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Quaternary Ammonium Salt Strategy and Molecular Docking Studies of Novel 5-Acyl-8-(Arylamino)-Quinolines by Acetyl and Methanesulfonyl Chloride for Dual Evaluation Bioactivity

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Abstract—Six quinoline derivatives containing quaternary ammonium salts and acyl chloride groups were synthesized from ethyl 8-chloro-[1,3]dioxolo[4,5-*g*]quinoline-7-carboxylate in several step. With berberine as the positive control, three human cancer cell lines (HCT-116, Hela and A549) and human normal liver L-02 cell lines were used to evaluate the cytotoxicity of the newly synthesized compounds in vitro. Compound (**V**–**X**) showed good antitumor activity, and the test result of compound (**VII**) was better than that of positive control group. In terms of antibacterial activity, compound (**V**–**X**) has obvious inhibitory effect on *Staphylococcus aureus* (ATCC 29213) and *Escherichia coli* (ATCC 8739), and its antibacterial activity is about 1–4 times that of positive control amoxicillin and 1–2 times that of ciprofloxacin. Among them, the most effective compounds (**VII**) and (**X**) have 4-fold the antibacterial activity of amoxicillin and 2-fold the antibacterial activity of ciprofloxacin.

Keywords: acetonium chlorine, methanesulfonium chloride, anticancer activity, antibacterial activity, molecular docking

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INTRODUCTION

Infectious diseases have become one of the most common diseases threatening human health, but the abuse of antibiotics for decades has led to an unanticipated increased bacterial resistance even gradually lost its function [1]. Therefore, it is urgent to find new ideal solutions in the treatment of infectious diseases at present. As an important intermediate of chemical synthesis, quinoline derivatives [2] (nitrobenzo heterocyclic compound) have antibacterial [3], antitumor [4], anti-malaria [5, 6], anti-inflammatory [7], anti-oxidation [8, 9] and other pharmacological effects, which are gradually being discovered. Since 1962, the first-generation artificial antibacterial agent quinolone has been developed. Structural modification has undergone four generations of changes. Due to its poor therapeutic effect, the first-generation antibacterial drugs represented by naphthalenedicarboxylic acid were gradually phased out. The second- and third-generation antibacterial spectrum has certain limitations, namely that the more stable second generation only has a specific antibacterial effect against a few Gram-negative bacteria such as Enterobacteriaceae, and is mainly used for clinical application of urinary tract and intestinal infections. Subsequently, fluoride was introduced into the structure to obtain the third generation, which has an inhibitory effect on Gram-positive bacteria. On this basis, structural modifications were made to obtain the fourth generation, including the introduction of 8-methoxy, C-7 nitrodioxane structures, etc., to further expand the antibacterial spectrum, enhance antibacterial activity, and reduce the adverse reactions of quinolone drugs [10–12]. With the continuous research on quinolone drugs, the structure-activity relationship of quinolines ring was studied by structural modification for many times, and it was found that the change of substituent could enhance the affinity with mammalian topoisomerase, so that the research on quinolone drugs changed from antibacterial activity to antibacterial and anticancer activity [13, 15].

Quinolones have broad-spectrum antibacterial effects, which is achieved by inhibiting DNA gyrase and inhibiting bacterial DNA replication [16]. And then, it could inhibit the proliferation of tumor cells and reduce the drug resistance of tumor cells by inhibiting kinase and *p*-glycoprotein [17–19]. As for structural modification, existing studies have shown that the synthesized quaternary ammonium salt derivatives can achieve stronger antibacterial activities and less cytotoxicity than the original compounds, and the antibacterial activities of the quaternary ammonium

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salt derivatives are related to the length of the side chain alkyl groups and the strength of the electron absorption capacity [20]. Meanwhile, introducing halogen elements to the structure of quinoline derivatives has a positive significance in improving the anticancer properties of the products, in addition augment the antibacterial properties.

