Research Article

Novel Fe\textsuperscript{II} and Co\textsuperscript{II} Complexes of Natural Product Tryptanthrin: Synthesis and Binding with G-Quadruplex DNA

Yi-ning Zhong,\textsuperscript{1} Yan Zhang,\textsuperscript{1,2} Yun-qiong Gu,\textsuperscript{2,3} Shi-yun Wu,\textsuperscript{1} Wen-ying Shen,\textsuperscript{2} and Ming-xiong Tan\textsuperscript{1,2,3}

\textsuperscript{1}College of Pharmacy of Guangxi University of Chinese Medicine, Nanning, Guangxi 530299, China
\textsuperscript{2}Guangxi Key Laboratory for Agricultural Resources Chemistry and Efficient Utilization (Cultivation Base), Yulin Normal University, Yulin, Guangxi 537000, China
\textsuperscript{3}The Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, Guangxi Normal University, Guilin, Guangxi 541004, China

Correspondence should be addressed to Ming-xiong Tan; tanmx00@163.com

Received 18 May 2016; Revised 12 July 2016; Accepted 27 July 2016

Academic Editor: Zhe-Sheng Chen

Copyright © 2016 Yi-ning Zhong et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Tryptanthrin is one of the most important members of indoloquinoline alkaloids. We obtained this alkaloid from \textit{Isatis}. Two novel Fe\textsuperscript{II} and Co\textsuperscript{II} complexes of tryptanthrin were first synthesized. Single-crystal X-ray diffraction analyses show that these complexes display distorted four-coordinated tetrahedron geometry via two heterocyclic nitrogen and oxygen atoms from tryptanthrin ligand. Binding with G-quadruplex DNA properties revealed that both complexes were found to exhibit significant interaction with G-quadruplex DNA. This study may potentially serve as the basis of future rational design of metal-based drugs from natural products that target the G-quadruplex DNA.

1. Introduction

G-quadruplexes is regarded as four-stranded structures that are made up of guanine (G) bases in a purine-rich DNA duplex [1, 2]. Considerable evidence suggests that these structures are found at the telomeric ends of chromosomes and regulate the expression of several important oncogenes [3, 4]. Based on these observations, G-quadruplexes have been proposed as a potential target for anticancer drug design [5–7]. Detailed investigations have been carried out for human telomeric and c-myc, c-kit, k-ras, and bcl-2 quadruplexes [8–12]. The first example of a small-molecule TMPyP4 was found to reduce the transcriptional activity of a gene (c-myc) with a promoter-G-quadruplex motif as a target [13]. An isoalloxazine small-molecule G-quadruplex ligand that binds both c-kit G-quadruplexes was shown to reduce the levels of c-kit mRNA in c-kit expressing cell line [14]. Studies have also confirmed the presence of a G-quadruplex-forming sequence within the promoter of k-ras [15], which is also sensitive to a reduction in transcriptional activity induced by the G-quadruplex interactive ligand TMPyP4. A zinc(II) isopropylguanidinium-phthalocyanine complex was shown to be of very high affinity and selectivity for c-myc, H-telo, and Kras mutation [16]. Quindoline derivatives show that turning off transcription of the \textit{bcl-2} Gene by stabilizing the bcl-2 promotes quadruplex structure [17]. Metal complexes from alkaloids with a large planar \(\pi\)-aromatic conjugated system would be beneficial to increase affinity to the grooves of the quadruplex by \(\pi\)-\(\pi\) stacking and electrostatic interactions [18–20].

Tryptanthrin (Figure 1) is one of the most important members of indoloquinoline alkaloids [21]. This alkaloid is found in a number of plants like \textit{Isatis} [22], \textit{Calanthe} [23], \textit{Strobilanthes} [24], \textit{Couroupita} [25], and \textit{Wrightia} [26]. Tryptanthrin exhibits diverse biological effects, such as antimicrobial, antitumor, and anti-inflammatory activities [24, 27, 28]. Tryptanthrin has been used as Chinese medicine and folk medicine for treatment of anti-inflammatory, antipyretic, and analgesic effects [29]. Studies have shown that alkaloids such as cryptolepine [30], berberine [31], liriodenine [32],
sanguinarine [33], and nitidine [34] exhibit G-quadruplex strong stabilization activities and structure-dependent interactions. However, relatively less attention has been paid to tryptanthrin and its derivatives that bind to and stabilize G-quadruplex DNA. We conceive that tryptanthrin derivatives would be of interest for G-quadruplex DNA binding due to the planar structure and large $\pi$-conjugated system.

