Bioorganic & Medicinal Chemistry 19 (2011) 1400–1408

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthesis and biological assay of 4-aryl-6-chloro-quinoline derivatives as novel non-nucleoside anti-HBV agents

Rui-Hua Guo [a,b], Quan Zhang [a], Yun-Bao Ma [a], Xiao-Yan Huang [a], Jie Luo [a], Li-Jun Wang [a,b], Chang-An Geng [a,b], Xue-Mei Zhang [a], Jun Zhou [a], Zhi-Yong Jiang [a], Ji-Jun Chen [a,*]

[a] State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, Kunming 650204, PR China
[b] Graduate School of Chinese Academy of Sciences, Beijing 100039, PR China

ARTICLE INFO

Article history:
Received 2 December 2010
Revised 4 January 2011
Accepted 5 January 2011
Available online 11 January 2011

Keywords:
Hepatitis B virus
4-Aryl-6-chloro-quinoline
Derivatives
Synthesis

ABSTRACT

A series of 4-aryl-6-chloro-quinoline derivatives were synthesized and evaluated for their anti-hepatitis B virus (HBV) activities, namely the abilities to inhibit the secretion of HBV surface antigen (HBsAg), HBV e antigen (HBeAg), and replication of HBV DNA in HepG 2.2.15 cells. Most of the compounds exhibited moderate inhibitory activity against the secretion of HBsAg and HBeAg. Nine compounds (**3**, **5**, **6**, **7**, **10**, **14**, **17**, **20**, **24**) showed significant inhibition against HBV DNA replication with IC_{50} values in the range of 4.4–9.8 μM, which were comparative to that of positive control tenofovir. Of them, compounds **10**, **17**, and **20** had low cytotoxicities, resulting in high SI values, >551.2, >143.7, and >284.5, respectively.

1. Introduction

Persistent infection with hepatitis B virus (HBV) remains a serious global health problem, leading to 1.2 million deaths per year according to the world health organization.[1] HBV infection can result in acute, fulminant, or chronic disease, liver cirrhosis, and the development of hepatocelluar carcinomas.[2] Current treatments for chronic HBV infection include the usage of α-interferon (interferon alpha-2a and PEGylated interferon alpha-2a) and nucleoside drug (i.e., lamivudine, adefovir, entecavir, telbivudine, and tenofovir). The mechanism of action of nucleoside analogues is suggested to be through the interaction of their triphosphate derivatives, formed after cellular metabolic transformation, with HBV DNA polymerase or reverse transcriptase as substrates and/or inhibitors.[3] However, the use of α-interferon can lead to low response rate in the patient, while treatment with nucleoside analogues results in development of drug-resistant virus after long-term treatment.[4,5] Nowadays, the development of new anti-HBV agents is focused on discovering diverse compounds with either novel structures or a new mechanism of action. Non-nucleosides with various skeleton types exhibit inhibitory activity on the secretion of HBeAg, HBsAg, and HBV DNA replication in vitro. The anti-HBV mechanism of non-nucleosides is not confined to the HBV DNA polymerase, which made them more potent to be developed as anti-HBV agents.[6,7] So far, non-nucleosides have also been reported to inhibit HBV infection.[7–18] Nevertheless, the search for compounds with novel anti-HBV target and mechanism is still a fascinating topic.

Previously, we first reported that 4-aryl-6-chloroquinoline-2-one analogues (Fig. 1) exhibited in vitro anti-HBV activity and revealed their preliminary structure–activity relationship (SAR).[19] Compound **1** showed moderate activity against the secretion of HBV surface antigen (HBsAg) and HBV e antigen (HBeAg). In view of its novel structural template, with compound **1** as starting material, a series of 4-aryl-6-chloroquinoline analogues were designed and synthesized (Fig. 1) via chemical modification at position 2 and C-3 hydroxyethyl moiety, and evaluated for their anti-HBV activities in vitro in order to further study the structure–activity relationships (SARs).

