The investigation of interaction between Thioguanine and human serum albumin by fluorescence and modeling

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Abstract The interaction between Thioguanine (6-TG) and human serum albumin (HSA) under simulative physiological conditions was studied using fluorescence spectroscopy in combination with UV absorption and molecular modeling method. A strong fluorescence quenching reaction of 6-TG to HSA was observed and the quenching mechanism was suggested as static quenching according to the Stern–Volmer equation. The binding constants (K) at different temperatures as well as thermodynamic parameters, enthalpy change (ΔH) and entropy change (ΔS), were calculated according to relevant fluorescent data and thermodynamic equation. It was indicated that the hydrophobic interaction was a predominant intermolecular force in order to stabilize the copolymer, which was in agreement with the results of molecular modeling study. In addition, the binding distance between 6-TG and the tryptophan residue of HSA was studied according to Förster’s non-radiative energy transfer theory and the effects of common ions on the binding constant of 6-TG-HSA copolymer were also discussed at room temperature.

Keywords Human serum albumin (HSA); Thioguanine (6-TG); Fluorescence spectra; Interaction; Modeling

1. Introduction

Thioguanine (6-TG, Fig. 1) is an efficient type of nucleoside drug with a wide range of biological activities, such as antitumor, antiviral and anticancer activities, which have significantly curative effect for acute lymphoblastic leukemia and other tumors. The interactions between drugs and proteins may affect the apparent distribution volume and the elimination rate of drugs. Therefore, the interaction of 6-TG and human serum albumin (HSA) is extremely important in life science, biochemistry and clinical medicine. It is reported that in 69 cases of the 6-TG treatments of acute leukemia, 70% is efficient, and 6-TG can also support other anticancer drugs for the treatments of gastric cancer, lymph sarcoma and villus epithelial cancer. When 6-TG enters the circulatory system, it plays the role in anti-leukemia by HPRT direct catalytic guanine phosphorylated form sulfur-based compounds (TGNs), and also generates aerosol catalytic methylation of products such as 6-meTG, or me-TGMP to achieve anti-tumor effect (Evans and Relling, 1994).

Protein is an important chemical substance in our life and the main target of all medicines in an organism. Serum
albumin, the most abundant protein in the circulatory system, is one of the most extensively studied proteins because it can interact with many endogenous and exogenous substances. Binding of drugs to plasma proteins is an important pharmacological parameter, since it frequently affects the distribution and elimination of a drug as well as the duration and intensity of its physiological action. The effect is especially significant for highly protein bound drugs, as only a small alteration in bound fraction can produce a profound change in the pharmacodynamically active free drug concentration (Li et al., 2012; Seedher and Bhatia, 2006). The studies on this aspect can provide information of the structural features that determine the therapeutic effectivity of drugs, and have become an interesting research field in life science, chemistry, biochemistry and clinical medicine. Among various methods concerning the interactions of drugs and proteins, fluorescence techniques are great aids in the study of interactions between drugs and plasma proteins in general and serum albumin in particular because of its high sensitivity, rapidity, and ease of implementation (Bian et al., 2003). The fluorescence measurements can give information such as the binding mechanism, binding mode, binding constants, binding sites, intermolecular distance, etc. (Sulkowska, 2002). In addition, UV absorption measurement is a very simple method and applicable to explore the structure (Hu et al., 2002) and the copolymer formation (Bi et al., 2005; Kandagal et al., 2006). The molecular interactions are often monitored by these methods because they have advantages in sensitivity and efficiency over conventional approaches such as affinity and size exclusion chromatography, equilibrium dialysis, ultrafiltration and ultracentrifugation (Kandagal et al., 2006). The modeling method is also used to elucidate the binding mode between HSA and 6-TG. This study was designed to investigate the copolymer between 6-TG and HSA by spectroscopic in combination with modeling method under simulative physiological conditions. Attempts were made to investigate the binding mechanism between 6-TG and HSA regarding the binding constants, the thermodynamic functions and the effect of ions on the binding constants. Furthermore, the binding mode was evaluated using the molecular modeling method; the results were in good agreement with the thermodynamic parameters.

