a**–**r**). Synthesis of the new derivatives (**7a**–**r**) was carried out by a stereoselective route starting from L-DOPA (Scheme 1). L-DOPA was esterified by $SOCl_2$ and CH_3OH to the corresponding ester **8**. The synthesis of **9** was accomplished *via* an asymmetric Pictet–Spengler reaction from L-DOPA methyl ester and aromatic aldehydes under acidic conditions. The major product with *cis* configuration was obtained *via* 1,3-diastereoselective induction [11]. Treatment of compound **9** with $HCOOH/Ac_2O/HCOONa$ at rt afforded the *N*-protected product. Methylation of the *N*-protected product with Me_2SO_4/K_2CO_3 in acetone under refluxing produced the corresponding *O*-methylated product. Then the *O*-methylated product was refluxed in HCl/CH_3OH to cleave the formyl group and product **10** was afforded [12]. Compound **10** was converted to the *N*-Boc amino ester **11** in almost quantitative yield by treatment with Boc_2O in the presence of triethylamine. The *N*-Boc esters **11** were reduced with DIBAL-H in dichloromethane at −78 °C to give the amino aldehydes **12**, which was then coupled with various *para*- or *meta*-substituted aryl amines through reductive amination. Subsequently, removal of Boc in the presence of trifluoroacetic acid and dimethyl sulfide led to compound **14**. The platinum (II) complexes (**7a**–**r**) were prepared by treatment of the tetrahydroisoquinoline ligands with potassium tetrachloroplatinate in a mixture of dimethylformamide and water at 60 °C.



Scheme 1. Reagents and conditions: (a) (1) $SOCl_2$, CH_3OH, rt, 72 h (2) *para*-substituted aromatic aldehyde, CH_3COOH, CH_3COONa, rt, 20 h (b) (1) HCOOH, HCOONa, $(CH_3CO)_2O$, rt, 4 h, then 1 N HCl, CH_3OH, rt, 24 h (2) K_2CO_3, Me_2SO_4, Acetone, reflux 10 h (3) $HCl–CH_3OH$, reflux 3 h (c) Boc_2O, TEA, CH_2Cl_2, rt, 16 h (d) DIBAL-H, toluene, −78 °C, 1 h. (e) *para*- or *meta*-substituted aniline, CH_3OH, rt, 30 min, then $NaBH_3CN$, rt, 2 h (f) Me_2S, TFA, CH_2Cl_2, rt, 30 min (g) K_2PtCl_4, DMF, H_2O, 60 °C, 24 h.

3. Cytotoxicity

The cytotoxicities of the *cis*-dichloroplatinum complexes of tetrahydroisoquinoline were tested against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549 and BGC-823 cell lines by the MTT method. The results are summarized in Table 1. Cisplatin was used as control substance. From the screening results, it is evident that all of these compounds exhibited good activity against the tested cell lines except A549. MCF-7 was the most sensitive cell line to all the platinum complexes. Most of these compounds are more active against MCF-7 cell line than cisplatin except **7c**. On the other hand, all of the compounds are less active against A549 cell line than cisplatin. Also, they are less active against Hela cell line than cisplatin except **7l**. Furthermore, they are less active against BGC-823 cell line than cisplatin except **7i**. Compounds **7g**–**l** with chloro-substituent at the C-4 position of phenyl (C-1 position of tetrahydroisoquinoline) are more active than the other compounds.

4. Results and discussion

Based on the comparison of the IC_{50} values of these compounds, the structure–activity relationship can be summarized as follows: (a) The existence of chloro-substituent at the C-4 position of phenyl group of the 1,2,3,4-tetrahydroisoquinoline ring would improve the activity (**7g**–**l**). (b) Compounds with electron-donating group (R_2 = MeO) or strong electron-withdrawing groups at the C-4 position of the aniline ring would decrease the antitumor activity (**7c**, **7e**, **7o** and **7q**). (c) Compounds with R_2 = 3-CF_3 (**7f**, **7l, 7r**) and compounds with R_2 = 4-Cl (**7d**, **7j**, **7p**) showed stronger cytotoxic activity against most cell lines than the compounds in the three sub-groups with the same substituent R_1 (R_1 = H, Cl, OMe).

It could be seen from Table 1 that the antitumor activities of this series of platinum complexes increase in the sequence: H < 4-MeO < 4-Cl (R_1). According to the research of Kuo, the "*trans* effect" theory can explain why compounds **7j**–**l** are more active than the other compounds [8e,13]. The inductive effect of chloro-group at the 4-position of phenyl group of tetrahydroisoquinoline ring (C-1) makes the amino group in the tetrahydroisoquinoline ring more acidic and the Pt–N bond was less stable than the other compounds (Fig. 2**A**). However, it is hard to explain why compounds **7m**–**r** (R_1 = 4-MeO) are more active than compounds **7a**–**f** (R_1 = H). It seems that the "*trans* effect" theory is not the only factor influencing the antitumor activities.

The substituent R_2 on the aniline ring has much influence on the biological activity. The compounds containing electron-donating group on the aniline ring are less active than others, probably due

Table 1
Cytotoxicity of compounds **7a**–**r** against human tumor cells (IC_{50} ± SD, μM).[a]