2. Chemistry

Treatment of compound **1** with phenylphosphonic dichloride gave compound **2**.[20] Reaction of compound **1** with methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 afforded derivative **3**. Acylation of compound **1** yielded compound **4**, which was treated with phenylphosphonic dichloride to produce 2-Cl derivative **5**. Reaction of compound **5** with MeOH afforded

Abbreviations: HBV, hepatitis B virus; HBsAg, hepatitis surface antigen; HBeAg, hepatitis e antigen; SARs, structure–activity relationships; SI, selectivity index; CC_{50}, 50% cytotoxic concentration; IC_{50}, 50% inhibitory concentration.

* Corresponding author. Tel./fax: +86 871 5223265.
E-mail address: chenjj@mail.kib.ac.cn (J.-J. Chen).

0968-0896/$ - see front matter Crown Copyright © 2011 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.01.006

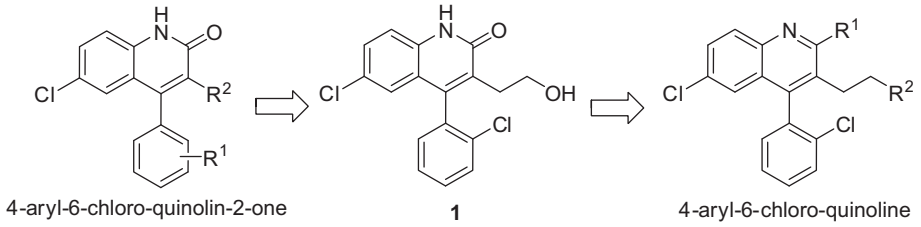


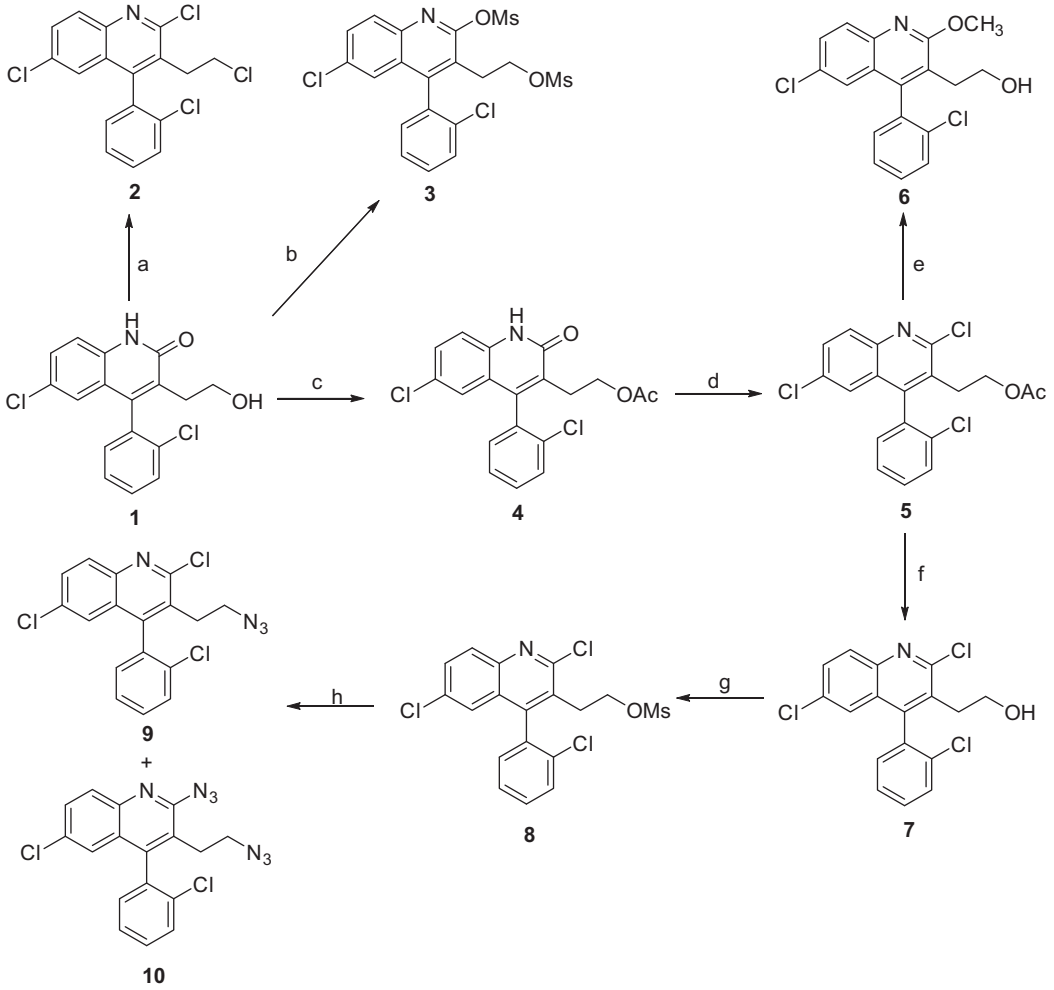
Figure 1. Structures of 4-aryl-6-chloro-quinoline-2-one, compound **1**, and 4-aryl-6-chloro-quinoline.