2. Experimental

2.1. Reagents

Appropriate amount of human serum albumin (Sigma) was directly dissolved in water to the prepare stock solution at a final concentration of $5.0 \times 10^{-5}$ mol L$^{-1}$ and stored in the dark at 0–4 °C; $2.0 \times 10^{-4}$ mol L$^{-1}$ 6-TG (synthesized by the microwave-assisted methods without solvent) solution was obtained by dissolving it in double distilled water; 0.5 mol L$^{-1}$ NaCl working solution, 0.1 mol L$^{-1}$ Tris–HCl buffer solution of pH 7.4 and 1.0 mg mL$^{-1}$ other ionic solutions were prepared. Unless otherwise mentioned, all chemicals were of analytical reagent grade and used without further purification. Double distilled water was used throughout the experiments.

2.2. Apparatus

All fluorescence measurements were carried out on a FP-6200 spectrofluorimeter (JASCO, Japan) and RF-540 spectrofluorimeter (Shimadzu, Japan) equipped with a thermostath bath and 1.0 cm quartz cells, using 5/5 nm slit widths. The pH values were measured on a pH-3 digital pH-meter (Shanghai Lei Ci Device Works, Shanghai, China) with a combined glass electrode. All calculations were performed on SGI workstation while studying the molecular model.

2.3. Optimization of experimental conditions

In order to get the best results, the optimal conditions were investigated. Various experimental parameters including medium, pH, and addition order and reaction temperature were studied with 6-TG concentration being $0.4 \times 10^{-6}$ mol L$^{-1}$ in all conditions. As a result, 0.1 mol L$^{-1}$ Tris–HCl buffer solution of pH 7.4 was chosen as the supporting media; the sequence of Tris–HCl + NaCl + HSA + 6-TG was selected and 24 °C was suggested as the preferable reaction temperature.

2.4. Measurements of spectra

According to the optimum physiological conditions, 2.0 mL Tris–HCl buffer solution, 2.0 mL NaCl solution, appropriate amounts of HSA and 6-TG were added to a 10.0 mL standard flask and diluted to 10.0 mL with double distilled water. Fluorescence quenching spectra of HSA were obtained at excitation wavelength (280 nm) and emission wavelength (300–450 nm). Fluorescence spectra in the presence of other ions and synchronous fluorescence spectra were also measured at the same conditions. In addition, the UV absorption spectra of different systems were recorded.

3. Results and discussion

3.1. The fluorescence quenching studies

HSA has three intrinsic fluorophores, viz tryptophan, tyrosine, and phenylalanine residues (Tang et al., 2006). Actually, the intrinsic fluorescence of HSA is almost contributed by tryptophan alone and this viewpoint was supported by the experimental observation of Sulkowska (2002). The change of intrinsic fluorescence intensity of HSA is almost contributed by tryptophan residue when small molecule substances are bound to HSA. Fig. 2 shows the fluorescence emission spectra of HSA at various concentrations of 6-TG. HSA had a strong fluorescence...
and correlation coefficient values, and of the (the linear relationship between \( F_0/F \) and \([Q]\)) obtained at different temperatures are listed in Table 1. The result showed that the possible quenching mechanism between 6-TG and HSA was static quenching instead of dynamic quenching. In order to confirm this point, the procedure was assumed to be dynamic quenching. The fluorescence quenching data were analyzed by the Stern–Volmer equation:

\[
F_0/F = 1 + K_q[Q] = 1 + K_{sv}[Q]
\]  

Where \( F_0 \) and \( F \) are the fluorescence intensities in the absence and presence of quenchers, respectively. \( K_q \), \( K_{sv} \), \( \tau_0 \) and \([Q]\) are the quenching rate constant of the biomolecule, the Stern–Volmer quenching constant, the average lifetime of molecule without quencher and concentration of quencher, respectively. Obviously:

\[
K_{sv} = K_q\tau_0
\]  

Taking average lifetime of biomolecule fluorescence as around \( 10^{-8} \) s (Lakowicz and Weber, 1973), an approximate quenching constant \( (K_q, \text{ L mol}^{-1} \text{s}^{-1}) \) could be obtained according to the Eq. (2). The results are also listed in Table 1.

