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Synthesis and cytotoxic activity of benzopyran-based platinum(II) complexes

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ABSTRACT

A series of benzopyran-based platinum complexes of types **4** and **5** were synthesized as potential anticancer agents. The novel compounds were synthesized in several steps using simple and efficient chemistry. The newly synthesized compounds were evaluated for their biological efficacy and showed significant in vitro cytotoxic activity in different hormone-dependent and -independent breast cancer cell lines. Docking and other molecular modeling experiments were also performed for one of the potent compounds, **5f**, which showed that both the possible enantiomeric forms (**5f** with *3R,4R* and **5f** with *3S,4S*) of the molecule have comparable lowest energy (for **5f** with *3R,4R*, −31.953 kcal/mol and for **5f** with 3*S,4S*, −31.944 kcal/mol). The 3D QSAR was examined for the derivatives of both enantiomeric forms and a novel relationship for the *3S,4S* derivatives is discussed.

Breast cancer is a major health problem among women in the world. The successful treatment of this disease is limited by the fact that essentially all breast cancers become resistant to chemotherapy and endocrine therapy. Moreover, many patients with estrogen receptor positive tumors do not respond to endocrine manipulation.[1] Therefore, there is a need to design new chemotherapeutic agents able not only to target breast cancer but also to display increased efficacy and overall decreased systemic toxicity.

Platinum(II) complexes are widely used in cancer chemotherapy.[2–4] The most important platinum-based drugs are cisplatin (*cis*-diamminedichloroplatinum(II)), carboplatin (diammine[1,1-cyclobutane-dicarboxylato]-*O,O′*-platinum(II)), the first and second platinum(II) derivatives to hit the market, and more recently oxaliplatin, nedaplatin, iobaplatin, and heptaplatin (Fig. 1).[3–5] The first three platinum(II) complexes are used worldwide while the last three are used mainly in Asian countries.

Cisplatin (**1**, *cis*-diamminedichloroplatinum(II)) is still, to date, one of the most useful anticancer drugs in chemotherapy.[5,6] It reacts mainly with DNA, interferes with its replication and/or transcription, and eventually leads to cell apoptosis. Other biological targets are also involved and account for cisplatin's overall anticancer activity.[5,6]

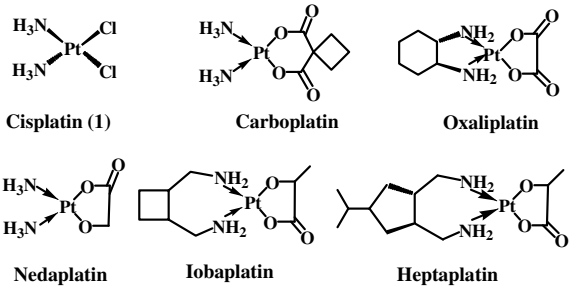

Figure 1. Structures of known platinum(II) complexes used in clinics.

However, cisplatin treatment causes several side effects as it spreads throughout the body, killing not only cancerous cells but also healthy cells. In particular, cisplatin causes severe nephrotoxicity and neurotoxicity.[7] Hence, site directed chemotherapy with platinum drugs could be an alternative for the treatment of cancers, which possibly could lead to increased activity with reduced adverse side effects. This could lead to a better and more tolerated chemotherapeutic treatment for cancer patients.

In our earlier efforts to design new anticancer drugs for site directed therapy, we reported a unique class of estradiol-Pt(II) hybrid derivatives, **2**, which showed good in vitro and in vivo potential for the treatment of hormone dependent cancers, in particular breast

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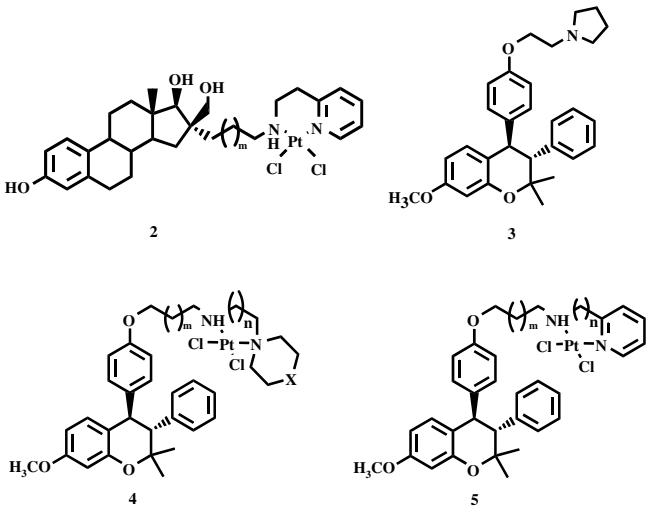