Compound	Compound descriptors	Human tumor cells						
		HCT-8	BEL-7402	A2780	MCF-7	Hela	A549	BGC-823
7a	R_1 = H, R_2 = H	5.51 ± 0.16	4.78 ± 0.65	8.21 ± 0.31	**3.02**[b]±**0.57**	8.92 ± 0.77	5.24 ± 0.32	2.93 ± 0.38
7b	R_1 = H, R_2 = 4-Me	8.92 ± 0.57	4.62 ± 0.43	3.52 ± 0.41	**4.61** ± **0.34**	4.79 ± 0.32	5.11 ± 0.81	2.52 ± 0.24
7c	R_1 = H, R_2 = 4-OMe	7.84 ± 0.17	12.17 ± 0.57	25.42 ± 2.05	17.45 ± 2.47	6.43 ± 0.77	36.24 ± 0.36	8.71 ± 0.91
7d	R_1 = H, R_2 = 4-Cl	3.92 ± 0.75	3.52 ± 0.81	8.90 ± 0.18	**3.82** ± **0.07**	4.93 ± 0.31	22.15 ± 2.55	4.15 ± 0.73
7e	R_1 = H, R_2 = 4-$COOCH_3$	3.43 ± 0.67	8.59 ± 0.19	7.61 ± 0.23	**4.05** ± **0.73**	4.72 ± 0.54	33.90 ± 3.17	4.02 ± 0.29
7f	R_1 = H, R_2 = 3-CF_3	**2.95** ± **0.14**	4.02 ± 0.73	5.20 ± 0.38	**3.02** ± **0.55**	2.83 ± 0.71	4.82 ± 0.28	3.24 ± 0.57
7g	R_1 = Cl, R_2 = H	**2.14** ± **0.83**	**2.41** ± **0.15**	**1.92** ± **0.05**	**1.23** ± **0.17**	2.41 ± 0.08	8.14 ± 0.55	0.93 ± 0.13
7h	R_1 = Cl, R_2 = 4-Me	**2.21** ± **0.45**	**3.32** ± **0.23**	3.41 ± 0.75	**1.92** ± **0.45**	2.23 ± 0.33	9.21 ± 0.17	1.92 ± 0.58
7i	R_1 = Cl, R_2 = 4-OMe	**2.32** ± **0.32**	**2.17** ± **0.74**	**2.74** ± **0.33**	**1.27** ± **0.38**	2.24 ± 0.39	8.63 ± 0.32	**0.63** ± **0.03**
7j	R_1 = Cl, R_2 = 4-Cl	**1.81** ± **0.23**	**2.23** ± **0.35**	**2.21** ± **0.09**	**2.01** ± **0.95**	2.71 ± 0.77	5.52 ± 0.25	1.72 ± 0.06
7k	R_1 = Cl, R_2 = 4-$COOCH_3$	3.64 ± 0.13	8.21 ± 0.43	2.88 ± 0.12	**2.33** ± **0.87**	2.83 ± 0.65	8.78 ± 0.30	2.13 ± 0.35
7l	R_1 = Cl, R_2 = 3-CF_3	**2.19** ± **0.57**	**1.92** ± **0.37**	**1.91** ± **0.43**	**1.01** ± **0.65**	**0.91** ± **0.47**	14.22 ± 1.51	19.92 ± 3.58
7m	R_1 = OMe, R_2 = H	3.12 ± 0.85	3.91 ± 0.58	3.01 ± 0.38	**1.53** ± **0.49**	4.73 ± 0.52	24.01 ± 2.32	2.21 ± 0.08
7n	R_1 = OMe, R_2 = 4-Me	8.78 ± 0.48	5.03 ± 0.43	8.72 ± 0.33	**2.72** ± **0.37**	2.41 ± 0.36	18.34 ± 3.38	2.74 ± 0.43
7o	R_1 = OMe, R_2 = 4-OMe	4.65 ± 0.33	3.17 ± 0.74	3.42 ± 0.25	**3.01** ± **0.78**	2.43 ± 0.89	49.45 ± 5.55	1.62 ± 0.83
7p	R_1 = OMe, R_2 = 4-Cl	**2.88** ± 0.72	3.23 ± 0.32	2.91 ± 0.48	**2.23** ± **0.55**	3.01 ± 0.57	5.82 ± 0.73	2.24 ± 0.74
7q	R_1 = OMe, R_2 = 4-$COOCH_3$	6.03 ± 0.35	5.71 ± 0.65	8.72 ± 0.91	**2.51** ± **0.03**	2.92 ± 0.78	44.38 ± 2.75	3.72 ± 0.90
7r	R_1 = OMe, R_2 = 3-CF_3	3.14 ± 0.49	3.23 ± 0.31	**2.54** ± **0.31**	**1.32** ± **0.60**	3.23 ± 0.85	7.03 ± 0.28	1.13 ± 0.48
Control	Cisplatin	2.92 ± 0.33	2.51 ± 0.02	2.72 ± 0.58	5.31 ± 0.08	1.43 ± 0.15	1.42 ± 0.03	0.83 ± 0.05

[a] Mean value ± SD (standard deviation from three experiments).
[b] Boldface: $IC_{50} \leq$ the control.

to its lower *trans* effect. The electron-donating group on the aniline ring makes the amino group in the aniline more basic, so the Pt–N bond is stronger than the other compounds (Fig. 2**B** and **C**). On the contrary, the strong electron-withdrawing group ($COOCH_3$) at the C-4 position of the aniline ring (compounds **7e**, **7k** and **7q**) lowered the antitumor activity.

5. Conclusion

In conclusion, we have synthesized a series of new platinum complexes with chiral 1,2,3,4-tetrahydroisoquinolines as the ligands. The cytotoxicities of the series of complexes were screened against HCT-8, BEL-7402, A2780, MCF-7, Hela, A549 and BGC-823 cell lines by the MTT test. Some compounds exhibited better cytotoxic activity than cisplatin. The structure–activity relationship has been analyzed, and this study would be helpful in designing new platinum anticancer drugs.

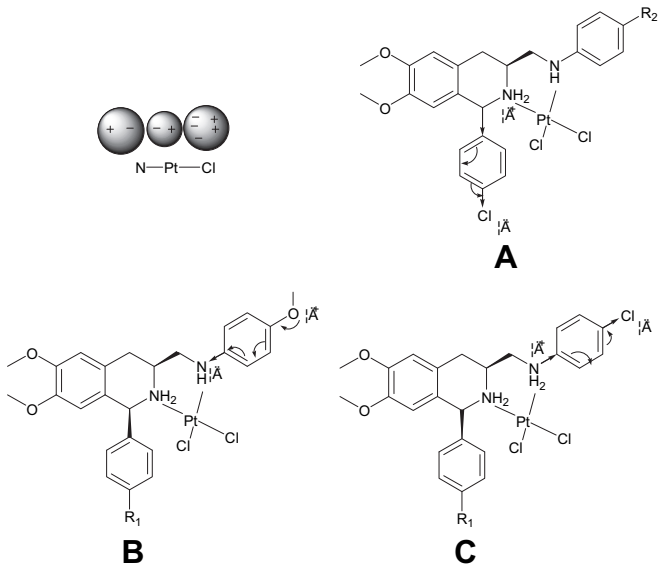


Fig. 2. *Trans* influence of amino group in both tetrahydroisoquinoline and aniline ring. (**A**: the *trans* influence of R_1; **B** and **C**: the *trans* influence of R_2).

6. Experimental

6.1. General

Melting points were measured on a Yanaco Micro Melting Point Apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer at 24 °C in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded at Mercury 75 MHz spectrometer at 24 °C in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. HRMS were carried out by Agilent LC/MSD TOF. Optical rotations were measured on a PerkinElmer Polarimeter 341LC using 10 cm cells and the sodium D line (589 nm) at 15 °C and concentration indicated. Diethyl ether and tetrahydrofuran were dried and distilled over sodium under nitrogen. Toluene, methylene chloride and hexane were distilled with P_2O_5. Other solvents used were purified and dried by standard procedures. The synthesis of compound **10** starting from commercially available L-DOPA was performed according to previously described procedures [12].

6.2. General procedure for the syntheses of *11a–c*

To a DCM (150 mL) solution of **10** (14.7 mmol) at rt was added TEA (10 mL) and Boc_2O (29.4 mmol). After stirring the mixture at room temperature for 16 h, the solution was washed with aqueous 1 M HCl, saturated $NaHCO_3$ and brine. The organic layer was separated, dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue was purified by a column chromatography on silica (3:1, v/v, EtOAc-petroleum ether) to afford pure product **11**.