The maximum scatter collision quenching constant of various quenchers with the biopolymer is \( 2.0 \times 10^{10} \text{ L mol}^{-1} \text{s}^{-1} \) (Ware, 1962). Obviously, the rate constant of protein quenching procedure initiated by 6-TG was greater than the \( K_q \) of the scatter procedure. This confirmed that the quenching was not initiated by dynamic collision but from the formation of a new copolymer.

The UV absorption spectra were also utilized to enucleate interaction of 6-TG with HSA. Fig. 4 shows the UV absorption spectra of HSA in the absence and presence of different

\[
\text{Table 1} \quad \text{The quenching constants (L mol}^{-1} \text{s}^{-1}) \text{ of the 6-TG-HSA system at different temperatures.}
\]

<table>
<thead>
<tr>
<th>( T(\degree C) )</th>
<th>Stern–Volmer equation</th>
<th>( K_q ) (L mol(^{-1}) s(^{-1}))</th>
<th>( R )</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>( Y = 0.9987 + 3.106 \times 10^6[Q] )</td>
<td>3.106 \times 10^{12}</td>
<td>0.9995</td>
</tr>
<tr>
<td>34</td>
<td>( Y = 1.0014 + 2.853 \times 10^6[Q] )</td>
<td>2.853 \times 10^{12}</td>
<td>0.9993</td>
</tr>
<tr>
<td>44</td>
<td>( Y = 1.0017 + 2.698 \times 10^6[Q] )</td>
<td>2.698 \times 10^{12}</td>
<td>0.9973</td>
</tr>
</tbody>
</table>

\[
\text{Figure 3} \quad \text{The Stern–Volmer curves of HSA with 6-TG at pH 7.4; } C_{\text{HSA}} \text{ and } C_{6-\text{TG}} \text{ are the same as those in Fig. 2.}
\]

\[
\text{Figure 4} \quad \text{UV absorption spectra of HSA in tris-HCl buffer solution (pH 7.4. 24\degree C) in the presence of different 6-TG concentrations from 1 to 3: (1) } 0.8 \times 10^{-6} \text{ mol L}^{-1}, \quad (2) \ 0.4 \times 10^{-6} \text{ mol L}^{-1}, \quad (3) \ C_{\text{HSA}} = 2.0 \times 10^{-6} \text{ mol L}^{-1}, \quad (4) \ the \ spectra \ of \ 6-\text{TG}, \ C_{6-\text{TG}} = 0.4 \times 10^{-6} \text{ mol L}^{-1}.
\]
concentrations of 6-TG under the simulative physiological conditions. HSA had a strong absorbance with a peak at 212 nm and the absorbance increased with the addition of 6-TG. Meanwhile, the formation of the chromophore of 6-TG-HSA resulted in the distinct shift of 6-TG-HSA spectrum toward longer wavelength, indicating that a new copolymer was formed between HSA and 6-TG.

3.2. The binding constants and binding sites

In drug-protein binding studies, fluorescence quenching dates were used to calculate binding constant and the number of binding sites by Scatchard (1949):

$$r / D^c = nK - rK$$

(3)

Where $r$ represents the number of moles of bound drug per mole of protein, $D^c$ represents the concentration of unbound drug, $K$ is the binding constant, and $n$ is the number of binding sites. The slope of $r / D^c$ vs $r$ plot gives the binding constant and the number of binding sites that can be obtained from the intercept.

Fig. 5 shows the Scatchard plots for the 6-TG-HSA system at different temperatures. The linearity of the Scatchard plot indicated that 6-TG binds to a single class of binding sites on HSA, which was in agreement with the number of binding site $n$; and the binding constants $(K)$ decreased with increasing the temperature. The binding constants and the number of binding sites are summarized in Table 2. It could be concluded that there was a strong interaction of HSA with 6-TG which was weakened when the temperature increased, while the effect of temperature was small.

3.3. The binding modes

The forces acting between drugs and biomolecules are composed of weak interactions of molecules such as hydrogen bond formation, Van der Waals forces, electrostatic forces, and the hydrophobic interaction (Leckband, 2000). The thermodynamic parameters, enthalpy change $(\Delta H)$ and entropy change $(\Delta S)$ of binding reaction are the main evidence for confirming binding modes. From the thermodynamic standpoint, $\Delta H > 0$ and $\Delta S > 0$ implies a hydrophobic interaction; $\Delta H < 0$ and $\Delta S < 0$ reflects the van der Waals force or hydrogen bond formation; and $\Delta H \approx 0$ and $\Delta S > 0$ suggests an electrostatic force (Ross and Subramanian, 1981).