2-OMe derivative **6**. Deacylation of compound **5** without influence of 2-Cl was succeeded by refluxing with NH_4OAc in $MeOH/H_2O$ (4:1) to give compound **7**, which was converted to methanesulfonylate **8**. Subsequently, compound **8** underwent substitution reaction with NaN_3 to produce derivatives **9** and **10** as show in Scheme 1.

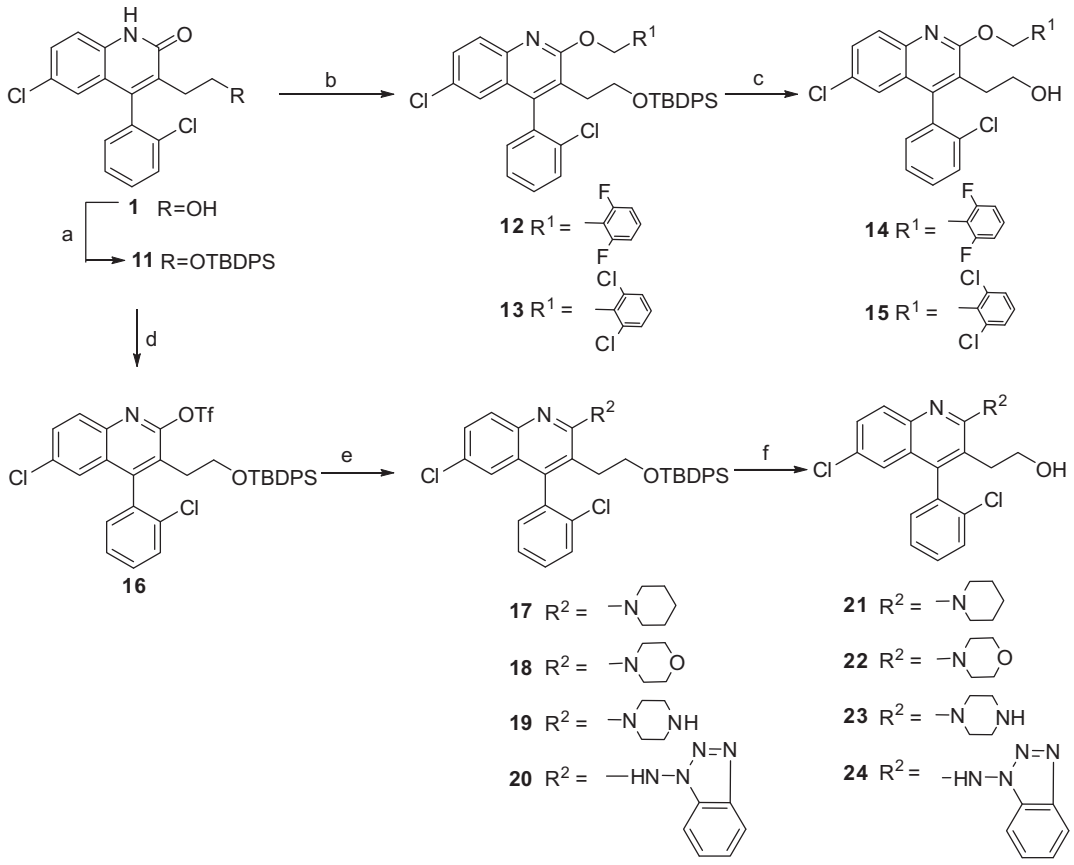
As shown in Scheme 2, compound **1** was protected as *tert*-butyldiphenylsilyl (TBDPS) ether (**11**), followed by treatment with 2,6-difluorobenzyl bromide/2,6-dichorobenzyl bromide in the presence of K_2CO_3 in acetone to afford derivatives **12/13**.[21] Deprotection of TBDPS with TBAF (tetra-butylammoniumfluoride) gave compounds **14/15**.[22] TBDPS ether (**11**) was converted to compounds **17–20** through triflate formation, nucleophilic substitution reaction with various amines. Compounds **21–24** were obtained by deprotection of TBDPS group with TBAF in THF.