6.3. General procedure for the syntheses of *12a–c*

Diisobutylaluminum hydride (1 M solution in toluene, 34.3 mL, 5 equiv) was added to a cooled (−78 °C) solution of the ester **11** (6.87 mmol) in toluene (100 mL). After 1.5 h at −78 °C, methanol (2 mL) was added and the mixture was poured into a stirred solution of Rochelle salt (20 mL of saturated aqueous solution diluted with 120 mL of H_2O at 0 °C). The mixture was filtered through Celite, and the aqueous phase was extracted with EtOAc. The combined organic

extracts were dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by column chromatography (100:1, v/v, $CHCl_3$–CH_3OH) to afford the *N*-protected α-aminoaldehyde **12** as white foam.

6.4. General procedure for the syntheses of **13a–r**

A solution of **12** (0.468 mmol) and substituted aniline (0.493 mmol) in MeOH (10 mL) containing 0.5 g of 4 Å molecular sieves was stirred at rt for 0.5 h. Glacial acetic acid (0.2 mL) was added followed by portionwise addition of $NaBH_3CN$ (63 mg) under nitrogen. The mixture was stirred for 2 h. After the mixture was cooled to 0 °C, saturated $NaHCO_3$ (50 mL) was slowly added. The mixture was then extracted with ethyl acetate. The ethyl acetate layer was washed with water and brine, dried, concentrated, and column chromatographed (100:1, v/v, $CHCl_3$–CH_3OH) to yield **13** as white foam.

6.5. General procedure for the syntheses of **14a–r**

A solution of **13** (200 mg) in 2 mL of 1:1 TFA/CH_2Cl_2 was added Me_2S (35 μL) and stirred at room temperature for 0.5 h. The solvents were removed in vacuo, and the oily residue was dissolved in ethyl acetate. The organic solution was washed by saturated aqueous solution of $NaHCO_3$, dried, concentrated, and recrystallized with methyl alcohol to yield **14** as white foam.

6.5.1. *N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine (**14a**)*

Yield: 79%. M. P.: 96–98 °C, $[\alpha]_D^{24} = +27.2$ ($c = 0.36$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.77 (br, 1H, –NH), 2.79 (m, 2H, CH_2–Ar), 3.19 (dd, 1H, $J = 8.7, 13.5$, –CH–N), 3.36 (m, 2H, $-CH_2-$N), 3.59 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.10 (br, 1H, –NH), 5.04 (s, 1H, Ar–CH–Ar), 6.16 (s, 1H, Ar–H), 6.60–6.68 (m, 3H, Ar–H), 6.71 (t, 1H, $J = 7.8$ Ar–H), 7.17 (t, 3H, $J = 7.2$, Ar–H), 7.30–7.40 (m, 5H, Ar–H). ESI-MS: 375 ($m/z + 1$); HRMS (ESI) calcd. for $C_{24}H_{27}N_2O_2$ 375.2072, found 375.2079.

6.5.2. *N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine (**14b**)*

Yield: 47%. M. P.: 89–91 °C, $[\alpha]_D^{24} = +26.4$ ($c = 0.26$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.23 (s, 3H, CH_3), 2.79 (m, 2H, CH_2–Ar), 3.17 (dd, 1H, $J = 8.7, 13.5$, –CH–N), 3.35 (m, 2H, $-CH_2-$N), 3.58 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.04 (s, 1H, Ar–CH–Ar), 6.15 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.56 (d, 2H, $J = 8.4$, Ar–H), 6.99 (d, 2H, $J = 8.4$, Ar–H), 7.30–7.40 (m, 5H, Ar–H). ESI-MS: 389 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{29}N_2O_2$ 389.2229, found 389.2247.

6.5.3. *N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine (**14c**)*

Yield: 74%. M. P.: 68–70 °C, $[\alpha]_D^{24} = +18.6$ ($c = 0.14$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.78 (m, 2H, CH_2–Ar), 3.14 (dd, 1H, $J = 8.4, 12.3$, –CH–N), 3.31 (m, 2H, $-CH_2-$N), 3.59 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.05 (s, 1H, Ar–CH–Ar), 6.16 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.61 (d, 2H, $J = 8.4$, Ar–H), 6.78 (d, 2H, $J = 9.0$, Ar–H), 7.30–7.40 (m, 5H, Ar–H). ESI-MS: 405 (m/z+1); HRMS (ESI) calcd. for $C_{25}H_{29}N_2O_3$ 405.2178, found 405.2192.

6.5.4. *N-(4-Chlorophenyl)-N-[(1S,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine (**14d**)*

Yield: 66%. M. P.: 82–84 °C, $[\alpha]_D^{24} = +18.1$ ($c = 0.16$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.68 (br, 1H, –NH), 2.77 (m, 2H, CH_2–Ar), 3.14 (dd, 1H, $J = 9.0, 12.9$, –CH–N), 3.34 (m, 2H, $-CH_2-$N), 3.59 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.16 (br, 1H, –NH), 5.04 (s, 1H, Ar–CH–Ar), 6.16 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.56 (d, 2H, $J = 8.7$, Ar–H), 7.11 (d, 2H, $J = 8.7$, Ar–H), 7.30–7.40 (m, 5H, Ar–H). ESI-MS: 409 ($m/z + 1$); HRMS (ESI) calcd. for $C_{24}H_{26}N_2O_2Cl$ 409.1677, found 409.1693.

6.5.5. *Methyl 4-([(1S,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate (**14e**)*

Yield: 86%. M. P.: 74–76 °C, $[\alpha]_D^{24} = +25.8$ ($c = 0.31$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.77 (br, 1H, –NH), 2.81 (m, 2H, CH_2–Ar), 3.22 (m, 1H, –CH–N), 3.40 (m, 2H, $-CH_2-$N), 3.59 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.69 (br, 1H, –NH), 5.06 (s, 1H, Ar–CH–Ar), 6.17 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.58 (d, 2H, $J = 8.7$ Ar–H), 7.30–7.40 (m, 5H, Ar–H). 7.85 (d, 2H, $J = 8.7$, Ar–H) ESI-MS: 433 ($m/z + 1$); HRMS (ESI) calcd. for $C_{26}H_{29}N_2O_4$ 433.2127, found 433.2142.

6.5.6. *N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl]amine (**14f**)*

Yield: 71%. M. P.: 135–137 °C, $[\alpha]_D^{24} = +13.7$ ($c = 0.30$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.71 (br, 1H, –NH), 2.81 (m, 2H, CH_2–Ar), 3.18 (m, 1H, –CH–N), 3.38 (m, 2H, $-CH_2-$N), 3.59 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.39 (br, 1H, –NH), 5.06 (s, 1H, Ar–CH–Ar), 6.17 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 6.77 (d, 1H, $J = 8.1$ Ar–H), 6.82 (s, 1H, Ar–H), 6.92 (d, 1H, $J = 8.1$, Ar–H), 7.23 (d, 1H, $J = 8.1$ Ar–H), 7.30–7.40 (m, 5H, Ar–H). ESI-MS: 443 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{26}N_2O_2F_3$ 443.1946, found 443.1959.