The temperature dependence of the binding constants was studied at different temperatures (24, 34 and 44 °C). Because the temperature effect was very small, the interaction enthalpy change could be regarded as a constant if temperature range was not too wide. Thus, $\Delta H$ and $\Delta S$ were considered to be constants. According to the following thermodynamic equations:

$$\ln K = - \Delta H / R T + \Delta S / R$$

(4)

$$\Delta G = \Delta H - T \Delta S = -RT \ln K$$

(5)

Where $K$ is the binding constant at corresponding temperature and $R$ is the gas constant, $\Delta H$ and $\Delta S$ of reaction could be determined from the linear relationship between $\ln K$ and the reciprocal absolute temperature. The free energy change $(\Delta G)$ could be calculated by the Eq. (5). The results are represented in Table 2.

As shown in Table 2, $\Delta G$ and $\Delta H$ were negative, while $\Delta S$ was positive. Therefore, the formation of 6-TG-HSA coordination compound was spontaneous and exothermic reaction accompanied a positive $\Delta S$ value. According to the views of Orwcora and Bochs (1996), Masaki Otagiri (Mohammed et al., 1993), and Ross and Subramanian (1981), the positive $\Delta S$ value is frequently taken as an evidence for hydrophobic interaction. Furthermore, specific electrostatic interactions between ionic species in aqueous solution are characterized by a positive value of $\Delta S$ and a negative $\Delta H$ value. Accordingly, it was not possible to account for the thermodynamic parameters of 6-TG-HSA compound on the basis of a single interaction molecular force model (Gonzalez et al., 1992). It was more likely that hydrophobic and electrostatic interactions were involved in the binding process. However, 6-TG might be considered to be largely unionized under the experimental conditions, as could be expected from its structure. Thus, electrostatic interaction could not play a major role in the binding, and 6-TG bound to HSA was mainly based on the hydrophobic interaction.

3.4. The energy transfer of 6-TG with HSA

According to Förster (1996) non-radiative energy transfer theory, the rate of energy transfer depends on: (i) the relative orientation of the donor and acceptor dipoles, (ii) the extent of overlap of the emission spectrum of the donor with the absorption spectrum of the acceptor and (iii) the distance between the donor and the acceptor. The energy transfer effect is related

<table>
<thead>
<tr>
<th>$T$(°C)</th>
<th>$K$ (L mol$^{-1}$)</th>
<th>$n$</th>
<th>$\Delta G$ (kJ mol$^{-1}$)</th>
<th>$\Delta H$ (kJ mol$^{-1}$)</th>
<th>$\Delta S$ (J mol$^{-1}$ K$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>$4.24 \times 10^4$</td>
<td>0.8073</td>
<td>$-26.31$</td>
<td>-21.11</td>
<td>17.5</td>
</tr>
<tr>
<td>34</td>
<td>$3.13 \times 10^4$</td>
<td>0.9799</td>
<td>$-26.42$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>$2.47 \times 10^4$</td>
<td>1.1192</td>
<td>$-26.66$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
not only to the distance between the acceptor and the donor, but also to the critical energy transfer distance \( R_0 \), that is

\[
E = R_0^6 / (R_0^6 + r^6)
\]

(6)

Where \( r \) is the distance between the acceptor and the donor and \( R_0 \) is the critical distance when the transfer efficiency is 50%, which can be calculated by

\[
R_0^6 = 8.8 \times 10^{-25} \lambda^2 N^{-4} \phi J
\]

(7)

Where \( k^2 \) is the spatial orientation factor between the emission dipole of the donor and the absorption dipole of the acceptor. The dipole orientation factor, \( k^2 \), is the least certain parameter in the calculation of the critical transfer distance, \( R_0 \). Although theoretically \( k^2 \) can range from 0 to 4, the extreme values require very rigid orientations. If both the donor and acceptor are tumbling rapidly and free to assume any orientation, then \( k^2 \) equals 2/3 (Yang, 1991). If only the donor is free to rotate, then \( k^2 \) can vary from 1/3 to 4/3 (Wu and Stryer, 1972; Lakowicz, 1983). \( N \) is the refractive index of the medium, \( \phi \) the fluorescence quantum yield of the donor and \( J \) is the overlap integral of the fluorescence emission spectrum of the donor and the absorption spectrum of the acceptor, given by

\[
J = \Sigma F(\lambda) (\epsilon(\lambda))^2 \Delta \lambda / \Sigma F(\lambda) \Delta \lambda
\]