Therefore, we synthesized the first example of metal-mediated natural product tryptanthrin complexes of iron(II) (Figure 2, complex 1) and cobalt(II) (Figure 2, complex 1) as the G-quadruplex binders and investigated their abilities to act as selective and effective G-quadruplex binders. The approach is based on $\pi$-conjugation planar of indoloquinoline alkaloids, the remarkable biological effects, and the photophysical, magnetic, or catalytic properties of metal complexes. It would be anticipated that the formation of metal complexes with the planar tryptanthrin ligand does have the potential to stack on or intercalate with guanine of G-quadruplex, and the charged molecules as a whole can bind to the grooves and loops in the negatively charged sugar-phosphate backbone of the DNA.

2. Experimental

2.1. Materials and Methods. Infrared spectra were obtained on a PerkinElmer FT-IR spectrometer. Fluorescence measurements were performed on a Shimadzu RF-5301/PC spectrofluorophotometer. The X-ray diffraction data were collected on a Bruker Smart Apex II and a Rigaku Saturn CCD diffractometer equipped with graphite monochromated Mo-Ka radiation ($\lambda = 0.71074$ Å).

All chemical reagents were commercially available and received without further purification, unless noted specifically. Tryptanthrins were isolated from the Chinese plants of *Isatis* according to the literature methods [24]. G-quadruplex DNA HTG21 (5'-GGGGTTAGGGTTAGGGTTAGG-3'), stored at 4°C; long-term storage at −20°C) are obtained from Shanghai Sangon Biological Engineering Technology & Services (Shanghai, China). The DNA concentration per pair was determined based on the absorbance value at $\lambda = 260$ nm ($\epsilon_{260} = 3.81 \times 10^5$ M (strand)$^{-1}$ cm$^{-1}$) for DNA oligomers by using UV/Vis absorption spectroscopy. Unless otherwise stated, spectroscopic titration experiments were carried out in 10 mM Tris-HCl (pH 7.35) containing 100 mM KCl. All tumor cell lines were obtained from the Shanghai Institute for Biological Science (China).

Stock solutions of all the compounds (2 mM) were made in DMSO. Further dilutions to working concentrations were made with corresponding buffer. The formation of all intramolecular G-quadruplexes was analyzed as follows: the oligomers samples, dissolved in Tris-KCl-HCl buffer, were heated to 95°C for 10 min, gently cooled to room temperature, and then incubated at 4°C overnight. All the spectroscopic experiments were performed at room temperature.

2.2. Spectra Characteristics Analysis. Absorption titrations and fluorescence emission titration were performed by using a fixed compounds concentration ($2.0 \times 10^{-3}$ M) and varying the concentration of G4-HTG21 ($1.0 \times 10^{-5}$ M, 5 $\mu$L per scan). While measuring absorption titrations, the solutions were allowed to incubate for 10 min before the spectra were recorded and an equal amount of G4-HTG21 was added to both the compound solution and the reference solution to eliminate the absorbance of G4-HTG21 itself [35, 36]. Fluorescence quenching spectra of ethidium bromide (EthBr) bound with G4-DNA were performed with increasing amounts of complexes 1 and 2, ranging ratios of [complex]/[EthBr] from 0:1 to 10:1, when the ration
of [DNA]/[EthBr] remained 10:1, excited at 453 nm. The quenching constant, $K_{SV}$, was calculated according to the classic Stern-Volmer equation.