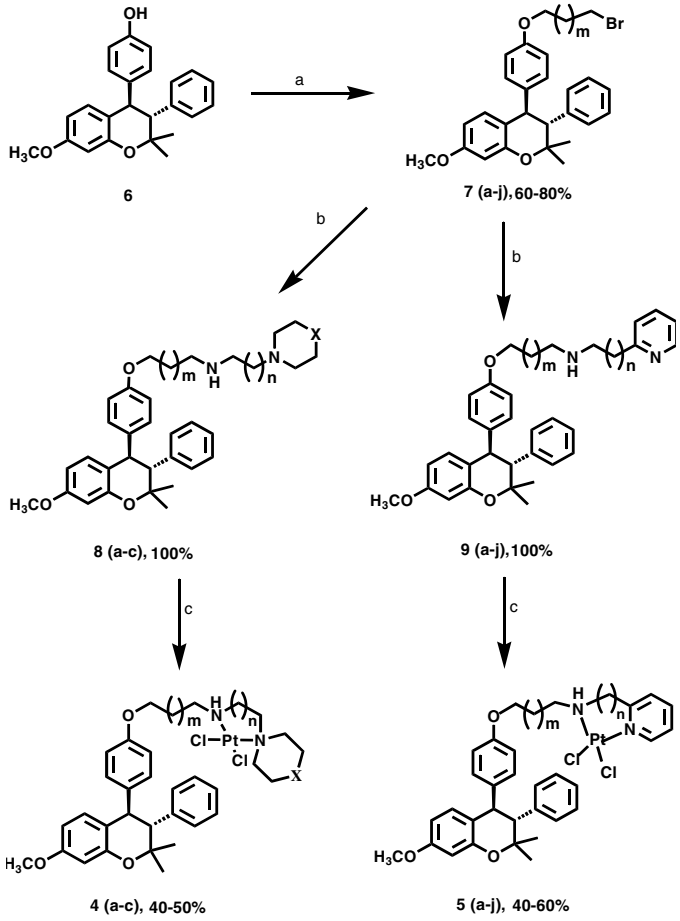
Figure 2. Steroidal and non-steroidal drug molecules.

cancer without any apparent side effects (Fig. 2).[8–11] Recent evidence has showed that this type of hybrid (**2**, $n = 4$) binds DNA bases indirectly through the H-bonding network with a weaker binding constant, while being more effective than cisplatin itself against several types of cancers.[12] Conversely, a stronger interaction with tRNA bases when compared to cisplatin was observed.[13] These results clearly indicate an alternate mechanism of action for this type of hybrid molecules.[12,13]

In addition to the above, selective estrogen receptor modulators (SERMs) are prospective pharmaceutics for the treatment of estrogen-dependent cancers such as breast and uterine cancers mainly due to their antiproliferative activity. An essential feature of SERMs is to possess an aminoalkyl residue at a position corresponding to the 7α or 11β position of the 17β-estradiol.

In continuation of our search for better chemotherapeutic drugs, we have designed and synthesized 3,4-diaryl benzopyran-based platinum(II) complexes of types **4** and **5** as hybrids of selective estrogen receptor modulators and cytotoxic agent like cisplatin and other experimental platinum complexes (Fig. 2). In the present study, 3,4-diaryl benzopyran nucleus as present in ormeloxifene (Centchroman, **3**), well known for its affinity with estrogen receptors (ERs) with selectivity for ERα, was selected as the carrier moiety whereas diamminodichloroplatinum(II) group was chosen as the cytostatic function, a part of cisplatin. The diamminodichloroplatinum(II) group was linked with the carrier through a linker of various lengths at a position corresponding to the 7α or 11β position of the 17β-estradiol. As a result, it was hypothesized that the new compounds will be able to reach the target site more efficiently and that their possible free amine metabolite could also act as a selective estrogen receptor modulator.

The synthesis of targeted compounds of types **4** and **5** was carried out from 4-(4-hydroxyphenyl)-7-methoxy-3-phenyl benzopyran (**6**) using simple and efficient chemistry (Scheme 1). Compound **6** was synthesized in four steps using a reported methodology,[14] which was alkylated with dibromoalkanes of different chain lengths under basic reaction conditions, which gave compound **7** in 60–80% yield.[15] Compound **7** was reacted with different alkyl amines in methanol under reflux, which yielded compounds **8** and **9** in excellent yields.[15] The crude compounds **8** and **9** were subjected to complexation with potassium tetrachloroplatinate(II) in DMF and water mixture (3:1) at room temperature. The progress of this reaction was monitored by use of pH indicator, since during the reaction the pH changes from 8 to 5. The complexation reaction yielded compounds **4** and **5** in good yields (40–65%).[15] The synthesized compounds were characterized by the use of IR, NMR spectroscopy. The purity of benzopyran complexes (**4** and **5**) was checked through their HPLC analyses.