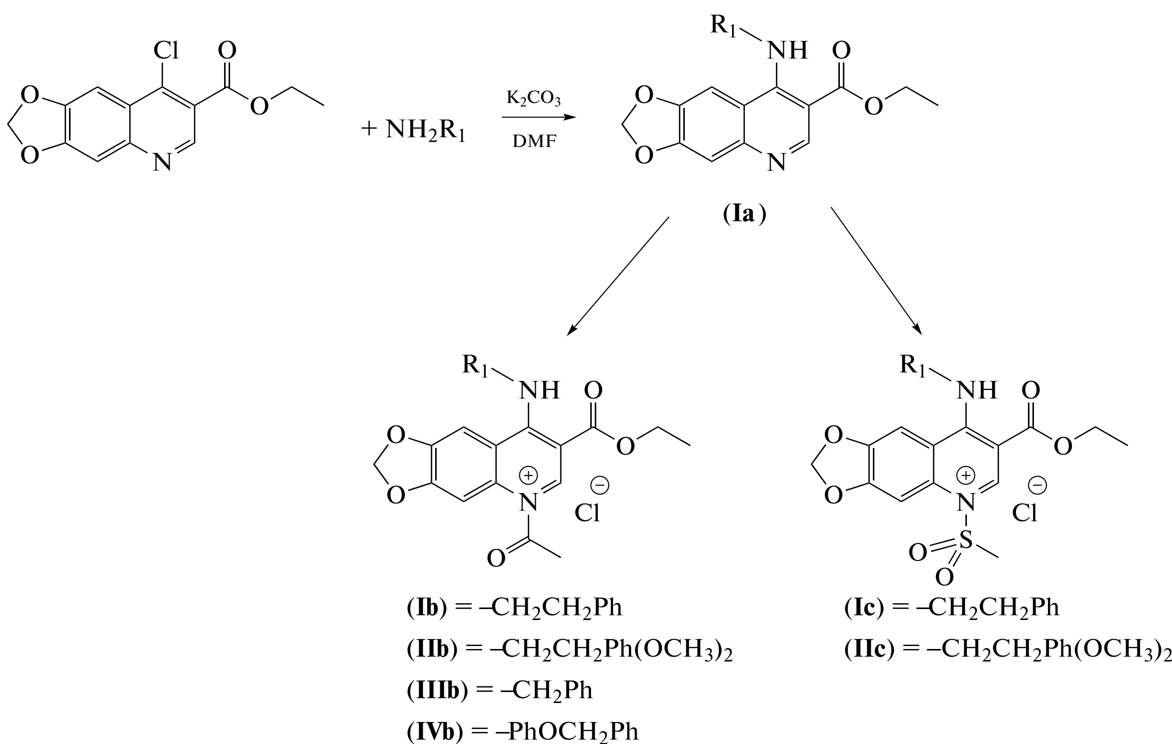
Novel coronavirus pneumonia, which appeared in late 2019 and erupted in early 2020, brought the world to an ephemeral pause. In this severe situation, many effective drugs have been developed based on the modification of structure similar to the quinolone core. In clinical reports on the treatment of coronavirus, chloroquine has the potential to treat this virus [21, 22]. Therefore, it is of practical significance to modify the structure of quinolones in the current and future diagnosis and treatment.

In this study, quinoline was used as the parent nucleus, and acyl chloride and quaternary ammonium salt groups were added to this structure, in the hope that the newly synthesized compounds would have antibacterial and anticancer biological activities, providing a favorable basis for the subsequent public medicine.

RESULTS AND DISCUSSION

The quinoline ring as the parent nucleus, new compounds were obtained by appending or changing the side chain groups (Fig. 1). Studies have shown that quinoline derivatives have antibacterial effects by inhibiting DNA helicotropin and inhibiting bacterial DNA replication. In this design, the 5-position and 8-position of the quinoline ring were modified by adding side chain groups, in an attempt to make the newly synthesized quinoline derivatives have antibacterial and anticancer double biological activities. Methanesulfonyl chloride or acetyl chloride was introduced at 5-position, which were converted into quaternary ammonium salt type, and halogen element was added to obtain better antibacterial effect of derivatives. The introduction of aromatic amines at the 8-position increased the ability of the compound to bind to DNA, while increasing the π-H ability of the quinoline ring to the protein. The functional groups at 5-position and 8-position were changed to observe the effects of different functional groups on antibacterial and anticancer activities. The synthesis of the target compounds was carried out according to the synthesis plan outlined, and their antibacterial and anticancer activities were evaluated.

The 7-ethoxycarbonyl-8-arylamino-[1,3]dioxolo[4,5-*g*]quinolin-5-chloride derivatives were synthesized according to Scheme 1. Ethyl 8-aryl-[1,3]-dioxolo [4,5-*g*] quinolone-7-carboxylate derivatives **(Ia)** were chlorinated with excessive acetyl chloride or methanesulfonyl chloride at room temperature to yield the target compounds **(Ic–IVb)** in moderate yield (Scheme 1).



Scheme 1. General synthetic route of quinoline derivatives.

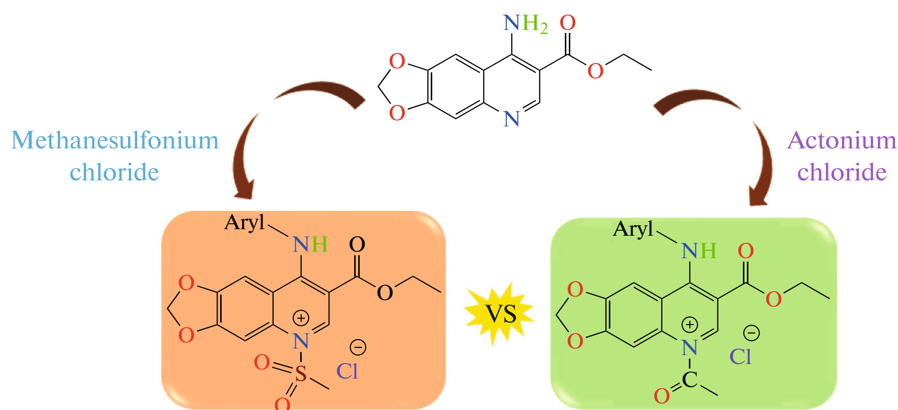


Fig. 1. Schematic diagram of overall design simulation of quinoline derivatives.