2.3. Synthesis of Complexes

2.3.1. Synthesis of [Fe(Try)$_2$] (I). 1 was synthesized in a mixture of Try (0.05 mmol, 0.0124 g), FeCl$_2$·4H$_2$O (0.06 mmol, 0.0119 g), CH$_3$OH (1 mL), and DMF (1.5 mL) placed in a thick Pyrex tube. The sealed tube was heated at 100°C for 3 d to yield brown prismatic-shaped crystals. The crystals were washed with ethanol, dried, and stored under vacuum suitable for X-ray diffraction analysis. Yield: 89.6%. Elemental analysis for C$_{61}$H$_{12}$FeN$_4$O$_8$: calcd (%). C 65.48, H 2.56, N 10.18; found (%). C 65.11, H 3.00, N 9.83; IR (KBr, cm$^{-1}$): 2929.0, 1685.3, 1594.5, 1438.0, 1362.0, 1232.0, 1188.0, 744.0, 586.0 cm$^{-1}$.

2.3.2. Synthesis of [Co(Try)$_2$]CH$_3$OH (2). 2 was synthesized in a mixture of Try (0.05 mmol, 0.0124 g), CoCl$_2$·6H$_2$O (0.06 mmol, 0.0158 g), CH$_3$OH (0.5 mL), and DMF (2 mL) placed in a thick Pyrex tube. The sealed tube was heated at 100°C for 3 d to yield brown prismatic-shaped crystals. The crystals were washed with ethanol, dried, and stored under vacuum suitable for X-ray diffraction analysis. Yield: 89.6%. Elemental analysis for C$_{31}$H$_{49}$CoN$_4$O$_4$: calcd (%). C 63.38, H 3.43, N 9.54; found (%). C 63.19, H 3.20, N 9.23; IR (KBr, cm$^{-1}$): 3468.0, 1674.0, 1592.0, 1438.0, 1362.0, 1232.0, 1188.0, 744.0, 586.0 cm$^{-1}$.

3. Results and Discussion

3.1. X-Ray Crystal Structures Analysis. Complexes 1 and 2 were prepared via the reaction of Try with FeCl$_2$·4H$_2$O or CoCl$_2$·6H$_2$O in the presence of CH$_3$OH and DMF under solvothermal conditions. Single-crystal X-ray diffraction analyses for their structure revealed that in each case the metal ion(II) center is coordinated by Try ligand via two heterocyclic nitrogen and oxygen atoms to form a tetrahedron geometry. One of the major differences is that complex 2 contains a CH$_3$OH molecule in the unit cell (Figure 2). The X-ray crystal data collection for two complexes is shown in Table 1.

Table 1: The X-ray crystal data collection for complexes 1 and 2.

| Identification code | 1 | 2 |
|---------------------|---|---|
| Empirical formula   | C$_{61}$H$_{12}$FeN$_4$O$_8$ | C$_{31}$H$_{49}$CoN$_4$O$_4$CH$_3$OH |
| Formula weight      | 1016.79 | 541.97 |
| Temperature/K        | 122(3) | 296.15 |
| Space group          | C2/c | Monoclinic |
| a/Å, b/Å, c/Å        | 22.1273(20), 16.2600(9), 15.7165(14) | 22.010(18), 18.811(16), 15.132(12) |
| Volume/Å$^3$         | 4879.1(7) | 5540(8) |
| Z                    | 4 | 8 |
| $\rho_{calc}$/mg mm$^{-3}$ | 1.384 | 1.360 |
| $\mu$/mm$^{-1}$      | 0.373 | 0.373 |
| F(000)               | 2088 | 2236 |
| Crystal size/mm$^3$  | 0.30 $\times$ 0.15 $\times$ 0.08 | 0.35 $\times$ 0.25 $\times$ 0.11 |
| 2θ range for data collection | 5.82 to 50.24° | 3.02 to 50.06° |
| Index ranges         | $-26 \leq h \leq 26, -19 \leq k \leq 18, -18 \leq l \leq 18$ | $-26 \leq h \leq 26, -22 \leq k \leq 22, -17 \leq l \leq 18$ |
| Reflections collected | 11653 | 19705 |
| Independent reflections | 4357 [R(int) = 0.0739] | 4867 [R(int) = 0.1359] |
| Data/restraints/parameters | 4357/0/340 | 4867/0/378 |
| Goodness-of-fit on $F^2$ | 1.021 | 1.633 |
| Final R indexes [$I > 2\sigma(I)$] | $R_1 = 0.0724, wR_2 = 0.1286$ | $R_1 = 0.1712, wR_2 = 0.4443$ |
| Final R indexes (all data) | $R_1 = 0.1345, wR_2 = 0.1555$ | $R_1 = 0.2737, wR_2 = 0.5060$ |
| Largest diff. peak/hole/e Å$^{-3}$ | 0.559/−0.541 | 0.803/−0.997 |