Scheme 1. Reagents and conditions: (a) dibromoalkane, 10% aqueous NaOH solution, benzyltriethyl ammoniumchloride, dichloromethane, reflux. (b) Alkyl amine, methanol and reflux. (c) Potassium tetracholoroplatinate(II), dimethylformamide: water, 22 °C.

The newly synthesized compounds were evaluated for their in vitro cytotoxic activity in estrogen receptor positive (MCF-7) and negative breast cancer cell lines (MDA-MB-468, MDA-MB-436, MDA-MB-231). Cisplatin (**1**), 4-(4-hydroxyphenyl)-7-methoxy-3-phenyl benzopyran precursor (**6**), and compounds **10** and **11** (Fig. 3) were used as control substances. Except for cisplatin (**1**, data shown in Table 1), the reference derivatives did not show any toxicity at the maximum (40 μM) concentration tested (data not shown in the table).[8] A complete structure activity relationship (SAR) was studied in terms of length of spacer between 3,4-diaryl benzopyran nucleus and platinum core, nature and size of platinum core. In MTT assay, the newly synthesized platinum complexes showed significant cytotoxic activity (Table 1).[16,17] In general, complexes from ethylaminopyridine compounds (compound **9**) showed superior activity to their methylaminopyridine analogs, probably because of the ring size of platinum core (six

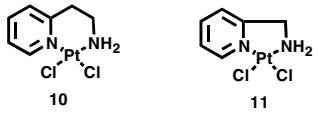


Figure 3. Structure of reference derivatives **10** and **11**.[8]

Table 1
IC_{50} values of compounds at 72 h of treatment in different cell lines

Compound	Compound descriptors	MCF − 7 IC_{50}[a]	MDA-MB-231 IC_{50}	MDA-MB-436 IC_{50}	MDA-MB-468 IC_{50}
4a	X = CH_2, *n* = 1, *m* = 4	NR[b]	NR	NR	8.07 ± 0.46
4b	X = O, *n* = 1, *m* = 4	NR	NR	NR	NR
4c	X = O, *n* = 2, *m* = 4	15.10 ± 1.14	7.91 ± 1.30	13.12 ± 2.37	6.71 ± 1.23
5a	*n* = 2, *m* = 4.	1.94 ± 0.44	2.08 ± 0.09	1.10 ± 0.03	0.70 ± 0.17
5b	*n* = 1, *m* = 4	4.83 ± 0.21	3.32 ± 0.95	2.64 ± 0.58	1.43 ± 0.21
5c	*n* = 2, *m* = 2	4.24 ± 0.24	2.26 ± 0.27	2.12 ± 0.18	1.27 ± 0.23
5d	*n* = 1, *m* = 2	NR	8.95 ± 0.86	8.07 ± 0.68	3.63 ± 0.29
5e	*n* = 1 *m* = 6	9.07 ± 0.46	3.56 ± 0.44	5.62 ± 1.02	1.82 ± 0.23
5f	*n* = 2, *m* = 6	1.96 ± 0.12	1.06 ± 0.01	0.98 ± 0.02	0.48 ± 0,02
5g	*n* = 2, *m* = 8	6.01 ± 0.64	1.75 ± 0.15	2.92 ± 0.44	1.63 ± 0,07
5h	*n* = 1, *m* = 8	NR	NR	NR	NR
5i	*n* = 2, *m* = 10	NR	NR	NR	NR
5j	*n* = 1, *m* = 10	NR	NR	NR	NR
9a	Oxalic acid salt (*n* = 2, *m* = 4)	15.61 ± 0.93	18.69 ± 2.03	15.66 ± 3.11	7.61 ± 1.15
Cisplatin (**1**)	Commercial drug	18.97 ± 0.43	17.33 ± 2.28	3.28 ± 0.38	0.99 ± 0.06

[a] Inhibitory concentration (IC_{50}, μM) as obtained by the MTT assay. Experiments were performed in duplicates and the results represent means ± SEM of three independent experiments. The cells were incubated for a period of 72 h.
[b] NR, not reached: IC_{50} > 40 μM.

to five membered ring system) and its stability as it was observed elsewhere.[8] Further, complexes from aromatic amines were found to be more potent than their aliphatic amine analogs. However, the length of linker chain has little effect on biological activity. In order to evaluate our hypothesis, we tested the free amine intermediate as its oxalic acid salt (compound **9a**·HO_2CCO_2H) of one of the most potent compounds in the series, compound **5a**, in our biological assay and discovered that it was active albeit less than the final platinum(II) hybrid.