6.5.7. *N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine (**14g**)*

Yield: 74%. M. P.: 164–166 °C, $[\alpha]_D^{24} = +54.5$ ($c = 0.31$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.88 (br, 1H, –NH), 2.62 (m, 2H, CH_2–Ar), 3.05 (m, 1H, –CH–N), 3.21 (m, 2H, $-CH_2-$N), 3.44 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.88 (br, 1H, –NH), 4.86 (s, 1H, Ar–CH–Ar), 5.95 (s, 1H, Ar–H), 6.50 (s, 1H, Ar–H), 6.47 (d, 2H, $J = 3.9$ Ar–H), 6.55 (t, 1H, $J = 6.9$, Ar–H), 7.02 (t, 2H, $J = 7.5$ Ar–H), 7.11 (d, 2H, $J = 8.1$, Ar–H), 7.15 (d, 2H, $J = 8.7$, Ar–H) ESI-MS: 409 ($m/z + 1$); HRMS (ESI) calcd. for $C_{24}H_{26}N_2O_2Cl$ 409.1677, found 409.1693.

6.5.8. *N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine (**14h**)*

Yield: 86%. M. P.: 142–144 °C, $[\alpha]_D^{24} = +54.6$ ($c = 0.56$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.23 (s, 3H, CH_3), 2.76 (m, 2H, CH_2–Ar), 3.16 (dd, 1H, $J = 12.9, 9.3$ –CH–N), 3.34 (m, 2H, $-CH_2-$N), 3.61 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.01 (s, 1H, Ar–CH–Ar), 6.11 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.58 (d, 2H, $J = 8.4$, Ar–H), 6.99 (d, 2H, $J = 8.1$, Ar–H), 7.26 (d, 2H, $J = 6.0$ Ar–H), 7.31 (d, 2H, $J = 9.0$, Ar–H). ESI-MS: 423 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_2Cl$ 423.1839, found 423.1857.

6.5.9. *N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine (**14i**)*

Yield: 80%. M. P.: 125–127 °C, $[\alpha]_D^{24} = +49.8$ ($c = 0.42$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.99 (br, 1H, –NH), 2.77 (m, 2H, CH_2–Ar), 3.15 (dd, 1H, $J = 9.9, 12.0$, –CH–N), 3.32 (d, 2H, $J = 9.6$, $-CH_2-$N), 3.61 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 5.02 (s, 1H, Ar–CH–Ar), 6.12 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 6.61 (d, 2H, $J = 6.0$ Ar–H), 6.78 (d, 2H, $J = 7.8$, Ar–H), 7.17 (t, 2H, $J = 7.5$ Ar–H), 7.29 (d, 2H, $J = 8.1$, Ar–H), 7.31 (d, 2H, $J = 8.7$, Ar–H) ESI-MS: 439 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_3Cl$ 439.1788, found 439.1802.

6.5.10. *N-(4-Chlorophenyl)-N-[(1S,3S)-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine (**14j**)*

Yield: 74%. M. P.: 140–142 °C, $[\alpha]_D^{24} = +49.6$ ($c = 0.46$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.80 (br, 1H, -NH), 2.76 (m, 2H, CH_2–Ar), 3.14 (m, 1H, –CH–N), 3.33 (m, 2H, $-CH_2-$N), 3.61 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.10 (br, 1H, –NH), 5.02 (s, 1H, Ar–CH–Ar), 6.12 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.56 (d, 2H, $J = 8.7$, Ar–H), 7.11

(d, 2H, $J = 8.1$, Ar–H), 7.26 (d, 2H, $J = 5.4$ Ar–H), 7.32 (d, 2H, $J = 8.4$, Ar–H). ESI-MS: 443 ($m/z + 1$); HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_2Cl_2$ 443.1293, found 443.1303.

*6.5.11. Methyl 4-([(1S,3S)-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate (**14k**)*

Yield: 77%. M. P.: 89–91 °C, $[\alpha]_D^{24} = +61.7$ ($c = 0.29$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.77 (m, 2H, CH_2–Ar), 3.23 (dd, 1H, $J = 12.3$, 6.6 –CH–N), 3.40 (m, 2H, $-CH_2$–N), 3.61 (s, 3H, CH_3), 3.84 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.60 (br, 1H, –NH), 5.03 (s, 1H, Ar–CH–Ar), 6.12 (s, 1H, Ar–H), 6.61 (s, 1H, Ar–H), 6.60 (d, 2H, $J = 10.8$, Ar–H), 7.26 (d, 2H, $J = 5.4$, Ar–H), 7.32 (d, 2H, $J = 8.4$ Ar–H), 7.86 (d, 2H, $J = 8.4$ Ar–H). ESI-MS: 467 ($m/z + 1$); HRMS (ESI) calcd. for $C_{26}H_{28}N_2O_4Cl$ 467.1738, found 467.1754.

*6.5.12. N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl] amine (**14l**)*

Yield: 64%. M. P.: 129–131 °C, $[\alpha]_D^{24} = +35.2$ ($c = 0.56$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.79 (m, 2H, CH_2–Ar), 3.19 (m, 1H, –CH–N), 3.38 (m, 2H, $-CH_2$–N), 3.62 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.33 (br, 1H, –NH), 5.04 (s, 1H, Ar–CH–Ar), 6.14 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 6.78 (d, 2H, $J = 7.8$, Ar–H), 6.84 (s, 1H, Ar–H), 6.94 (d, 2H, $J = 7.2$, Ar–H), 7.25 (d, 2H, $J = 10.2$, Ar–H), 7.29 (s, 1H, Ar–H), 7.33 (d, 2H, $J = 8.4$, Ar–H), ESI-MS: 477 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_2F_3Cl$ 477.1557, found 477.1559.

*6.5.13. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine (**14m**)*

Yield: 53%. M. P.: 143–145 °C, $[\alpha]_D^{24} = +32.0$ ($c = 0.35$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 1.79 (br, 1H, –NH), 2.77 (m, 2H, CH_2–Ar), 3.18 (m, 1H, –CH–N), 3.36 (m, 2H, $-CH_2$–N), 3.60 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.09 (br, 1H, –NH), 4.99 (s, 1H, Ar–CH–Ar), 6.18 (s, 1H, Ar–H), 6.68 (s, 1H, Ar–H), 6.62 (d, 2H, $J = 4.5$ Ar–H), 6.70 (t, 1H, $J = 7.5$, Ar–H), 6.87 (d, 2H, $J = 8.1$, Ar–H), 7.17 (t, 2H, $J = 7.5$ Ar–H), 7.24 (d, 2H, $J = 8.7$, Ar–H) ESI-MS: 405 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{29}N_2O_3$ 405.2178, found 405.2193.