3.2. Selectivity for Binding of G-Quadruplex by Spectroscopic Methods. UV-visible absorption titration was performed to determine the binding affinity of the complexes to G-quadruplex. The HTG21-G-quadruplex sample was added sequentially to the complexes of Tris/KCl buffer solutions. UV-vis absorbance spectra were recorded after each addition. As shown in Figure 3, with increasing concentration of HTG21-G-quadruplex, the absorbance at the ligand absorption band region, as well as the MLCT (metal-to-ligand charge transfer) band, decreased with 35% hypochromism at 286 nm for complex 1 and 35% at 286 nm for complex 2. This hypochromic phenomenon is attributed to the strong interaction between the complexes and G-quadruplex DNA.
In order to compare the affinities of the two complexes quantitatively, the Scatchard equation has been applied to evaluate the binding to DNA [37]:

$$\frac{D}{\Delta \varepsilon_{ap}} = \frac{D}{\Delta \varepsilon + \frac{1}{\Delta \varepsilon + K}}.$$  \hspace{1cm} (1)

Binding constants, $K$, were determined from a reciprocal plot of $D/\Delta \varepsilon_{ap}$ versus $D$. In (1), DNA is expressed in base pairs; the apparent molar extinction coefficients $\varepsilon_A = A_{obs}/[\text{complex}]$, $\Delta \varepsilon_{ap} = |\varepsilon_A - \varepsilon_F|$, and $\Delta \varepsilon = |\varepsilon_B - \varepsilon_F|$ with $\varepsilon_B$ and $\varepsilon_F$ representing the molar extinction coefficients of bound the complex that is intercalated within G-quadruplex and the free complex that is in solution, respectively. The plot of $D/\Delta \varepsilon_{ap}$ versus $D$ revealed that the binding constant $K$ of complexes 1 and 2 was $4.29 \times 10^4$ dm$^3$ mol$^{-1}$ and $3.40 \times 10^4$ dm$^3$ mol$^{-1}$, respectively, at 20.0$^\circ$C (Figure 3 inset).

The binding constant $K$ of complex 1 is larger than that of complex 2. It indicated that complex 1 bound to the DNA more tightly than complex 2 did. The two complexes have the same intercalative ligand. This is most likely due to the less solubility of complex 2 than complex 1 in water at the same condition.

Emission spectral measurements were used to further clarify the binding of complexes to G-quadruplex DNA [38]. The results of the fluorescence titration for these complexes with DNA are shown in Figure 4. Both of the complexes displayed a weakly emissive photoluminescence around 534 nm. The addition of HTG21-quadruplex resulted in an increase in emission intensity. It is worth noting that the increasing extent of the fluorescence intensity of complex 1 shows stronger ability to bind DNA than complex 2.

For further proof of intercalation, an ethidium bromide (EthBr) competitive binding study was undertaken. Ethidium bromide (EtBr) is a very fluorescent dye which has been
shown to intercalate with nucleotides. EtBr showed characteristic fluorescent emission around 610 nm when it bound to DNA and EtBr fluorescence emission exhibited quenching when complexes 1 and 2 were added slightly, indicating that the intercalated modes between the base pairs of DNA and the compounds exist just similar to EtBr. The quenching constant ($K_{SV}$) for complexes 1 and 2 was calculated to be $7.96 \times 10^3$ and $4.95 \times 10^3$, respectively, as shown in Figure 5. Results from these studies further confirm the ability to bind or stabilize G-quadruplex DNA.