Since 3,4-diaryl benzopyran nucleus is chiral and the relative configuration at its two stereogenic centers C-3 and C-4 is *trans*, these new derivatives also exist as a mixture of enantiomers. The new derivatives exist as enantiomers with *3R,4R* and *3S,4S* configurations. Molecular modeling, 3D quantitative structure activity relationship (3D QSAR), and docking experiments were performed using one of the most potent derivatives; compound **5f**. In order to identify the lowest energy structure, conformational analysis was performed using CONFLEX with MM3. As shown in Figure 4A (for **5f** *3R,4R*) and B (for **5f** *3S,4S*), the lowest energy structures of **5f** *3R,4R* (−31.953 kcal/mol) and **5f** *3S,4S* (−31.944 kcal/mol) have comparable energy. Calculation shows that **5f** *3R,4R* is only 0.009 kcal/mol more stable than **5f** *3S,4S*.

The orientation of the reactive site ($PtCl_2$), in these isomers, is significantly different. To examine the structural differences between the two enantiomers, the lowest energy structures of **5f** (*3R,4R* and *3S,4S*) are superimposed as shown in Figure 5.

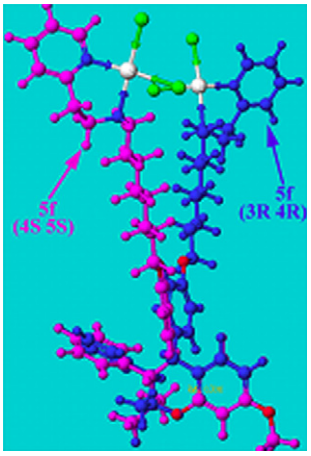


Figure 5. Superimposition of the lowest energy structures of **5f** *3S,4S* (pink) and **5f** *3R,4R* (blue), platinum and chlorine atoms are shown as white and green colors.

To further investigate the differences between these derivatives, a 3D QSAR was examined using various descriptors such as solvent accessible surface area (SAS), solvation energy (ΔH_f), log*P*, difference between the lowest unoccupied molecular orbital (LUMO) and the highest occupied molecular orbital (HOMO), dipole moment (in vacuum and in water), and the IC_{50} or log IC_{50}

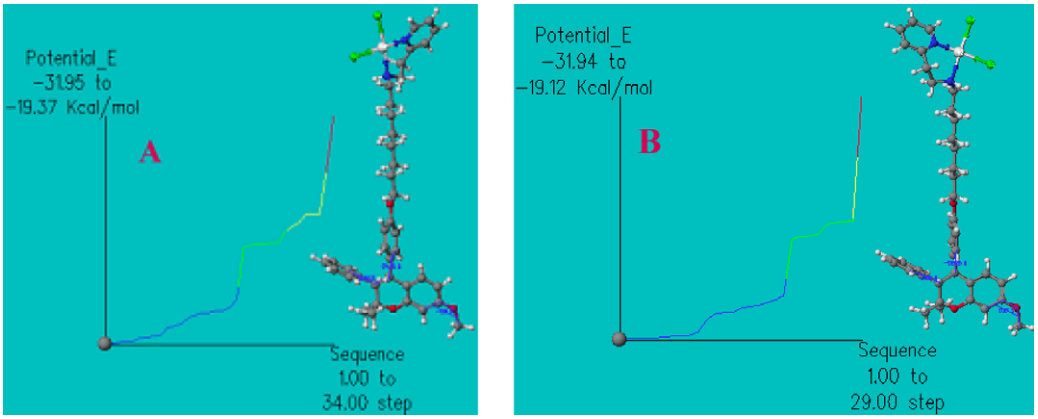


Figure 4. Conformational analysis of **5f** (*3R,4R*) and **5f** (*3S,4S*): (A) the lowest energy (−31.953 kcal/mol) structure for **5f** (*3R,4R*); (B) the lowest energy (−31.944 kcal/mol) structure for **5f** (*3S,4S*). The enantiomer with **5f** (*3R,4R*) configuration has about 0.009 kcal/mol greater stability as compared to **5f** (*3S,4S*) configuration.

for the derivatives with varying chain lengths. The PM5 computational method was used to examine the 3D QSAR. An interesting structure activity relationship was observed between cytotoxic potency and the solvation energy of the enantiomers with the *3S,4S* configurations of the derivatives with different chain lengths. Unlike *3S,4S* isomer, the *3R,4R* derivatives do not show any correlation between the cytotoxic potency and none of the above descriptors. This is interesting because the 3,4-diaryl benzopyran nucleus-based selective estrogen receptor modulator (SERM), Centchroman, **3**, with *3R,4R* configurations is more active than its other isomer with *3S,4S*. However, according to the 3D QSAR study, through the attachment of long chain carbon linkers between 3,4-diaryl benzopyran nucleus and cytostatic function, $PtCl_2$ moiety, the *3S,4S* isomer becomes active. Figure 6 shows the linear relationship between log(IC_{50}) and solvation energy (ΔH_f).