Compounds (**V–X**) were tested for cytotoxicity in vitro using MTT assay [23] in human colon cancer cell lines (HTC-116), human cervical cancer cell lines (Hela), human lung cancer cell lines (A549) and normal liver cell lines (L-02) from the us cell culture bank. The positive control was berberine.

The 7-ethoxycarbonyl-8-arylamino-[1,3]-dioxolo[4,5-*g*]quinolin-5-ium chloride derivatives were tested on human cancer cells, and the data are listed in Table 1 and Fig. 2. By comparing the data, it can be found that the change of 5-postion and 8-postion substituent group has a biggish influence on the titer of the compound. In the case of the same 8-position substituents, different 5-postion substituents lead to obvious differences in activity, that is, compounds containing methylsulfonyl chloride in each series are more active than those containing acetyl chloride, showing that (**Ic**) is superior to (**Ib**), while (**IIc**) is better than (**IIb**). Then again, it is also meaningful to consider the substitution of the N-5 position compound. Among compounds (**Ib**), (**IIb**), (**IIIb**) and (**IVb**) which the 5-postion substituents of the quinoline ring were acetylchloride, compound (**IVb**) with oxygen atoms in a long chain aryl substituent at 8-postion of the quinoline ring had the best titer, better than berberine in cancer cell test in vitro. The same is true when it comes to methanesulfonyl chloride substituents at 5-postion of the quinoline ring. For example, compound (**IIc**) also has a long chain substituent with oxygen atoms at 8-postion of the quinoline ring similar to (**IVb**), with slightly better activity than compound (**Ic**) against tested cell lines.

According to the above analysis, HTC-116, Hela and A549 were significantly inhibited by compounds (**IIc**) and (**IVb**). And the IC_{50} of compound (**IIc**) on HCT-116, Hela and A549 were 38.31 ± 8.19, 48.88 ± 4.53 and 24.30 ± 5.37, respectively, and the IC_{50} of compound 10 on HTC-116, Hela and A549 were 38.31 ± 8.19, 48.88 ± 4.53 and 24.30 ± 5.37, respectively.

The minimal inhibitory concentration (MIC) of compound (**Ic–IVb**) against *S. aureus* (ATCC 29213) and *E. coli* (ATCC 8739) [24–27] was determined by 96-well plate broth microdilution method. The test compounds were dissolved in DMSO to a final concentration of 1–25 nmol/mL and inoculated on a Muller–Hinton agar plate. The final bacterial concentration was about 10^6 CFU mL^{-1}. The MIC values were determined after incubation at 37°C for 24 h. Under the same conditions, amoxicillin and ciprofloxacin were used as control (Table 2 and Fig. 3).

It can be seen from the observation of experimental data that the compound (**Ic–IVb**) to *S. aureus* (ATCC 29213) and *E. coli* (ATCC 8739) has shown good antibacterial activity. The results has shown the same regularity as in vitro cytotoxicity test, that is, the antibacterial activity of 5-position substituted with methyl sulfonyl chloride on quinoline ring was better than 5-postion substituted with acetyl chloride. When the 5-postion substitutions on the quinoline ring are all acetyl chloride or all methanesulfonyl chloride, the compounds have better antibacterial activity provided that the 8-postion amino substitutions on the quinoline ring are long and contain oxygen atoms. Compounds (**IIc**) and (**IVb**) were the most prominent, with the MIC values of compound (**IIc**) to *S. aureus* (ATCC 29213) and *E. coli* (ATCC 8739) being 12.5 nmol/mL and compound (**IVb**) to *S. aureus* (ATCC 29213) and *E. coli* (ATCC 8739) being 12.5 nmol/mL, respectively.

Literature has shown that quinolones have antibacterial effects mainly by inhibiting DNA gyrase and topoisomerase IV. The Discovery Studio 2016 Client was used for docking operations to evaluate the 2D and 3D binding patterns of compounds (**IIc**) and (**IVb**) at the active postions of the enzyme. DNA gyrase and topoisomerase IV eutectic structures were downloaded from the protein database as docking receptor proteins (PDB ID: 2XCS, 1TL8). Discovery Studio 2016 Client was used for docking, and Pymol 1.5.6 was used to process and analyze the docking results (Table 3).

Table 1. MTT assay of compound (**V–X**) on HTC-116, HeLa, A549 and L-02)

Compound	IC_{50}, μg/mL			
	HCT-116	HeLa	A549	L-02
(Ic)	55.39 ± 3.11	57.53 ± 4.31	59.68 ± 7.13	66.77 ± 6.09
(Ib)	80.48 ± 11.74	93.11 ± 5.03	84.21 ± 3.80	23.29 ± 7.11
(IIc)	38.31 ± 8.19	48.88 ± 4.53	24.30 ± 5.37	91.80 ± 8.54
(IIb)	67.12 ± 5.65	98.36 ± 3.57	77.48 ± 11.95	65.02 ± 11.34
(IIIb)	82.92 ± 3.45	73.25 ± 6.55	71.33 ± 6.47	47.56 ± 10.04
(IVb)	30.16 ± 3.21	38.58 ± 3.66	43.30 ± 5.40	69.07 ± 8.55
Berberine	64.25 ± 4.41	72.31 ± 2.53	55.38 ± 3.17	137.46 ± 6.12

IC_{50}: Each value was averaged by three parallel groups of eight repeats and calculated using a SigmaPlot software.