### 4. Conclusion

In summary, we first synthesized and characterized Fe$^{II}$ and Co$^{II}$ complexes of natural product tryptanthrin and their G-quadruplex binding properties. Both complexes were found to display significant interaction with G-quadruplex. This study may potentially serve as the basis of future rational design of metal-based drugs from natural products that target the G-quadruplex. Consequently, future biological activities and the structure-activity relationships studies will be investigated.

### Competing Interests

The authors declare that they have no competing interests.

### Acknowledgments

The authors are grateful for financial support from the National Natural Science Foundation of China (no. 21261025), the Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, Ministry of Education of China (nos. CMEMR2011-09 and CMEMR2014-B08), Key Foundation Project of Colleges and Universities in Guangxi (no. ZD2014108), Innovative Team & Outstanding Talent Program of Colleges and Universities in Guangxi, Science and Technology Research Projects of Guangxi (1346008-4), and Natural Science Foundation of Guangxi.

### References

[1] D. Sen and W. Gilbert, "Formation of parallel four-stranded complexes by guanine-rich motifs in DNA and its implications for meiosis," *Nature*, vol. 334, no. 6180, pp. 364–366, 1988.
[2] C. H. Kang, X. Zhang, R. Ratliff, R. Moyzis, and A. Rich, “Crystal structure of four-stranded *Oxytricha* telomeric DNA,” *Nature*, vol. 356, no. 6365, pp. 126–131, 1992.

[3] F. W. Smith, P. Schultz, and J. Feigon, “Solution structures of unimolecular quadruplexes formed by oligonucleotides containing *Oxytricha* telomere repeats,” *Structure*, vol. 3, no. 10, pp. 997–1008, 1995.

[4] F. W. Smith and J. Feigon, “Quadruplex structure of *Oxytricha* telomeric DNA oligonucleotides,” *Nature*, vol. 356, no. 6365, pp. 164–168, 1992.

[5] D. Sun, B. Thompson, B. E. Cathers et al., “Inhibition of human telomerase by a G-Quadruplex-Interactive compound,” *Journal of Medicinal Chemistry*, vol. 40, no. 14, pp. 2113–2116, 1997.

[6] R. H. Shafer, “Stability and structure of model DNA triplexes and quadruplexes and their interactions with small ligands,” *Progress in Nucleic Acid Research & Molecular Biology*, vol. 59, pp. 55–94, 1998.

[7] N. V. Anantha, M. Azam, and R. D. Sheardy, “Porphyrin binding to quadruplexed T4G4,” *Biochemistry*, vol. 37, no. 9, pp. 2709–2714, 1998.

[8] A. Siddiqui-Jain, C. L. Grand, D. J. Bearss, and L. H. Hurley, “Direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 18, pp. 11593–11598, 2002.

[9] M. Bejugam, S. Sewitz, P. S. Shirude, R. Rodriguez, R. Shahid, and S. Balasubramanian, “Trisubstituted isoxazolines as a new class of G-quadruplex binding ligands: small molecule regulation of c-kit oncogene expression,” *Journal of the American Chemical Society*, vol. 129, no. 43, pp. 12926–12927, 2007.

[10] S. Cogoi and L. E. Xodo, “G-quadruplex formation within the promoter of the KRAS proto-oncogene and its effect on transcription,” *Nucleic Acids Research*, vol. 34, no. 9, pp. 2536–2549, 2006.

[11] S. N. Georgiades, N. H. Abd Karim, K. Suntharalingam, and R. Vilar, “Interaction of metal complexes with G-quadruplex DNA,” *Angewandte Chemie—International Edition*, vol. 49, no. 24, pp. 4020–4034, 2010.

[12] X.-D. Wang, T.-M. Ou, Y.-J. Lu et al., “Turning off transcription of the bcl-2 gene by stabilizing the bcl-2 promoter quadruplex with quinoline derivatives,” *Journal of Medicinal Chemistry*, vol. 53, no. 11, pp. 4390–4398, 2010.