A multiple linear regression was also performed to establish the relationship between the cytotoxic potency and various descriptors. With a number of *3S,4S* isomers of compounds, a reasonable multi-linear relationship was observed with moderate predictive power. Number of multiple linear relationships was observed between the descriptors and the IC_{50} for different cell lines. The relationships are shown in the following equations (1–4):

(1) $IC_{50\,(MDA-MB-468)} = -0.01834^{*}(SAS) + 1.05038^{*}(\Delta H_f) + 4.1543^{*}(\Delta(LUMO–HOMO)) - 69.4185$; $r^2_{cv} = 0.679556$ and $r^2 = 0.998984$.

(2) $IC_{50(MCF-7)} = +300507^{*}(\Delta H_f) + 7.73872^{*}(\Delta\ (LUMO–HOMO)) - 201.302$; $r^2_{cv} = 0.755614$ and $r^2 = 0.924263$.

(3) $IC_{50\,(MDA-MB-231)} = -2.20578^{*}\log P + 2.52948(\Delta H_f) - 1.37495^{*}$ (dipole moment, vacuum) $- 84.2698$; $r^2_{cv} = 0.826568$ and $r^2 = 0.956037$.

(4) $IC_{50\,(MDA-\ MB-436)} = -1.52837^{*}\log P + 2.88758(\Delta H_f) + 8.82603^{*}(\Delta(LUMO–HOMO)) - 194.421$; $r^2_{cv} = 0.937201$ and $r^2 = 0.99206$.

To understand the differences between these two enantiomers of **5f** with *3R,4R* and *3S,4S* configurations, molecular docking experiment was performed using known 3D structure (PDB code: 1UOM) of benzopyran derivative bound to ERα ligand binding domain.[18] The bound benzopyran derivative serves as a positive control. The AutoDock 4.0.1 and CAChe work System Pro docking tools were used.[19] According to the docking results, the *3R,4R* isomer has less number of atoms close together compared to the *3S,4S* isomer making *3R,4R* isomer more favorable. However, the *3R,4R* isomer made only one hydrogen bond (CH_3O-Arg394, 2.154 Å) with the ERα while *3S,4S* isomer formed four hydrogen bonds (CH_3O-Arg394, 2.090 Å; HN-Glu339, 1.536 Å; NH-Phe337, 2.074; and –

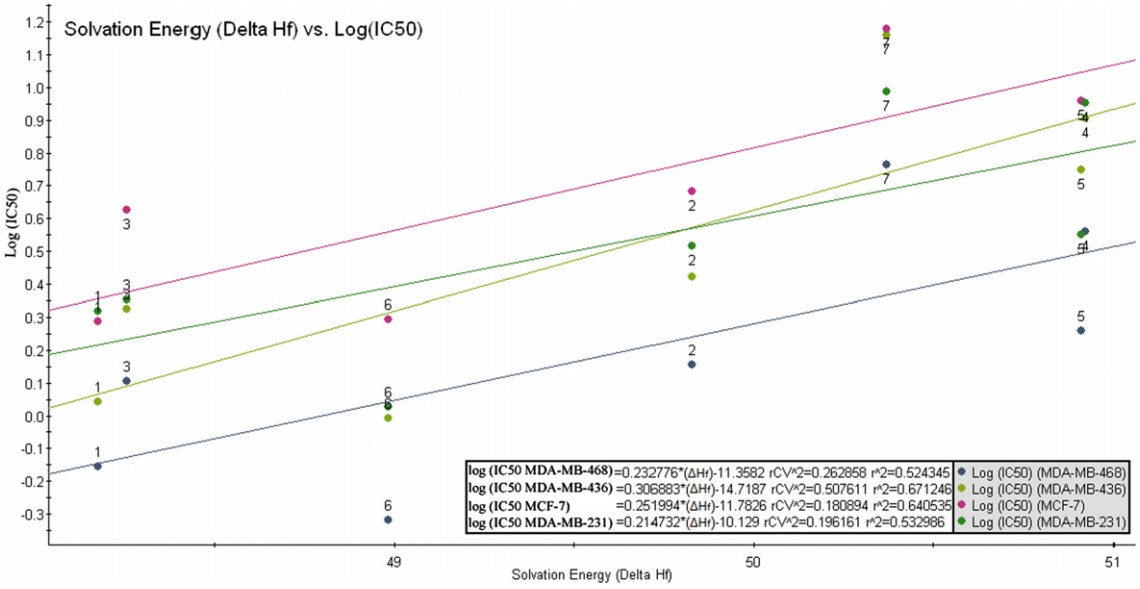


Figure 6. Shows the 3D QSAR relationship of *3S,4S* derivatives between solvation energy (ΔH_f) and log (IC_{50}) for four breast cancer cell lines.