*6.5.14. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine (**14n**)*

Yield: 35%. M. P.: 155–157 °C, $[\alpha]_D^{24} = +4.8$ ($c = 0.21$ CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 2.20, (s, 3H, CH_3), 3.06, (m, 2H, CH_2–Ar), 3.28 (m, 1H, –CH–N), 3.45 (s, 3H, CH_3), 3.51 (m, 1H, $-CH_2$–N), 3.69 (m, 1H, $-CH_2$–N), 3.76 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.80, (br, 1H, –NH), 5.66 (s, 1H, Ar–CH–Ar), 6.07 (s, 1H, Ar–H), 6.83 (s, 1H, Ar–H), 6.80–6.90 (m, 2H, Ar–H), 7.00–7.10 (m, 4H, Ar–H), 7.46 (d, 2H, $J = 8.7$, Ar–H). ESI-MS: 419 ($m/z + 1$); HRMS (ESI) calcd. for $C_{26}H_{31}N_2O_3$ 419.2329, found 419.2325.

*6.5.15. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine (**14o**)*

Yield: 30%. M. P.: 163–165 °C, $[\alpha]_D^{24} = -2.9$ ($c = 0.17$ CH_3OH) ^{1}H NMR (300 MHz, DMSO-d_6, δ ppm): 3.00 (m, 2H, CH_2–Ar), 3.33 (m, 1H, –CH–N), 3.46 (s, 3H, CH_3), 3.64 (m, 1H, $-CH_2$–N), 3.73–3.77 (m, 1H, $-CH_2$–N), 3.73 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.97, (br, 1H, –NH), 5.69 (s, 1H, Ar–CH–Ar), 6.09 (s, 1H, Ar–H), 6.83 (s, 1H, Ar–H), 6.97 (d, 2H, $J = 9.0$, Ar–H), 7.03 (d, 2H, $J = 8.7$, Ar–H), 7.25 (d, 2H, $J = 6.6$, Ar–H), 7.45 (d, 2H, $J = 8.7$ Ar–H). ESI-MS: 435 ($m/z + 1$); HRMS (ESI) calcd. for $C_{26}H_{31}N_2O_4$ 435.2283, found 435.2278.

*6.5.16. N-(4-Chlorophenyl)-N-[(1S,3S)-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine (**14p**)*

Yield: 64%. M. P.: 127–129 °C, $[\alpha]_D^{24} = +26.3$ ($c = 0.38$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.76 (m, 2H, CH_2–Ar), 3.13 (m, 1H, –CH–N), 3.32 (m, 2H, $-CH_2$–N), 3.60 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.15 (br, 1H, –NH), 5.00 (s, 1H, Ar–CH–Ar), 6.18 (s, 1H, Ar–H), 6.61 (s, 1H, Ar–H), 6.57 (d, 2H, $J = 8.4$, Ar–H), 6.87 (d, 2H, $J = 7.8$, Ar–H), 7.11 (d, 2H, $J = 8.4$, Ar–H), 7.24 (d, 2H, $J = 9.6$, Ar–H). ^{13}C NMR ($CDCl_3$, δ ppm): 159.09, 147.70, 147.22, 146.90, 136.63, 131.07, 129.96, 129.04, 126.75, 122.05, 114.00, 113.95, 111.40, 110.76, 62.35, 55.89, 55.27, 53.40, 46.84, 33.65. ESI-MS: 439 ($m/z + 1$); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_3Cl$ 439.1783, found 439.1794.

*6.5.17. Methyl 4-([(1S,3S)-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate (**14q**)*

Yield: 87%. M. P.: 75–77 °C, $[\alpha]_D^{24} = +50.0$ ($c = 0.11$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.78 (dd, 2H, $J = 3.6$, 16.8, CH_2–Ar), 3.21 (m, 1H, –CH–N), 3.39 (m, 2H, $-CH_2$–N), 3.61 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 4.66 (br, 1H, –NH), 5.01 (s, 1H, Ar–CH–Ar), 6.19 (s, 1H, Ar–H), 6.61 (s, 1H, Ar–H), 6.59 (d, 2H, $J = 9.0$, Ar–H), 6.87 (d, 2H, $J = 8.7$, Ar–H), 7.23 (d, 2H, $J = 8.7$, Ar–H), 7.86 (d, 2H, $J = 8.7$ Ar–H). ESI-MS: 463 ($m/z + 1$); HRMS (ESI) calcd. for $C_{27}H_{31}N_2O_5$ 463.2232, found 463.2239.

*6.5.18. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl] amine (**14r**)*

Yield: 63%. M. P.: 101–103 °C, $[\alpha]_D^{24} = +18.7$ ($c = 0.53$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.78 (m, 2H, CH_2–Ar), 3.18 (m, 1H, –CH–N), 3.36 (m, 2H, $-CH_2$–N), 3.61 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 4.39 (br, 1H, –NH), 5.01 (s, 1H, Ar–CH–Ar), 6.19 (s, 1H, Ar–H), 6.62 (s, 1H, Ar–H), 6.77 (d, 2H, $J = 8.1$, Ar–H), 6.83 (s, 1H, Ar–H), 6.88 (d, 2H, $J = 8.4$, Ar–H), 6.92 (d, 1H, $J = 8.1$, Ar–H), 7.20–7.30 (m, 3H, Ar–H). ESI-MS: 473 ($m/z + 1$); HRMS (ESI) calcd. for $C_{26}H_{28}N_2O_3F_3$ 473.2052, found 473.2061.

*6.6. General procedure for the syntheses **7a**–**r***

To a solution of **14** (0.20 mmol) in DMF (1 mL) at 23 °C was added potassium tetrachloroplatinate (II) (0.22 mmol) dissolved in a mixture of DMF/H_2O (2 mL:1.6 mL). The resulting mixture was stirred in the dark for 24 h at 60 °C. Then, a drop of dimethylsulfoxide was added to destroy the excessive K_2PtCl_4 and the stirring was continued for 1 h. The solvent was evaporated and the residue was stirred vigorously in a saturated aqueous potassium chloride solution (5 mL) for 15 min. The resulting suspension was filtered, washed with water (100 mL). The product was further purified by TLC (5:1, v/v, EtOAc/*n*-hexane) to give the title compound as a yellow solid which was finally crystallized from acetone–ether.