[13] E. Izbicka, R. T. Wheelhouse, and E. Raymond, “Effects of cationic porphyrins as G-quadruplex interactive agents in human tumor cells,” *Cancer Research*, vol. 59, no. 3, pp. 639–644, 1998.

[14] R. T. Wheelhouse, D. Sun, H. Han, F. X. Han, and L. H. Hurley, “Cationic Porphyrins as telomerase inhibitors: the interaction of tetra-(N-methyl-4-pyridyl) porphine with Quadruplex DNA,” *Journal of the American Chemical Society*, vol. 120, no. 13, pp. 3261–3262, 1998.

[15] D. L. Ma, C.-M. Che, and S.-C. Yan, “Platinum(II) complexes with dipyrrolophane ligands as human telomerase inhibitors and luminescent probes for G-quadruplex DNA,” *Journal of the American Chemical Society*, vol. 131, no. 5, pp. 1833–1846, 2009.

[16] K. M. Felsenstein, L. B. Saunders, J. K. Simmons et al., “Small molecule microarrays enable the identification of a selective, quadruplex-binding inhibitor of MYC expression,” *ACS Chemical Biology*, vol. 11, no. 1, pp. 138–148, 2016.

[17] P. Wang, C.-H. Leung, D.-L. Ma, S.-C. Yan, and C.-M. Che, “Structure-based design of platinum(II) complexes as c-myc oncogene down-regulators and luminescent probes for G-quadruplex DNA,” *Chemistry—A European Journal*, vol. 16, no. 23, pp. 6900–6911, 2010.

[18] M. Wang, W. Wang, T.-S. Kang, C.-H. Leung, and D.-L. Ma, “Development of an Iridium(III) complex as a G-quadruplex probe and its application for the G-quadruplex-based luminescent detection of picomolar insulin,” *Analytical Chemistry*, vol. 88, no. 1, pp. 981–987, 2016.

[19] F. X. Han, R. T. Wheelhouse, and L. H. Hurley, “Interactions of TMPyP4 and TMPyP2 with quadruplex DNA: Structural basis for the differential effects on telomerase inhibition,” *Journal of the American Chemical Society*, vol. 121, no. 15, pp. 3561–3570, 1999.

[20] J. Nagaji, R. Starosta, and M. Jeżowska-Bojczuk, “Acid-base characterization, coordination properties towards copper(II) ions and DNA interaction studies of ribavirin, an antiviral drug,” *Journal of Inorganic Biochemistry*, vol. 142, pp. 68–74, 2015.

[21] M. Brufani, W. Fedeli, F. Mazza, A. Gerhard, and W. Keller-Schierlein, “The structure of tryptanthrin,” *Experientia*, vol. 27, no. 11, pp. 1249–1250, 1971.

[22] H. Danz, S. Sotyanova, P. Wippich, A. Brattström, and M. Hammber, “Identification and isolation of the cyclooxygenase-2 inhibitory principle in latisis tinctoria,” *Planta Medica*, vol. 67, no. 5, pp. 411–416, 2001.

[23] T. Murakami, A. Kishi, T. Sakurama, H. Matsuda, and M. Yoshikawa, “Chemical constituents of two oriental orchids, *Calanthe discolor* and *C. liukiuensis*: precursor indole glycoside of tryptanthrin and indirubin,” *Heterocycles*, vol. 54, no. 2, pp. 957–966, 2001.

[24] G. Honda and M. Tabata, “Isolation of antifungal principle tryptanthrin, from *Stroblanthus cusia* O. Kuntze,” *Planta Medica*, vol. 36, no. 1, pp. 85–86, 1979.

[25] J. Bergman, J.-O. Lindström, and U. Tilstam, “The structure and properties of some indolic constituents in *Couroupita guianensis* aubl,” *Tetrahedron*, vol. 41, no. 14, pp. 2879–2881, 1985.

[26] V. M. Sharma, P. Prasanna, K. V. Adi Seshu et al., “Novel indolo[2,1-b]quinazoline analogues as cytostatic agents: synthesis, biological evaluation and structure-activity relationship,” *Bioorganic & Medicinal Chemistry Letters*, vol. 12, no. 17, pp. 2303–2307, 2002.