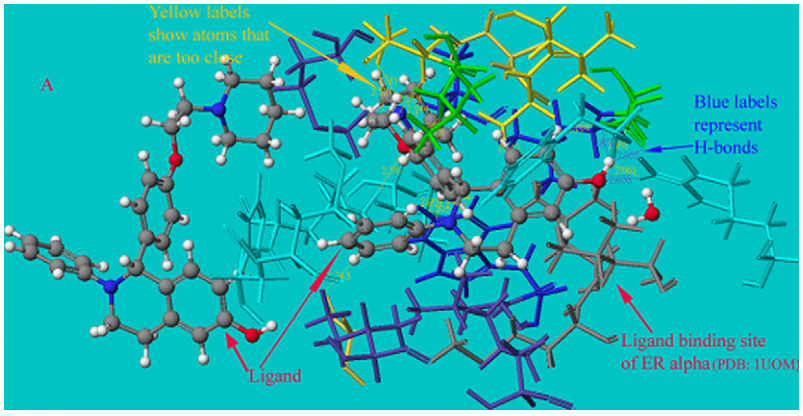


Figure 7-a. Presentation of docking results (PDB 1UOM): (A) the binding interactions of ERα and benzopyran derivative that serves as a positive control; (B) the interactions for **5f** *3R,4R*; and (C) shows the interactions for **5f** *3S,4S*. In (A), (B), and (C), blue labels represent H-bonds and yellow labels are used to represent atoms that are too close together.

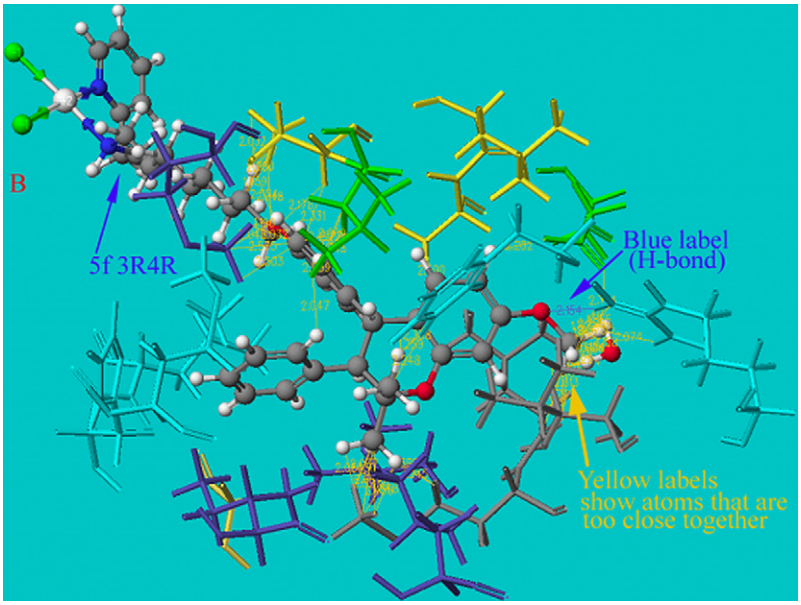


Figure 7-b. Presentation of docking results (PDB 1UOM).

O-Leu346, 1.648). The orientation of the reactive site ($PtCl_2$) in the two isoforms is different. Despite number of atoms close together in the *3S,4S*, isomer, the orientation of reactive site, the number of hydrogen bonds, and 3D QSAR would allow enantiomers with *3S,4S* configurations to be most potent. Figures 7-a, 7-b, and 7-c show the binding mode of benzopyran derivative (Fig. 7-a), **5f** *3R,4R* (Fig. 7-b), and **5f** *3S,4S* (Fig. 7-c) with the binding site of ERα ligand binding domain.

In conclusions, the new compounds of types **4** and **5** showed significant cytotoxic activity against estrogen receptor-dependent and -independent cancer cell lines. The MTT cytotoxicity studies of the compounds indicated that these novel complexes of types **4** and **5**, have significant chemotherapeutic potential, which could be used as cytotoxic agent as well as selective estrogen receptor modulators (an antiproliferative agent) in treatment of cancer. Molecular modeling predicts for the series **5** that the *3S,4S*, isomer may be the most active of the two enantiomers. Further, detailed investigation of these compounds would be helpful in designing new anticancer drugs.

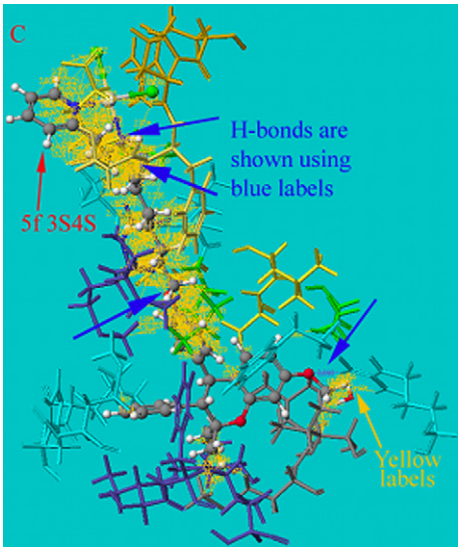


Figure 7-c. Presentation of docking results (PDB 1UOM).