The result of docking of compound **(IIc)** with topoisomerase IV (Fig. 4) showed LibDockScore of 131.666, the hydrogen bond between compound **(IIc)** and amino acid residue arg364 and base DA113, and the ion interaction between amino acid residue lys532 and base DG12 and benzene ring on the 8-postion substituent group. The result of docking of compound **(IIc)** with DNA gyrase (Fig. 5) showed LibDockScore of 206.172 and compound **(IIc)** had hydrogen bonds with amino acid residues ala1120 and base DC11, and base DG10 had ion interactions with N atoms on the quinoline ring.

The result of docking of compound **(IVb)** with topoisomerase **(IV)** (Fig. 6) showed LibDockScore of 141.994 and compound **(IVb)** had hydrogen bonds with amino acid residues arg364, asn722, base DA113 and DG112, and the base DG113 had ion interactions with N atoms on the quinoline ring. The result of docking of compound 10 with DNA cyclotron (Fig. 7) showed that LibDockScore of 171.061, and the base DG10 had ion interaction with N atoms on the quinoline ring. The above four docking results all have PI-PI stacked.

EXPERIMENTAL

Reagents and Instrumentation

The solvents and reagents used in the experiments were commercially sourced. All glassware is dried in an oven before use. The reaction process was monitored by thin layer chromatography (TLC), and the TLC results were analyzed under 254 and 365 nm UV lamp. The ^{1}H and ^{13}C spectra were recorded on the Bruker Avance II spectrometer of $CDCl_3$ (400 MHz for ^{1}H and 100 MHz for ^{13}C) and Carlo Erba Instruments CHNS-O EA1108 spectra analysis. The chemical shifts were expressed as ppm, and the internal tetramethylsilane were 0.

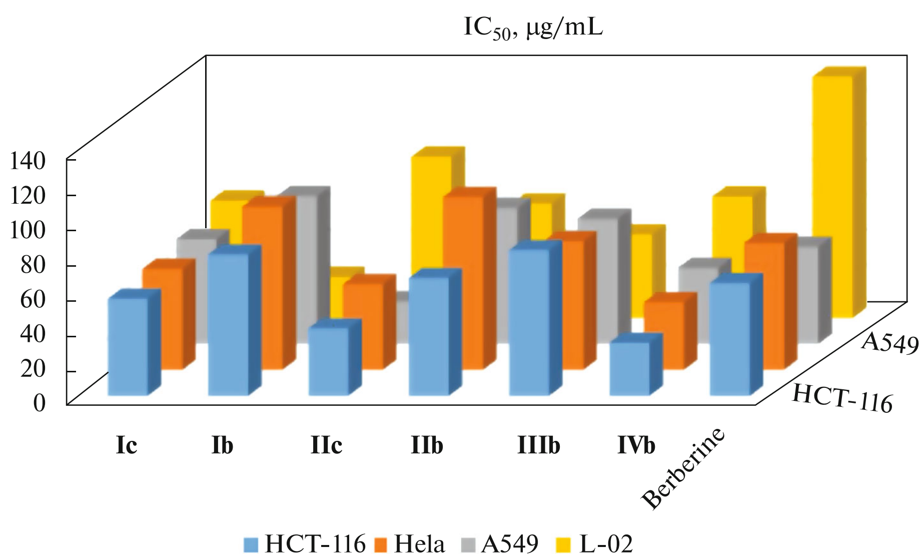


Fig. 2. MTT assay of compound (**V–X**) on HTC-116, HeLa, A549 and L-02.

Table 2. Antibacterial screening in terms of the MIC (nmol mL^{-1}) for compounds (**V–X**)

Compound	MIC, (nmol mL^{-1})[1]		ClogP[2]
	Escherichia coli	*Staphylococcus aureus*	
(Ic)	12.5	6.25	1.88
(Ib)	12.5	>25	1.47
(IIc)	12.5	6.25	2.83
(IIb)	6.25	25	2.24
(IIIb)	>25	12.5	2.51
(IVb)	12.5	6.25	2.07
Amoxicillin	**25**	**12.5**	
Ciprofloxacin	**12.5**	**6.25**	

[1](a) MIC (minimum inhibitory concentration) values represent the average of three readings; (b) calculated with the ACD/Labs website: https://www.acdlabs.com/ .
[2]ClogP (Lipophilicity Parameters compound) calculated on ACD/Labs website.