*6.6.1. N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine dichloroplatinate(II) (**7a**)*

Yield: 41%. M. P.: 218–220 °C, $[\alpha]_D^{24} = -43.3$ ($c = 0.15$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.26 (dd, 1H, $J = 12.0$, 24.0, CH–Ar), 2.61 (m, 2H, Ar–CH–CH–N), 3.22 (dd, 1H, $J = 9.0$, 16.2 –CH–N), 3.82 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.61 (m, 1H, –CH–N), 5.92 (s, 1H, Ar–CH–Ar), 6.14 (br, 1H, –NH), 6.70 (s, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 6.93 (d, 2H, $J = 6.3$, Ar–H), 7.21 (m, 3H, Ar–H), 7.51 (m, 3H, Ar–H), 8.16 (br, 1H, –NH), 8.39 (d, 2H, $J = 6.9$, Ar–H). ESI-MS: 604 ($m/z - 35.5$); HRMS (ESI) calcd. for $C_{24}H_{26}N_2O_2ClPt$ 652604.1331, found 604.1359.

*6.6.2. N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine dichloroplatinate (II) (**7b**)*

Yield: 31%. M. P.: 225–227 °C, $[\alpha]_D^{24} = -35.2$ ($c = 0.25$ $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm): 2.28 (s, 3H, CH_3), 2.32 (m, 1H, CH–Ar), 2.59 (m, 2H, Ar–CH–CH–N), 3.21 (dd, 1H, $J = 9.3$, 16.2 –CH–N), 3.82 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.61 (m, 1H, –CH–N),

5.91 (s, 1H, Ar–CH–Ar), 6.12 (br, 1H, –NH), 6.69 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 6.82 (d, 2H, J = 8.1, Ar–H), 6.99 (d, 2H, J = 7.8, Ar–H), 7.47–7.54 (m, 3H, Ar–H), 8.08 (br, 1H, –NH), 8.37 (d, 2H, J = 7.2, Ar–H). ESI-MS: 618 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_2ClPt$ 618.1487, found 618.1492.

*6.6.3. N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine dichloroplatinate (II) (**7c**)*

Yield: 45%. M. P.: 199–201 °C, $[\alpha]_D^{24} = -46.5$ (c = 0.17 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.19 (m, 1H, CH–Ar), 2.60 (m, 2H, Ar–CH–CH–N), 3.21 (dd, 1H, J = 8.7, 15.6 –CH–N), 3.77 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.59 (m, 1H, –CH–N), 5.91 (s, 1H, Ar–CH–Ar), 6.10 (br, 1H, –NH), 6.69 (s, 2H, Ar–H), 6.71 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 6.87 (d, 2H, J = 8.4, Ar–H), 7.51 (m, 3H, Ar–H), 8.11 (br, 1H, –NH), 8.38 (d, 2H, J = 6.6, Ar–H). ESI-MS: 634 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_3ClPt$ 634.1436, found 634.1437.

*6.6.4. N-(4-Chlorophenyl)-N-[(1S,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine dichloroplatinate (II) (**7d**)*

Yield: 13%. M. P.: 206–208 °C, $[\alpha]_D^{24} = -26.0$ (c = 0.10 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.19 (dd, 1H, J = 12.6, CH–Ar), 2.62 (m, 2H, Ar–CH–CH–N), 3.22 (dd, 1H, J = 9.3, 16.5 –CH–N), 3.81 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.57 (m, 1H, –CH–N), 5.89 (s, 1H, Ar–CH–Ar), 6.07 (br, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 6.85 (d, 2H, J = 8.1, Ar–H), 7.16 (d, 3H, J = 8.1, Ar–H), 8.23 (br, 1H, –NH), 8.35 (d, 2H, J = 6.0, Ar–H). ESI-MS: 638 (m/z – 35.5); HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_2Cl_2Pt$ 638.0941, found 638.0952.

*6.6.5. Methyl 4-([(1S,3S)-6,7-dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate dichloroplatinate (II) (**7e**)*

Yield: 39%. M. P.: 215–217 °C, $[\alpha]_D^{24} = -50.7$ (c = 0.15 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.28 (m, 1H, CH–Ar), 2.64 (m, 2H, Ar–CH–CH–N), 3.23 (dd, 1H, J = 9.0, 15.6 –CH–N), 3.82 (s, 3H, CH_3), 3.92 (s, 3H, $CH_3 \times 2$), 4.61 (m, 1H, –CH–N), 5.91 (s, 1H, Ar–CH–Ar), 6.10 (br, 1H, –NH), 6.69 (s, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 6.95 (d, 2H, J = 8.1, Ar–H), 7.54 (m, 3H, Ar–H), 7.90 (d, 2H, J = 8.4, Ar–H), 8.30 (br, 1H, –NH), 8.36 (d, 2H, J = 6.0, Ar–H). ESI-MS: 662 (m/z – 35.5); HRMS (ESI) calcd. for $C_{26}H_{28}N_2O_4ClPt$ 662.1385, found 662.1375.

*6.6.6. N-[(1S,3S)-6,7-Dimethoxy-1-phenyl-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl]amine dichloroplatinate(II) (**7f**)*

Yield: 53%. M. P.: 194–196 °C, $[\alpha]_D^{24} = -46.5$ (c = 0.16 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.28 (m, 1H, CH–Ar), 2.64 (m, 2H, Ar–CH–CH–N), 3.23 (dd, 1H, J = 9.9, 16.5 –CH–N), 3.82 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 4.61 (m, 1H, –CH–N), 5.91 (s, 1H, Ar–CH–Ar), 6.10 (br, 1H, –NH), 6.70 (s, 1H, Ar–H), 6.77 (s, 1H, Ar–H), 7.06 (d, 2H, J = 8.1, Ar–H), 7.17 (s, 1H, Ar–H), 7.31 (m, 1H, Ar–H), 7.45 (d, 1H, J = 8.1, Ar–H), 7.31 (m, 3H, Ar–H), 8.30 (br, 1H, –NH), 8.35 (d, 2H, J = 6.3, Ar–H). ESI-MS: 672 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_2Cl_2PtF_3$ 672.1204, found 672.1192.

*6.6.7. N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine dichloroplatinate(II) (**7g**)*

Yield: 49%. M. P.: 168–170 °C, $[\alpha]_D^{24} = -36.8$ (c = 0.22 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.29 (m, 1H, CH–Ar), 2.61 (m, 2H, Ar–CH–CH–N), 3.22 (m, 1H, –CH–N), 3.83 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.59 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.16 (br, 1H, –NH), 6.67 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 6.95 (m, 2H, Ar–H), 7.16–7.33 (m, 3H, Ar–H), 7.51 (d, 2H, J = 7.2, Ar–H), 8.19 (br, 1H, –NH), 8.32 (d, 2H, J = 7.2, Ar–H). ESI-MS: 638 (m/z – 35.5); HRMS (ESI) calcd. for $C_{24}H_{25}N_2O_2Cl_2Pt$ 638.0935, found 638.0956.