Acknowledgments

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References and notes

1. Varghese, C. *J. Clin. Dia. Res.* **2007**, *1*, 198.
2. Gust, R.; Ott, I. *Anti-cancer Agents Med. Chem.* **2007**, *7*, 95.
3. Wang, D.; Lippard, S. *J. Nature Rev. (Drug Discovery)* **2005**,*4*, 307.
4. Hall, M. D.; Mellor, H. R.; Callaghan, R.; Hambley, T. W. *J. Med. Chem.* **2007**, *50*, 3403.
5. Wong, E.; Giandomenico, C. M. *Chem. Rev.* **1999**, *99*, 2451.
6. van Zutphen, S.; Reedijk, J. *Coord. Chem. Rev.* **2005**, *249*, 2845.
7. von Angerer, E. In *Metal complexes Complexes in cancer chemotherapyCancer Chemotherapy*; Keppler, Ed.; VCH: Weinheim, 1993; pp 75–83.
8. Descôteaux, C.; Provencher-Mandeville, J.; Mathieu, I.; Perron, V.; Mandal, S. K.; Asselin, É.; Bérubé, G. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3927.
9. Gagnon, V.; St-Germain, M.-È.; Descôteaux, C.; Provencher-Mandeville, J.; Parent, S.; Mandal, S. K.; Asselin, É.; Bérubé, G. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5919.
10. Perron, V.; Rabouin, D.; Asselin, É.; Parent, S.; Gaudreault, R.-C. ; Bérubé, G. *Bioorg. Chem.* **2005**, *33*, 1.
11. Bérubé, G. US patent 7,153,844, **2006**.
12. N'soukpoé-Kossi, C. N.; Descôteaux, C.; Asselin, É.; Tajmir-Riahi, H.-A.; Bérubé, G. *DNA Cell Biol.* **2008**, *27*, 101.
13. N'soukpoé-Kossi, C. N.; Descôteaux, C.; Asselin, É.; Bariyanga, J.; Tajmir-Riahi, H.-A.; Bérubé, G. *DNA & Cell Biol.* **2008**, *27*, 337.
14. (a) Salman, M.; Ray, S.; Agarwal, A. K.; Durani, S.; Setty, B. S.; Kamboj, V. P.; Anand, N. *J. Med. Chem.* **1986**, *26*, 592; (b) Ray, S.; Gover, P. K.; Kamboj, V. P.; Setty, B. S.; Kar, A. B.; Anand, N. *J. Med. Chem.* **1976**, *19*, 276; (c) Singh, M. M. *Med. Res. Rev.* **2001**, *21*, 302.
15. *Typical procedure for the synthesis of benzopyran complexes: Preparation of 4-[4-(6-bromo-hexyloxy)-phenyl]-7-methoxy-2, 2-dimethyl-3-phenyl-chroman (***7a***):* A solution of **6** (0.72 g, 2.00 mmol), 1,6-dibromohexane (0.65 g, 1.67 mmol), benzyltriethyl-ammonium chloride (100 mg), and sodium hydroxide 10% w/v (4 mL), in 6 mL DCM, was stirred vigorously and heated to reflux for 20 h. The reaction mixture was diluted with diethyl ether (40 mL) and extracted with a saturated ammonium chloride solution (2×20 mL) and with water (4×50 mL). The organic phase was filtered, dried, and evaporated to an oil. The crude material was purified by flash chromatography with a mixture of acetone: hexane (1:9) to give pure compound **7a**.Yield: 65%. IR (cm^{-1}): 1618, 1584, 1239, 1157, 1099, 751; ^1H NMR ($CDCl_3$, δ ppm): 7.19 (bs, 5 H, ArH), 6.89 (d, $J = 8.00$ Hz, 2H, ArH), 6.63 (m, 3H, ArH), 6.42 (m, 2H, ArH), 4.34 (d, $J = 12.00$ Hz, 1H, CH), 3.83 (t, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.41 (t, 2H, CH_2), 3.21 (d, $J = 12.00$ Hz, 1H, CH), 1.85 (m, 2H, CH_2), 1.71 (m, 2H, CH_2), 1.47 (m, 2H, CH_2), 1.39 (s, 3H, CH_3), 1.26 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm):159.42,

157.49, 154.39, 139.67, 136.10, 131.18, 130.24, 128.18, 126.9, 118.86, 118.86, 114.17, 107.71, 101.59, 78.44, 67.65, 57.71, 55.46, 44.14, 34.07, 32.90, 29.38, 29.06, 28.16, 25.55, 20.40.