Table 3. Docking scored obtained for compounds (**VII**) and (**X**)

PDB code	Entry	LibDockScore	Interaction with receptor
2XCS	**(IIc)**	131.666	DG 10, DC 10, ALA 1118, ALA 1119, ALA 1120
	(IVb)	141.994	DG 10, DC 11, ALA 1118
1TL8	**(IIc)**	206.172	DT 10, DG 112, DA 113, DG 12, ARG 364, LYS 532, TPC 11
	(IVb)	171.061	DA 113, DG 112, DT 10 ARG 364, TPC 11, ASN 722, LYS 425

General Procedure for the Synthesis

The compounds 7-(ethoxycarbony)-5-(methylsulfonyl)-8-(phenethylamino)-[1,3]dioxolo[4,5-*g*]quinolone-5-ium chloride **(Ia)** were used as examples. The compound ethyl-8-(phenethylamino)-[1,3]dioxolo-[4,5-*g*]quinolone-7-carboxylate (1.0 eq) was weighed and placed in a round bottom flask ethyl acetate (5 mL) was added, and methyl sulfonyl chloride (3.0 eq) was slowly added under stirring conditions. The reaction process was monitored by TLC. The precipitate was filtered and wash the several time ethyl acetate 2 mL/time, and then dried afford a white solid.

5-Acetyl-7-(ethoxycarbony)-8-(phenethylamino)-[1,3]dioxolo[4,5-*g*]quinolone-5-ium chloride (Ib). A white powder (76.0%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 16.01 (s, 1H), 10.30 (s, 1H), 8.80 (s,

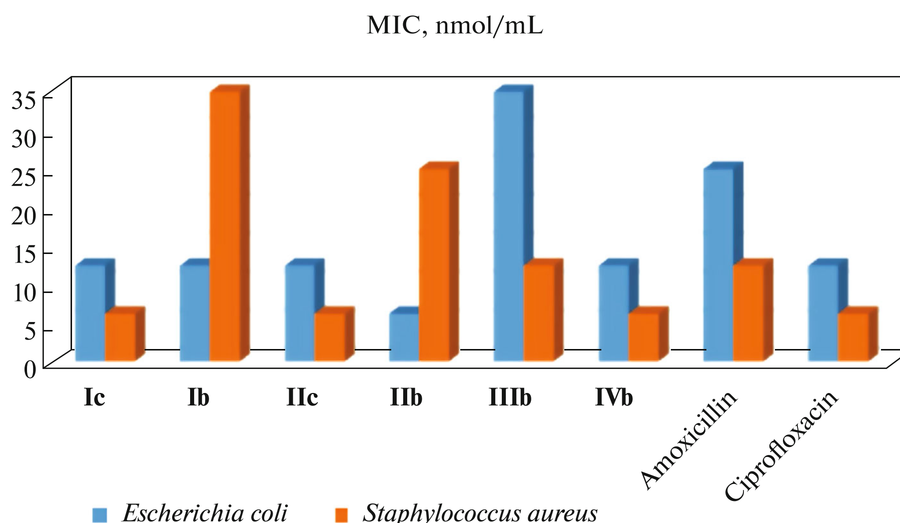


Fig. 3. Antibacterial screening in terms of the MIC (nmol mL^{-1}) for compounds (**V–X**).

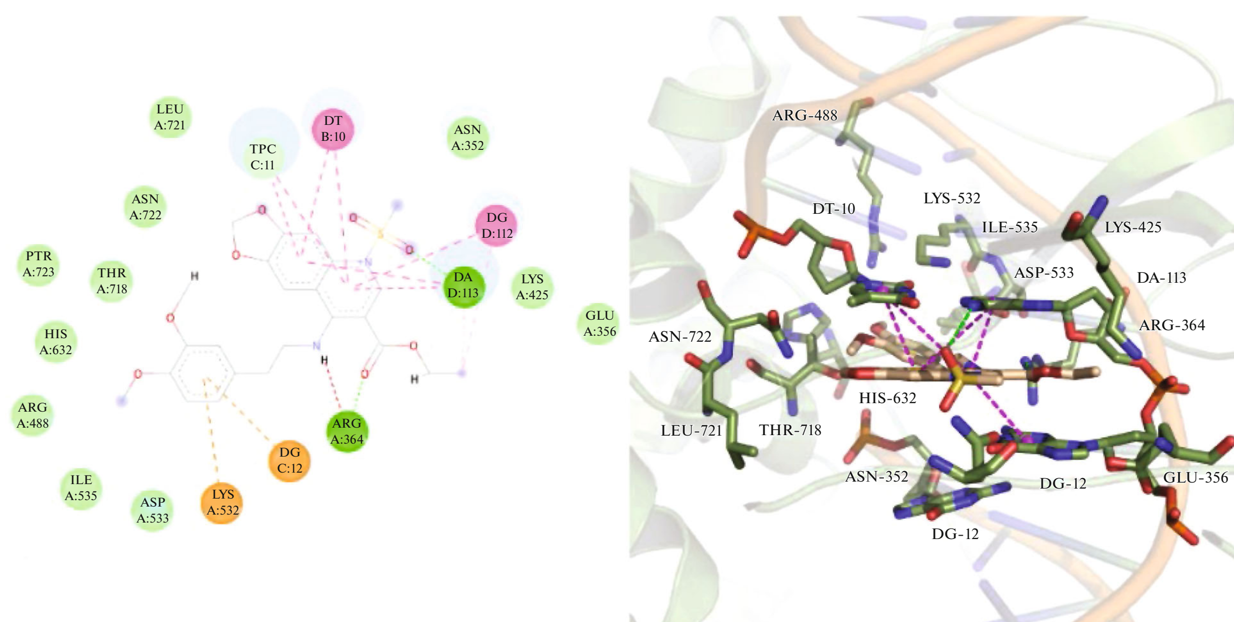


Fig. 4. The 2D binding mode and 3D binding mode of compound **(VII)** in the active site of topoisomerase IV (PDB ID: 1TL8).