*6.6.8. N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine dichloroplatinate(II) (**7h**)*

Yield: 37%. M. P.: 227–229 °C, $[\alpha]_D^{24} = -41.7$ (c = 0.18 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.30 (s, 3H, CH3), 2.32 (m, 1H, CH–Ar), 2.54 (m, 2H, Ar–CH–CH–N), 3.23 (dd, 1H, J = 9.3, 16.2, –CH–N), 3.82 (s, 3H, CH_3), 3.90 (s, 6H, CH_3), 4.59 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.15 (br, 1H, –NH), 6.66 (s, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.82 (d, 2H, J = 8.1 Ar–H), 7.04 (d, 2H, J = 7.8, Ar–H), 7.50 (d, 2H, J = 8.4, Ar–H), 8.08 (br, 1H, –NH), 8.31 (d, 2H, J = 8.4, Ar–H). ESI-MS: 652 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_2Cl_2Pt$ 652.1097, found 652.1088.

*6.6.9. N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine dichloroplatinate(II) (**7i**)*

Yield: 39%. M. P.: 179–181 °C, $[\alpha]_D^{24} = -36.0$ (c = 0.20 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.10 (m, 1H, CH–Ar), 2.44 (m, 2H, Ar–CH–CH–N), 3.10 (dd, 1H, J = 10.2, 15.0, –CH–N), 3.66 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 4.44 (m, 1H, –CH–N), 5.73 (s, 1H, Ar–CH–Ar), 6.00 (br, 1H, –NH), 6.53 (s, 1H, Ar–H), 6.60 (s, 1H, Ar–H), 6.62 (s, 2H, Ar–H), 6.74 (d, 2H, J = 8.1, Ar–H), 7.37 (d, 2H, J = 7.8, Ar–H), 7.96 (br, 1H, –NH), 8.19 (d, 2H, J = 7.2, Ar–H). ESI-MS: 668 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_3Cl_2Pt$ 668.1041, found 668.1023.

*6.6.10. N-(4-Chlorophenyl)-N-[(1S,3S)-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine dichloroplatinate(II) (**7j**)*

Yield: 38%. M. P.: 228–230 °C, $[\alpha]_D^{24} = -41.9$ (c = 0.32 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.32 (m, 1H, CH–Ar), 2.56 (m, 2H, Ar–CH–CH–N), 3.24 (dd, 1H, J = 9.3, 15.3, –CH–N), 3.82 (s, 3H, CH_3), 3.91 (s, 6H, CH_3), 4.55 (m, 1H, –CH–N), 5.85 (s, 1H, Ar–CH–Ar), 6.10 (br, 1H, –NH), 6.66 (s, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 6.85 (d, 2H, J = 8.1 Ar–H), 7.21 (d, 2H, J = 8.1, Ar–H), 7.50 (d, 2H, J = 7.8, Ar–H), 8.29 (br, 1H, –NH), 8.28 (d, 2H, J = 7.5, Ar–H). ESI-MS: 672 (m/z – 35.5); HRMS (ESI) calcd. for $C_{24}H_{24}N_2O_2Cl_3Pt$ 672.0551, found 672.0539.

*6.6.11. Methyl 4-([(1S,3S)-1-(4-chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate dichloroplatinate (II) (**7k**)*

Yield: 49%. M. P.: 204–206 °C, $[\alpha]_D^{24} = -50.9$ (c = 0.18 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.33 (m, 1H, CH–Ar), 2.69 (m, 2H, Ar–CH–CH–N), 3.24 (m, 1H, –CH–N), 3.83 (s, 3H, CH_3), 3.93 (s, 6H, $CH_3 \times 2$), 4.56 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.14 (br, 1H, –NH), 6.66 (s, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 6.98 (m, 2H, Ar–H), 7.53 (d, 2H, J = 8.1, Ar–H), 7.84 (br, 1H, –NH), 7.95 (d, 2H, J = 7.5, Ar–H), 8.30 (d, 2H, J = 6.3, Ar–H), ESI-MS: 696 (m/z – 35.5); HRMS (ESI) calcd. for $C_{26}H_{27}N_2O_4Cl_2Pt$ 696.0995, found 696.0981.

*6.6.12. N-[(1S,3S)-1-(4-Chlorophenyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl] amine dichloroplatinate (II) (**7l**)*

Yield: 47%. M. P.: 209–211 °C, $[\alpha]_D^{24} = -71.4$ (c = 0.14 $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.34 (m, 1H, CH–Ar), 2.65 (m, 2H, Ar–CH–CH–N), 3.22 (dd, 1H, J = 9.3, 16.5, –CH–N), 3.83 (s, 3H, CH_3), 3.93 (s, 3H, CH_3), 4.59 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.16 (br, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.78 (s, 1H, Ar–H), 7.06 (d, 1H, J = 7.5, Ar–H), 7.37 (t, 1H, Ar–H), 7.48–7.54 (m, 3H, Ar–H), 8.31 (d, 2H, J = 7.5, Ar–H), 8.35 (br, 1H, –NH). ESI-MS: 706 (m/z + 23); HRMS (ESI) calcd. for $C_{25}H_{24}N_2O_2Cl_2PtF_3$ 706.0814, found 706.0810.

*6.6.13. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-phenylamine dichloroplatinate (II) (**7m**)*

Yield: 43%. M. P.: 207–209 °C, $[\alpha]_D^{24} = -60.0$ ($c = 0.16$ $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.30 (dd, 1H, J = 11.7, 24.0, CH–Ar), 2.59 (m, 2H, Ar–CH–CH–N), 3.21 (dd, 1H, J = 6.3, 16.2 –CH–N), 3.82 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.59 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.05 (br, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 7.00 (d, 2H, J = 7.5, Ar–H), 7.05 (d, 2H, J = 8.7, Ar–H), 7.16–7.26 (m, 3H, Ar–H), 8.17 (br, 1H, –NH), 8.28 (d, 2H, J = 8.4, Ar–H). ESI-MS: 634 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{28}N_2O_3ClPt$ 634.1436, found 634.1434.

*6.6.14. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methylphenyl)amine dichloroplatinate (II) (**7n**)*

Yield: 49%. M. P.: 211–213 °C, $[\alpha]_D^{24} = -58.2$ ($c = 0.11$ $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.29 (s, 3H, Ar–CH_3), 2.20–2.40(m, 1H, CH–Ar), 2.69 (m, 2H, Ar–CH–CH–N), 3.20 (m, 1H, –CH–N), 3.82 (s, 3H, CH_3), 3.90 (s, 6H, $CH_3 \times 2$), 4.58 (m, 1H, –CH–N), 5.87 (s, 1H, Ar–CH–Ar), 6.05 (br, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.90 (m, 2H, Ar–H), 7.03 (m, 4H, Ar–H), 8.10 (br, 1H, –NH), 8.28 (d, 2H, J = 6.6, Ar–H). ESI-MS: 648 (m/z – 35.5); HRMS (ESI) calcd. for $C_{26}H_{30}N_2O_3ClPt$ 648.1587, found 648.1571.