*Preparation of {6-[4-(7-methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-hexyl}-(2-pyridin-2-yl-ethyl)-amine (***9a***):* A stirred solution of bromide **7a** (0.60 g, 1.00 mmol) and 2-(2-aminoethyl)pyridine (0.36 mL, 3 mmol) in methanol (5 mL) was refluxed for 3 days under an inert atmosphere of nitrogen. Then, the solvent was evaporated and the residue dissolved in diethyl ether (30 mL) was washed with water (5 × 50 mL). The aqueous phases are extracted with diethyl ether (2 × 15 mL). The combined organic phase was dried, filtered and evaporated to an oil. The crude amine (**9a**) was used without further purification at the next step.

Yield: 100%. IR (cm^{-1}): 3409, 1614, 1587, 1502, 1246, 1162, 1116, 758; ^1H NMR ($CDCl_3$, δ ppm): 8.50 (d, J = 6.00 Hz, 1H, a′-CH), 7.57 (m, 1H, c′-CH), 7.10 (bs, 7H, b′-CH, d′-CH and ArH), 6.86 (d, J = 10.00 Hz, 2H, ArH), 6.60 (d, J = 8.00 Hz, 3H, ArH), 6.37 (m, 2H, ArH), 4.30 (d, J = 12.00 Hz, 1H, CH), 3.80 (m, 5H, OCH_2 and OCH_3), 3.17 (d, J = 12.00 Hz, 1H, CH), 2.62 (t, J = 7.00 Hz, 2H, CH_2), 2.03 (bs, 4H, 2 × CH_2), 1.65 (m, 2H, CH_2), 1.49 (m, 6H, 3xCH_2), 1.35 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 160.49, 159.39, 157.54, 154.37, 149.54, 139.66, 136.60, 135.98, 131.18, 130.20, 128.61, 126.89, 123.52, 121.48, 118.85, 114.16, 107.67, 101.59, 78.40, 67.77, 57.69, 55.41, 49.89, 49.56, 44.12, 38.50, 30.09, 29.49, 29.05, 27.31, 26.21, 26.21, 20.39.

*Preparation of 4-[6-(2′-pyridylethylamino)-hexyloxy)-phenyl]-7-methoxy-2,2-dimethyl-3-phenyl-chroman dichloroplatinate(II) (***5a***):* To a solution of {6-[4-(7-methoxy-2,2-dimethyl-3-phenyl-chroman-4-yl)-phenoxy]-hexyl}-(2-pyridin-2-yl-ethyl)-amine (9a) (0.13 g, 0.16 mmol) in DMF (1 mL) at 23 °C was added potassium tetrachloroplatinate(II) (0.11 g, 0.18 mmol) dissolved in a mixture of DMF/H_2O (2: 1.6 ml). The resulting mixture (pH 8–9) was stirred in the dark for 2–3 days until the pH value reached 4–5. Then, a drop of dimethylsulfoxide was added and the stirring was continued for 2–3 h. The solvent was evaporated and the residue was stirred vigorously in a saturated aqueous potassium chloride solution (5 mL) for 15 min. A vigorous stirring was essential in order to pulverize the lumps of precipitated platinum(II) complex. The resulting suspension was filtered, washed with water (100 mL), and dried in a desiccator for a day. The product was further purified by flash column chromatography (hexanes: acetone, 3:2) to give the title compound 5a.

Yield: 65%. IR (cm^{-1}): 1619, 1587, 1508, 1240, 1119, 1162, 760; ^1H NMR ($CDCl_3$, δ ppm): 7.09 (bs, 5H, ArH), 6.79 (d, J = 8.00 Hz, 2H, ArH), 6.52 (m, 3H, ArH), 6.31 (m, 2H, ArH), 5.90 (bs, 1H, NH), 4.24 (d, J = 12.00 Hz, 1H, CH), 3.79 (m, 5H, OCH_2 and OCH_3), 3.28 (m, 2H, CH_2), 3.10 (d, J = 12.00 Hz, 1H, CH), 2.82 (m, 4H, 2 × CH_2), 2.35 (m, 4H, 2 × CH_2), 1.68 (bs, 10H, 5 × CH_2), 1.95 (bs, 7H, 2 × CH_2 and CH_3), 1.16 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, δ ppm): 159.41, 157.49, 154.38, 139.67, 139.02, 131.19, 130.24, 128.18, 126.91, 118.89, 114.16, 107.70, 101.59, 78.46, 67.59, 57.65, 55.47, 44.11, 31.21, 29.38, 29.06, 25.95, 20.39.

16. Carmichael, J.; DeGrapp, W. G.; Gazdar, A. F.; Minna, J. D.; Mitchell, J. B. *Cancer Res.* **1987**, *47*, 936.
17. Ford, C. H. J.; Richardson, V. J.; Tsaltas, G. *Cancer Chemother. Pharmacol.* **1989**, *24*, 295.
18. http://www.rcsb.org/pdb/.
19. CACheWorkSystem Pro, version 6.1.12, Fujitsu, USA, 2006.