3. Results and discussion

The potential anti-HBV activity and cytotoxicity of the synthesized 4-aryl-6-chloro-quinoline analogues (**1–3**, **5–10**, and **12–24**) were tested in HepG 2.2.15 cells, and tenofovir was used as a reference antiviral drug. The results were summarized in Table 1. The anti-HBV activity of each compound was expressed as the concentration of compound that achieved 50% inhibition (IC_{50}) of HBsAg, HBeAg, and HBV DNA replication. The cytotoxicity of each compound was expressed as the concentration of compound required to kill 50% (CC_{50}) of the HepG 2.2.15 cells. The selectivity index (SI), an important pharmaceutical parameter that estimates possible future clinical development, was determined as the ratio of CC_{50} value to IC_{50} value. The bioactivity of each compound was evaluated by the combination of its IC_{50} values and SI.



Scheme 1. Reagents and conditions: (a) phenylphosphonic dichloride, 100 °C, 91%; (b) MsCl, TEA, DCM, rt, 8%; (c) Ac_2O, pyridine, rt, 88%; (d) phenylphosphonic dichloride, 100 °C, 81%; (e) K_2CO_3, $MeOH/H_2O$ (4:1), refluxed, 69%; (f) NH_4OAc, $MeOH/H_2O$ (4:1), refluxed, 84%; (g) MsCl, TEA, DCM, rt, 77%; (h) NaN_3, DMF, 80 °C, 52% (**9**), 47% (**10**).

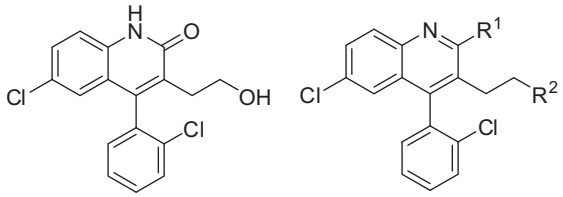


Scheme 2. Reagents and conditions: (a) TBDPSCl, DMF, DIEPA, rt, 86%; (b) for **12**: 2,6-difluorobenzyl bromide K_2CO_3, acetone, rt, 54%; for **13**: 2,6-dichorobenzyl bromide, K_2CO_3, acetone, rt, 49%; (c) TBAF, THF, rt, 90–91%; (d) Tf_2O, DIEPA, pyridine, 86%; (e) DIEA, CH_3CN, refluxed, 56–89%; (f) TBAF, THF, rt, 50–81%.