(8)

where \( F(\lambda) \) is the fluorescence intensity of the fluorescent donor in wavelength \( \lambda \) and dimensionless, \( \epsilon(\lambda) \) the molar absorption coefficient of the acceptor in wavelength \( \lambda \) and unit is \( \text{cm}^{-1} \text{mol}^{-1} \text{L} \). The energy transfer efficiency is frequency calculated from the relative fluorescence yield in the presence \( (F) \) and absence of acceptor \( (F_0) \):

\[
E = 1 - F / F_0
\]

(9)

The overlap of UV absorption spectra of 6-TG with the fluorescence emission spectra of HSA is shown in Fig. 6. J can be evaluated by integrating the spectra in Fig. 6.

It was reported for HSA that \( k^2 = 2/3, \phi = 0.118 \) and \( N = 1.336 \) (Yu et al., 2013), so the value of the overlap integral calculated from Fig. 6 is \( 4.1235 \times 10^{-14} \text{cm}^2 \text{L}^{-1} \), and \( R_0 \) is 3.10 nm and \( r \) is 4.37 nm, respectively. The binding distance between 6-TG and tryptophan residue of HSA is 4.37 nm, which is smaller than 7 nm. According to conditions of Förster’s non-radioactive energy transfer theory the static quenching interaction between HSA and 6-TG could be confirmed.

3.5. The effect of coexisting foreign substances on binding constant

The previous studies indicated that HSA has a high-affinity metal-binding site at N-terminus. The multiple binding sites underlie the exceptional ability of HSA to interact with many organic and inorganic molecules and make this protein an important regulator of intercellular fluxes and the pharmacokinetic behavior of many drugs (Carter and Ho, 1994). Therefore, the existence of other ions can directly influence the binding force of small molecules with protein. The effect of other ions on binding constants was investigated by analyzing their different binding constants, which can be used as a model for investigating the interaction of 6-TG with HSA. Table 3 summarizes the results of the effect of common ions on binding constants at 24°C.

It was shown that the binding constants between the protein and 6-TG increased in the presence of other ions, signifying a stronger binding between 6-TG and HSA. The higher binding constant obtained in the presence of ions might result from the interaction of cation/anion with 6-TG to form a complex, which in turn interacted with HSA. From the pharmacokinetics perspective, the increasing of the binding constant would abate the drug concentration in the blood and prolong the duration in the plasma in some way. Hence, maximum effectiveness of the drug was achieved. Thus, the increase in the binding constant of 6-TG-HSA in the presence of ions described above prolonged the storage time in blood plasma and enhanced the maximum effectiveness of 6-TG. Therefore, in the presence of other ions, 6-TG could be stored and transferred better and released slower action by the protein in the body (He et al., 2005).

3.6. Molecular model study

The complementary applications of molecular modeling have been employed by computer methods to help the understanding of the interaction of 6-TG with HSA. The investigation of 3-D structure of crystalline albumin showed that HSA contains three homologous domains (I, II and III): I (residues 1–195), II (196–383), and III (384–585) and each domain can be divided into two subdomains (A and B). The crystallographic analysis reveals that HSA has binding sites of com-

Table 3 The binding constants (L mol\(^{-1}\)) of 6-TG-HSA at 24°C in the presence of common ions.