*6.6.15. N-[(1S,3S)-6,7-Dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-(4-methoxyphenyl)amine dichloroplatinate (II) (**7o**)*

Yield: 41%. M. P.: 209–211 °C, $[\alpha]_D^{24} = -53.8$ ($c = 0.13$ $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.23 (dd, 1H, J = 9.0, CH–Ar), 2.59 (m, 2H, Ar–CH–CH–N), 3.20 (dd, 1H, J = 6.3, 16.2, –CH–N), 3.77 (s, 3H, CH_3), 3.81 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 4.57 (m, 1H, –CH–N), 5.86 (s, 1H, Ar–CH–Ar), 6.02 (br, 1H, –NH), 6.67 (s, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.70 (d, 2H, J = 8.7, Ar–H), 6.93 (d, 2H, J = 8.7, Ar–H), 7.04 (d, 2H, J = 8.4, Ar–H), 8.11 (br, 1H, –NH), 8.28 (d, 2H, J = 8.4, Ar–H). ESI-MS: 722 (m/z + 23); HRMS (ESI) calcd. for $C_{26}H_{30}N_2O_4Cl_2PtNa$ 722.1128, found 722.1135.

*6.6.16. N-(4-Chlorophenyl)-N-[(1S,3S)-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamine dichloroplatinate (II) (**7p**)*

Yield: 46%. M. P.: 215–217 °C, $[\alpha]_D^{24} = -60.7$ ($c = 0.15$ $CHCl_3$)^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.23 (m, 1H, CH–Ar), 2.63 (m, 2H, Ar–CH–CH–N), 3.21 (m, 1H, –CH–N), 3.81 (s, 3H, CH_3), 3.89 (s, 6H, $CH_3 \times 2$), 4.55 (m, 1H, –CH–N), 5.85 (s, 1H, Ar–CH–Ar), 5.98 (br, 1H, –NH), 6.66 (s, 1H, Ar–H), 6.74 (s, 1H, Ar–H), 6.70–6.80 (br, 1H, –NH), 6.92 (d, 2H, Ar–H), 7.04 (d, 2H, J = 6.3, Ar–H), 7.16, (d, 2H, Ar–H), 8.23 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$, δ ppm): 160.12, 149.29, 148.21, 144.34, 132.67, 132.52, 128.82, 128.68, 128.07, 124.34, 124.09, 113.88, 111.64, 110.28, 67.55, 61.44, 57.70, 56.01, 55.91, 55.50, 26.80. ESI-MS: 668 (m/z – 35.5); HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_3Cl_2Pt$ 668.1046, found 668.1033.

*6.6.17. Methyl 4-([(1S,3S)-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methylamino)benzoate dichloroplatinate (II) (**7q**)*

Yield: 19%. M. P.: 227–229 °C, $[\alpha]_D^{24} = -14.3$ ($c = 0.23$ $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.50 (m, 1H, CH–Ar), 2.90 (m, 2H, Ar–CH), 3.27 (m, 1H, –CH–N), 3.73 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 4.73 (m, 1H, –CH–N), 6.00 (s, 1H, Ar–CH–Ar), 6.34 (br, 1H, –NH), 6.43 (s, 1H, Ar–H), 6.63 (s, 1H, Ar–H), 6.94 (d, 3H, J = 7.2, Ar–H), 7.05 (d, 1H, J = 8.1, Ar–H), 7.40 (br, 1H, –NH), 7.71 (d, 1H, J = 8.1, Ar–H), 7.83 (d, 1H, J = 7.2 Ar–H). ESI-MS: 722 (m/z – 35.5); HRMS (ESI) calcd. for $C_{27}H_{30}N_2O_5ClPt$ 692.1491, found 692.1495.

*6.6.18. N-[(1S,3S)-6,7-dimethoxy-1-(4-methoxyphenyl)-1,2,3,4-tetrahydro-3-isoquinolinyl]methyl-N-[4-(trifluoromethyl)phenyl] amine dichloroplatinate (II) (**7r**)*

Yield: 46%. M. P.: 189–191 °C, $[\alpha]_D^{24} = -54.3$ ($c = 0.18$ $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.33 (m, 1H, CH–Ar), 2.65 (m, 2H, Ar–CH–CH–N), 3.22 (dd, 1H, J = 9.3, 16.5 –CH–N), 3.82 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 3.91 (s, 3H, CH_3), 4.59 (m, 1H, –CH–N), 5.86 (s, 1H, Ar–CH–Ar), 6.05 (br, 1H, –NH), 6.68 (s, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 7.05 (d, 2H, J = 7.8, Ar–H), 7.12 (d, 2H, J = 7.8, Ar–H), 7.26 (s, 1H, Ar–H), 7.32 (t, 1H, J = 7.8, Ar–H), 8.25 (d, 2H, J = 8.4, Ar–H), 8.38 (br, 1H, –NH). ESI-MS: 722 (m/z – 35.5); HRMS (ESI) calcd. for $C_{26}H_{27}N_2O_3ClF_3Pt$ 702.1310, found 702.1299.

6.7. Cell lines

The tumor cell lines panel consisted of BCT-8 (Human colon carcinoma cell line), BEL-7402 (Human hepatoma cell line), A2780 (Human ovarian cancer cell line), MCF-7 (Human breast adenocarcinoma cell line), Hela (Human cervix carcinoma cell line), A549 (Human lung adenocarcinoma cell line), and BGC-823 (Human gastric cancer cell line).

6.8. Cytotoxicity evaluation

Human cancer cells were cultured in PRMI1640 or DMEM/F12 supplemented with 10% fetal bovine serum, containing penicillin, streptomycin at 37 °C and humidified at 5% CO_2. Briefly, cells were placed in the appropriate media on 96-well plates in a 100 μL total volume at a density of 1–2.5 × 10^4 cells/mL and were allowed to adhere for 24 h before treatment with tested drugs in DMSO solution (10^{-5}, 10^{-6}, 10^{-7} mol/L final concentration). Triplicate wells were treated with media and agents. Cell viability was assayed after 96 h of continuous drug exposure with a tetrazolium compound [3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium salt; MTT (0.5 mg/mL, 100 μL), Ameresco Corp] in fresh medium. After the medium was removed, 150 μL of DMSO was added to each well. The plates were gently agitated until the color reaction was uniform and the OD_{570} was determined using microplate reader (Wellscan MK3, Labsystems Dragon). Microsoft Excel 2003 was used for data analysis. Media-only treated cells served as the indicator of 100% cell viability. The 50% inhibitory concentration (IC_{50}) was defined as the concentration that reduced the absorbance of the untreated wells by 50% of vehicle in the MTT assay. Assays were performed in triplicate on three independent experiments.

6.9. Statistical analysis

Data were collected from three separate experiments. The results are expressed as mean ± SD. The statistical differences were analyzed using SPSS' *t*-test. *P* value less than 0.05 was considered to indicate statistical differences.

Acknowledgements

This research was financially supported by the National Science & Technology Major Project "Key New Drug Creation and Manufacturing Program" China (Number: 2009ZX09301-003-9-1).

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