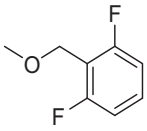
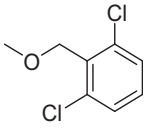
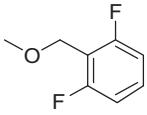
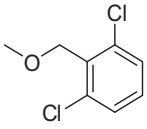
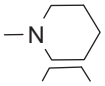
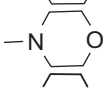
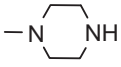
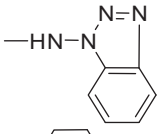
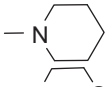
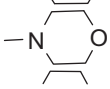
Compound **1** showed moderate inhibitory potency to the secretion of HBsAg (IC_{50} = 70.2 μM), HBeAg (IC_{50} = 340.5 μM), and replication of HBV DNA (IC_{50} = 72.1 μM), which led to relatively low SI values (SI_{HBsAg} = 5.5, SI_{HBeAg} = 1.1, $SI_{HBV\ DNA}$ = 5.4). When quinolin-2-one compound **1** was converted to 2-Cl quinoline derivative **7**, the inhibitory activity against secretion of HBeAg and HBV DNA replication were increased by 30- and 7.4-fold, respectively, but inhibition to the secretion of HBsAg was increased slightly (IC_{50} = 45.3 μM vs IC_{50} = 70.2 μM). However, compound **7** was toxic (CC_{50} = 42.5 μM), which led to low SI values. For compounds **2**, **5**, **8**, **9** with different patterns of modification on C-3 hydroxyethyl moiety, compounds **2**, **5**, **9** exhibited high activities against HBV DNA replication and had low cytotoxicities with IC_{50} values of 19.0 μM (SI >73.8), 6.1 μM (SI = 19.1), 16.6 μM (SI >151.4), respectively, and were almost inactive against the secretion of HBsAg and HBeAg. The methanesulfonylate **8** almost lost anti-HBV activity. Compounds **3**, **6**, **10** had different substitutions on C-2 as shown in Table 1, these compounds generally exhibited good potency against HBV DNA replication (IC_{50} = 6.8 μM, 6.1 μM, 4.5 μM, respectively). The results indicated that at position C-2 could accommodate some substitutions for their suppressant potency against HBV comparing to 2-Cl derivative **7**. Furthermore, compound **3** showed the highest activity against the secretion of HBsAg (IC_{50} = 16.5 μM). It is worth noting that the most active compound **10** was more potent and had low cytotoxicity (CC_{50} >2480.4 μM), resulting in high SI value of >551.2. These results indicated that C-2 might be a good target for further lead optimization.

To further explore the influence of C-2 of quinoline on anti-HBV activity, compounds **12–24** were synthesized and evaluated for their anti-HBV activities and cytotoxicities, the results were shown in Table 1. For 2-O-substituted derivatives **12–16**, compounds **14** and **15** showed good efficacy against HBV DNA replication (IC_{50} = 4.8, 17.7 μM, respectively) and moderate inhibition against the secretion of HBsAg (IC_{50} = 43.5, 18.2 μM, respectively), but appeared toxic (CC_{50} = 108.9, 38.5 μM, respectively), resulting in low SI values ($SI_{HBV\ DNA}$ = 22.7, 2.2, respectively; SI_{HBsAg} = 2.5, 2.1, respectively). Decreased cytotoxicities were observed with the protection of hydroxyl groups of compounds **14** and **15** by TBDPS (compounds **12** and **13**), but the conversion resulted in the loss of anti-HBV activity. 2-N-substituted subseries of compounds **17–24** were also synthesized to detect their anti-HBV activities. For derivatives **21–24** with free hydroxyl groups at C-3 hydroxyethyl moiety, compound **24** showed potent activity against HBV DNA replication with a IC_{50} value of 8.3 μM and moderate inhibitory activities against the secretion of HBsAg (IC_{50} = 37.7 μM) and HBeAg (IC_{50} = 111.4 μM). However, its high cytotoxicity (CC_{50} = 82.4 μM) led to low SI values (SI_{HBsAg} = 2.2, SI_{HBeAg} <1.0, $SI_{HBV\ DNA}$ = 10.0). Conversion of compound **24** to the corresponding TBDPS substituted derivative **20** induced 2-fold improvement on inhibiting HBV DNA replication (IC_{50} = 4.4 μM vs IC_{50} = 8.3 μM) and reduced cytotoxicity resulting in high SI value (SI >284.5), whereas compound **20** lost suppressant property against the secretion of HBsAg and HBeAg. Compound **21** showed weak potency against HBV DNA replication (IC_{50} = 151.2 μM). When introduction of TBDPS to hydroxyethyl moiety (compound **17**), its anti-HBV activity was enhanced by 22.6-fold (IC_{50} = 6.7 μM vs IC_{50} = 151.2 μM). Moreover, decreased activities against the secretion of HBsAg and HBeAg were also observed.