[27] S.-T. Yu, T.-M. Chen, J.-W. Chern, S.-Y. Tseng, and Y.-H. Chen, “Downregulation of GSTpi expression by tryptanthrin contributing to sensitization of doxorubicin-resistant MCF-7 cells through c-jun NH2-terminal kinase-mediated apoptosis,” *Anticancer Drugs*, vol. 20, no. 5, pp. 382–388, 2009.

[28] T. Ishihara, K. Kohno, S. Ushio, K. Iwaki, S. Ikeda, and M. Kurihara, “Tryptanthrin inhibits nitric oxide and prostaglandin *E*2 synthesis by murine macrophages,” *European Journal of Pharmacology*, vol. 407, no. 1-2, pp. 197–204, 2000.

[29] Y. Takei, T. Kunikata, M. Agra et al., “Tryptanthrin inhibits interferon-γ production by Peyer’s patch lymphocytes derived from mice that had been orally administered staphylococcal enterotoxin,” *Biological & Pharmaceutical Bulletin*, vol. 26, no. 3, pp. 365–367, 2003.

[30] Y.-J. Lu, T.-M. Ou, J.-H. Tan et al., “5-N-methylated quinoline derivatives as telomeric G-quadruplex stabilizing ligands: effects of 5-N positive charge on quadruplex binding affinity and cell proliferation,” *Journal of Medicinal Chemistry*, vol. 51, no. 20, pp. 6381–6392, 2008.
[31] Y. Ma, T.-M. Ou, J.-Q. Hou et al., “9-N-substituted berberine derivatives: stabilization of G-quadruplex DNA and down-regulation of oncogene c-myc,” *Bioorganic and Medicinal Chemistry*, vol. 16, no. 16, pp. 7582–7591, 2008.

[32] Y.-L. Li, Q.-P. Qin, Y.-C. Liu, Z.-F. Chen, and H. Liang, “A platinum(II) complex of liriodenine from traditional Chinese medicine (TCM): cell cycle arrest, cell apoptosis induction and telomerase inhibition activity via G-quadruplex DNA stabilization,” *Journal of Inorganic Biochemistry*, vol. 137, pp. 12–21, 2014.

[33] S. Yang, J. Xiang, Q. Yang et al., “Distinct G-quadruplex structures of human telomeric DNA formed by the induction of sanguinarine and nitidine under salt-deficient condition,” *Fitoterapia*, vol. 81, no. 8, pp. 1026–1032, 2010.

[34] L. Zhang, H. Liu, Y. Shao et al., “Selective lighting up of epi-berberine alkaloid fluorescence by fluorophore-switching aptamer and stoichiometric targeting of human telomeric DNA G-Quadruplex multimer,” *Analytical Chemistry*, vol. 87, no. 1, pp. 730–737, 2015.

[35] M. Tan, Y. Liu, X. Luo, Z. Chen, and H. Liang, “Antioxidant activities of plumbagin and its Cu (II) complex,” *Bioinorganic Chemistry and Applications*, vol. 2011, Article ID 898726, 5 pages, 2011.

[36] Z.-F. Chen, M.-X. Tan, Y.-C. Liu et al., “Synthesis, characterization and preliminary cytotoxicity evaluation of five Lanthanide(III)-Plumbagin complexes,” *Journal of Inorganic Biochemistry*, vol. 105, no. 3, pp. 426–434, 2011.

[37] C. V. Kumar and E. H. Asuncion, “DNA binding studies and site selective fluorescence sensitization of an anthryl probe,” *Journal of the American Chemical Society*, vol. 115, no. 19, pp. 8547–8553, 1993.

[38] J. Sun, Y. An, L. Zhang et al., “Studies on synthesis, characterization, and G-quadruplex binding of Ru(II) complexes containing two dppz ligands,” *Journal of Inorganic Biochemistry*, vol. 105, no. 2, pp. 149–154, 2011.