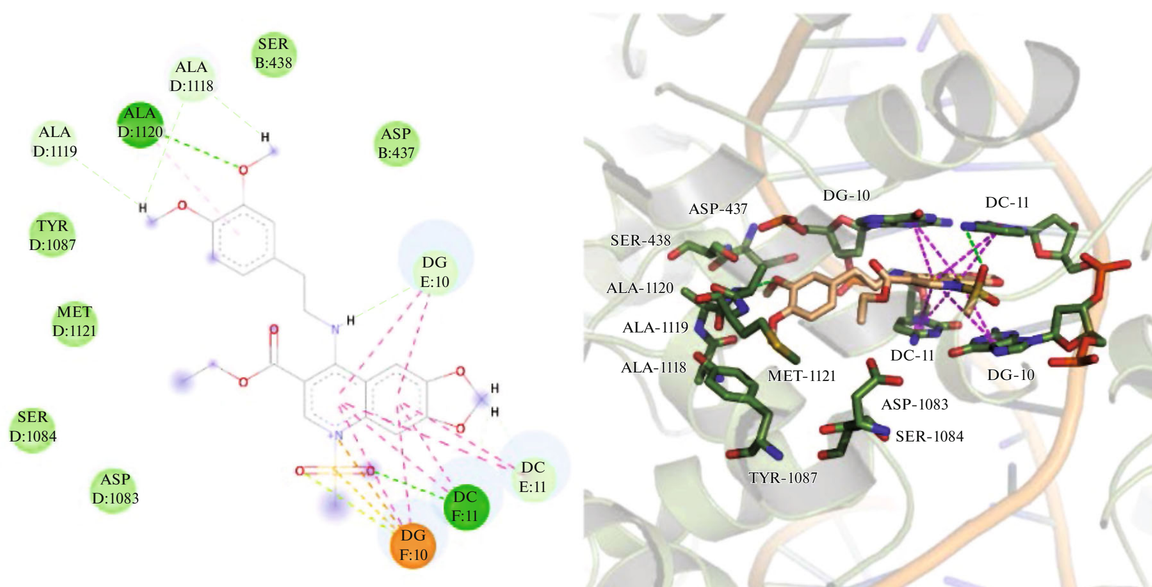


Fig. 5. The 2D binding mode and 3D binding mode of compound **(VII)** in the active site of DNA gyrase (PDB ID: 2XCS).

1H), 7.85 (s, 1H), 7.63 (s, 1H), 7.33–7.23 (m, 5H), 6.19 (s, 2H), 4.36–4.31 (m, 2H), 4.20–4.16 (m, 2H), 3.13 (t, $J = 6.0$ Hz, 2H), 1.37 (t, $J = 6.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 171.93, 166.53, 157.27, 153.79, 148.10, 142.90, 138.75, 136.54, 128.92, 128.82, 127.35, 112.99, 103.59, 102.98, 101.53, 100.11, 62.25, 50.23, 36.55, 25.19, 14.13.

7-(Ethoxycarbony)-5-(methylsulfonyl)-8-(phenethylamino)-[1,3]dioxolo[4,5-*g*]quinolone-5-ium chloride (Ic). A white powder (46.51%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 14.87 (s, 1H), 10.35 (s, 1H), 8.92 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.36–7.26 (m, 5H), 6.19 (s, 2H), 4.40–4.35 (m, 2H), 4.20–4.15 (m, 2H), 3.15 (t, $J = 6.0$ Hz, 2H), 2.91 (s, 3H), 1.40 (t, $J = 6.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.62, 157.38, 153.98, 148.07, 142.90, 138.89, 136.56, 128.96, 128.81, 127.38, 112.97, 103.52, 102.95, 101.83, 100.25, 62.31, 50.26, 39.44, 36.57, 14.17.