<table>
<thead>
<tr>
<th>Ions</th>
<th>(k_{HSA}(10^4))</th>
<th>(R_{HSA})</th>
<th>Ions</th>
<th>(k_{HSA}(10^4))</th>
<th>(R_{HSA})</th>
</tr>
</thead>
<tbody>
<tr>
<td>K(^+)</td>
<td>4.0643</td>
<td>0.9999</td>
<td>Mg(^2+)</td>
<td>6.1108</td>
<td>0.9998</td>
</tr>
<tr>
<td>Ca(^2+)</td>
<td>5.7784</td>
<td>0.9997</td>
<td>Pb(^2+)</td>
<td>6.5945</td>
<td>0.9999</td>
</tr>
<tr>
<td>NH(_4)(^+)</td>
<td>5.4533</td>
<td>0.9998</td>
<td>Al(^3+)</td>
<td>6.9182</td>
<td>0.9995</td>
</tr>
<tr>
<td>Bi(^3+)</td>
<td>7.7048</td>
<td>0.9979</td>
<td>F(^-)</td>
<td>5.1314</td>
<td>0.9997</td>
</tr>
<tr>
<td>Hg(^2+)</td>
<td>7.0341</td>
<td>0.9985</td>
<td>Cd(^2+)</td>
<td>5.5335</td>
<td>0.9995</td>
</tr>
<tr>
<td>Zn(^2+)</td>
<td>5.2806</td>
<td>0.9997</td>
<td>NO(_3)(^-)</td>
<td>5.8559</td>
<td>0.9996</td>
</tr>
<tr>
<td>Co(^2+)</td>
<td>5.5572</td>
<td>0.9987</td>
<td>CO(_3)(^2-)</td>
<td>4.2852</td>
<td>0.9997</td>
</tr>
<tr>
<td>Ni(^2+)</td>
<td>6.1627</td>
<td>0.9988</td>
<td>PO(_4)(^3-)</td>
<td>5.6543</td>
<td>0.9979</td>
</tr>
<tr>
<td>SO(_4)(^2-)</td>
<td>5.1925</td>
<td>0.9992</td>
<td>Fe(^3+)</td>
<td>7.5306</td>
<td>0.9982</td>
</tr>
</tbody>
</table>

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pounds within hydrophobic cavities in subdomains IIA and IIIA, which are corresponding to site I and site II, respectively, and the sole tryptophan residue (Trp 214) of HSA is in subdomain IIA (He and Carter, 1992; Petitpas et al., 2001). There is a large hydrophobic cavity present in the subdomain IIA to which many drugs can bind. The crystal structure of HSA in complex with warfarin was taken from the Brookhaven Protein Data Bank (entry codes 1h9z). The potential of the 3-D structure of HSA was assigned according to the Amber 4.0 force field with Kollman-all-atom charges. The initial structure of the thioguanine was generated by molecular modeling software Sybyl 6.9.1 (Louis, 2003). The geometry of the molecule was subsequently optimized to minimal energy using the tripos force field with Gasteiger–Marsili charges. Then it was used to replace warfarin in the HSA-warfarin crystal structure. At last, Flexx program was used to establish the interaction mode between the 6-TG and HSA.

Fig. 7 exhibits the optimal energy ranked result of 6-TG interaction with the residues of HSA. It can be seen that the 6-TG molecule was situated within the subdomain IIA hydrophobic cavity, and the 6-TG was adjacent to hydrophobic residues Leu(219), Leu(238), Phe(223), Phe(211), Glu(292), Val(293), Ala(291), Ala(215), Ala(261), Ile(290), His(242) etc., of the subdomain IIA of HSA. The results of molecular modeling suggested that the interaction between HSA and 6-TG was dominated by hydrophobic force, which was in agreement with the binding mode proposed in thermodynamic analysis. It also provided a good structural basis to explain the efficient fluorescence quenching of HSA emission in the presence of 6-TG. In addition, there were some hydrogen bonds between 6-TG and residues of HSA such as Arg(222) and Ala(291). Furthermore, this phenomenon provided a good structural basis to explain the very efficient fluorescence quenching of HSA emission in the presence of 6-TG.

4. Conclusion

An approach for studying the interactions of fluorescent protein with 6-TG using fluorescence and molecular modeling techniques was presented. The results showed that HSA fluorescence was quenched by 6-TG through static quenching and 6-TG could bind to HSA through the hydrophobic interaction and hydrogen bond. The biological significance of this work was evident since albumin served as a carrier molecule for multiple drugs and the interactions of 6-TG with albumin had not been characterized so far. These experimental and theoretical data might be a useful guide for the synthesis of efficient nucleotide drugs, providing some important data for clinical study of nucleotide drugs, and have a great significance in pharmacology and clinical medicine as well as methodology.

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References