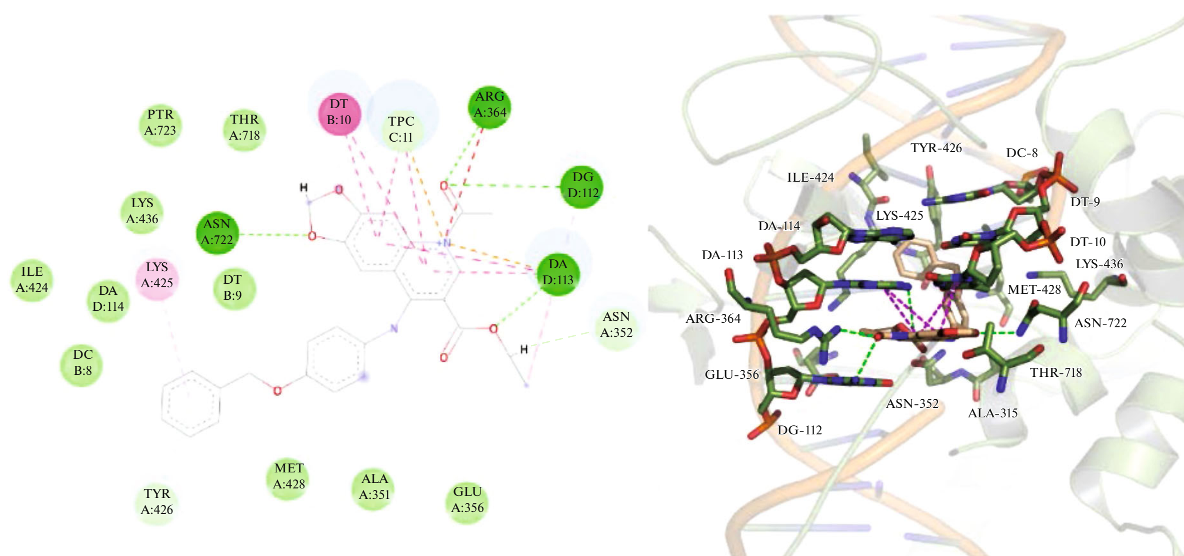


Fig. 6. Fluorescence spectra of different equivalents hydrogen peroxide PyBODIPY and different amino acid.

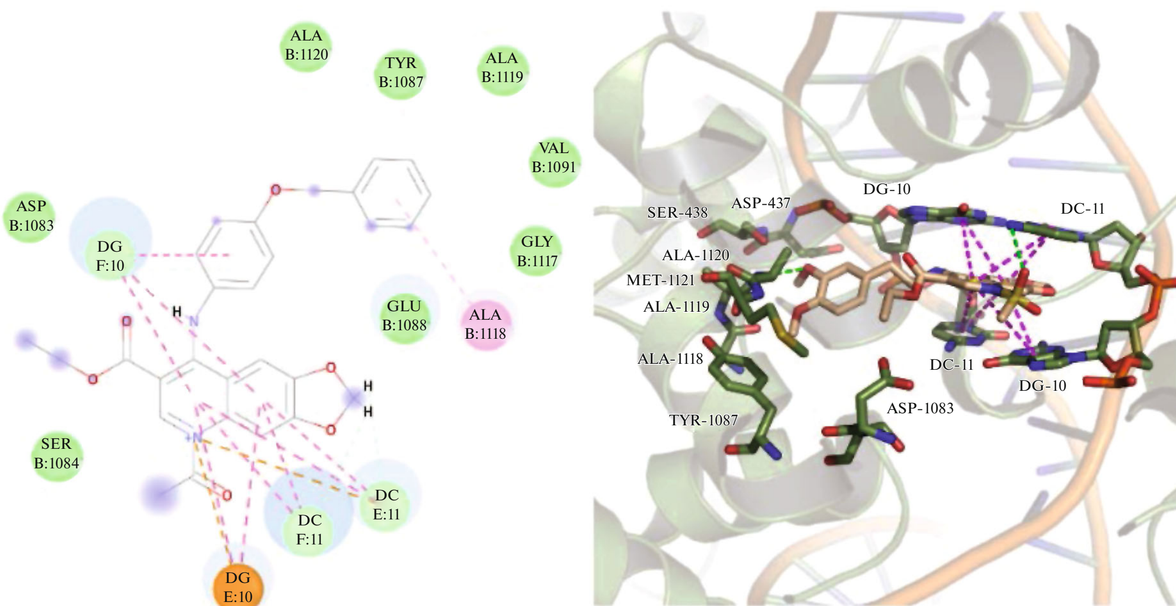


Fig. 7. Changes in response to PyBODIPY and different amino acids.

5-Acetyl-8-((3,4-dimethoxyphenethyl)amino)-7-(ethoxycarbony)-[1,3]dioxolo[4,5-*g*]quinolone-5-ium chloride (IIb). A white powder (79.35%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 16.02 (s, 1H), 10.34 (s, 1H), 8.85 (d, J = 8.0 Hz, 1H), 7.89 (s, 1H), 7.66 (s, 1H), 6.85 (d, J = 4.0 Hz, 3H), 6.21 (s, 2H), 4.38–4.32 (m, 2H), 4.19 (d, J = 8.0 Hz, 2H), 3.90 (s, 2H), 3.86 (s, 3H), 3.08 (t, J = 6.0 Hz, 2H), 2.14 (s, 1H), 1.40 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 174.89, 166.58, 157.20, 153.75, 149.14, 148.06, 141.89, 138.75, 129.02, 120.84, 112.99, 112.32, 111.59, 103.57, 103.08, 101.40, 100.13, 62.22, 55.93, 55.87, 50.58, 36.11, 25.22, 14.12.

8-((3,4-Dimethoxyphenethyl)amino)-7-(ethoxycarbony)-5-(methylsulfonyl)-[1,3]dioxolo[4,5-*g*]quinolone-5-ium chloride (IIc). A white powder (63.54%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 15.21 (s, 1H), 10.36 (s, 1H), 8.90 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 6.85 (d, J = 4.0 Hz, 3H), 6.20 (s, 2H), 4.39–4.34 (m, 2H), 4.20–4.15 (m, 2H), 3.91 (s, 3H),

3.87 (s, 3H), 3.69 (s, 1H), 3.08 (t, J = 6.0 Hz, 2H), 2.93 (d, J = 12.0 Hz, 3H), 1.39 (d, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 166.61, 153.89, 149.16, 148.28, 148.05, 142.51, 138.78, 129.05, 120.84, 112.98, 112.33, 111.61, 103.55, 103.10, 101.62, 100.13, 62.26, 55.94, 55.87, 50.60, 39.41, 36.11, 14.13.

5-Acetyl-8-(benzylamino)-7-(ethoxycarbonyl)-1,3]-dioxolo[4,5-*g*]quinolin-5-ium chloride (IIIb). A white powder (53.42%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 15.93 (s, 1H), 10.61 (s, 1H), 8.91 (s, 1H), 7.89 (s, 1H), 7.66 (s, 1H), 7.46–7.37 (m, 5H), 6.21 (s, 2H), 5.11 (d, J = 4.0 Hz, 2H), 4.36–4.31 (m, 2H), 2.05 (s, 1H), 1.36 (t, J = 8.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 174.42, 166.62, 157.38, 153.98, 148.27, 142.07, 138.90, 135.53, 129.49, 128.84, 127.29, 112.84, 103.58, 103.05, 101.79, 100.19, 62.36, 52.20, 20.82, 14.08.

5-Acetyl-8-((4-(benzyloxy)phenyl)amino)-7-(ethoxy-carbonyl)-[1,3]dioxolo[4,5-*g*]quinolin-5-ium chloride (IVb). A yellow powder (91.34%) yield: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 16.42 (s, 1H), 11.56 (s, 1H), 9.01 (s, 1H), 7.91 (s, 1H), 7.44–7.29 (m, 6H), 7.15 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 6.13 (s, 2H), 5.10 (s, 2H), 4.44–4.39 (m, 2H), 1.42 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 171.93, 166.68, 158.41, 156.10, 154.01, 147.74, 142.12, 138.99, 136.15, 131.52, 128.69, 128.24, 127.48, 126.25, 116.38, 112.96, 103.42, 103.05, 102.73, 100.08, 70.42, 62.69 25.19, 14.16.

In vitro cytotoxicity. HCT-116, Hela, A549 and normal liver L-02 cells were screened for cytotoxicity in vitro from American type culture collection (USA). HCT-116, Hela and A549 cells were routinely cultured in rpmi-1640, while L-02 cells were routinely cultured in DMEM. 10% fetal bovine serum (FBS) was added to the medium, and the cells were subjected to sub-melting in a humidifying atmosphere of 37°C and 5% CO_2. These cells are monitored daily and maintained at 80% cell density.

Cytotoxicity of each cell line was measured in the MTT cancer cells (HCT-116, Hela and A549) and human lung L-02 at logarithmic growth. All cells were seeded on the 96-well plate at a rate of 10^6 cells/Wells. The samples were then treated with berberine at different concentrations of 1, 3, 5, 10 or 20 mol/mL and tested for 24 h. Take the supernatant, dissolve it in 100 mL DMSO, and shake well for 10 min. A microplate photometer was used to measure the optical density of the sample at 490 nm. Cell activity is expressed as a percentage change in absorbance relative to the control value.

In vitro antimicrobial evaluation. The microdilution method of 96-well plate broth was used to determine the compounds of two strains of bacteria, and the MIC value, that is, the minimum concentration of the test sequence, was determined. The microorganisms were screened for *S. aureus* (ATCC 29213) and *E. coli* (ATCC 8739). It was placed on a muller-hinton AGAR plate after inoculation, and the test compound was dissolved in DMSO, resulting in a final concentration of 1–25 nmol mL^{-1}. The final bacterial concentration was about 10^6 CFU mL^{-1}. MIC values were determined after incubation at 37°C for 24 h. Berberine was used as the control and measured under the same condition. All experiments are in triplicate.

Molecular docking. The Discovery Studia 2016 Client was used for molecular docking operation.

CONCLUSIONS

Quinoline quaternary ammonium salt derivatives have been comprehensively analyzed and compared in terms of anti-tumor and antibacterial activities. Among them, compounds **(IIc)** and **(IVb)** have good antibacterial and anticancer effects, and through molecular docking simulation, it was found that the mother nucleus of positively charged quaternary ammonium salt has good calculation results in terms of binding force. This shows the clarity of the design direction. But its toxicity to normal cell lines is still a problem to be solved. In the process of synthesis of novel chlorine-quaternary ammonium salt quinoline derivatives, the introduction of chloride ions from the outside increases the antibacterial effect and cytotoxicity of the compounds. This is also the most important research topic to be solved in the future.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest.

This article does not contain any studies involving animals or human participants performed by any of the authors.

SUPPLEMENTARY INFORMATION

The online version contains supplementary material available at https://doi.org/10.1134/S1068162023020097.

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