Table 1
Anti-HBV activity, cytotoxicity, and selectivity index of analogues (**1–3**, **5–10**, **12–24**)

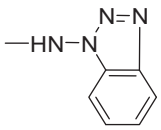


1 **2, 3, 5-10, 12-24**

Compd	R^1	R^2	CC_{50}[a] (μM)	HBsAg[b]		HBeAg[c]		HBV DNA	
				IC_{50}[d] (μM)	SI[e]	IC_{50} (μM)	SI	IC_{50} (μM)	SI
1	–	–	387.5	70.2	5.5	340.5	1.1	72.1	5.4
2	Cl	Cl	>1401.6	>1401.6	–	>1401.6	–	19.0	>73.8
3	OMs	OMs	804.1	16.5	48.6	367.3	2.2	6.8	118.2
5	Cl	OAc	116.4	146.8	<1	70.9	<1	6.1	19.1
6	OCH_3	OH	141.2	66.3	2.1	>2708.9	<1	6.9	20.5
7	Cl	OH	42.5	45.3	<1	11.3	3.8	9.8	4.3
8	Cl	OMs	881.7	1020.9	<1	646.6	>1.4	>881.7	–
9	Cl	N_3	>2513.2	>2513.2	–	>2513.2	–	16.6	>151.4
10	N_3	N_3	>2480.4	>2480.4	–	>2480.4	–	4.5	>551.2
12		OTBDPS	>1865.1	>1865.1	–	>1865.1	–	>1865.1	–
13		OTBDPS	>1026.0	>1026.0	–	>1026.0	–	>1026.0	–
14		OH	108.9	43.5	2.5	1634.0	<1	4.8	22.7
15		OH	38.5	18.2	2.1	12.2	3.2	17.7	2.2
16	OTf	OTBDPS	>1562.5	454.5	3.4	767.0	2.0	>1562.5	–
17		OTBDPS	>968.8	>968.8	–	>968.8	–	6.7	>143.7
18		OTBDPS	>1203.1	>1203.1	–	>1203.1	–	>1203.1	–
19		OTBDPS	<18.8	18.8	<1	>1173.7	<1	42.8	<4.43
20		OTBDPS	>1251.9	>1251.9	–	>1251.9	–	4.4	>284.5
21		OH	155.0	37.5	4.1	50.0	3.1	151.2	1.0
22		OH	>1592.0	323.4	>4.9	>1592.0	–	>1592.0	–
23		OH	<5.0	>5.0	<1	>5.0	<1	>5.0	–

(*continued on next page*)

Table 1 (*continued*)

Compd	R^1	R^2	CC_{50}[a] (μM)	HBsAg[b]		HBeAg[c]		HBV DNA	
				IC_{50}[d] (μM)	SI[e]	IC_{50} (μM)	SI	IC_{50} (μM)	SI
24		OH	82.4	37.7	2.2	111.4	<1	8.3	10.0
Tenofovir[f]	–	–	>1740	1450.1	>1.2	1160.2	>1.5	0.54	>3222

[a] CC_{50}: 50% cytotoxic concentration.
[b] HBsAg: HBV surface antigen.
[c] HBeAg: HBV e antigen.
[d] IC_{50}: 50% inhibitory concentration.
[e] SI (selectivity index) = CC_{50}/IC_{50}.
[f] Tenofovir: an antiviral agent used as positive control.

4. Conclusions

A series of 4-aryl-6-chloro-quinoline derivatives mainly modified on C-2 and C-3 hydroxyethyl moiety were synthesized and assayed for their anti-HBV activities and cytotoxicities in vitro. Most compounds exhibited moderate inhibitory activity against the secretion of HBsAg and HBeAg. Nine compounds (**3**, **5**, **6**, **7**, **10**, **14**, **17**, **20**, **24**) showed significant inhibition against HBV DNA replication with IC_{50} values in the range of 4.4–9.8 μM, which were comparative to that of positive control tenofovir. Of them, compounds **10**, **17**, and **20** had low cytotoxicities, resulting in high SI values, >551.2, >143.7, and >284.5, respectively. Based on the above results, the following conclusion could be made: (a) for C-2 substituted quinoline derivatives, the anti-HBV activity largely depends on the size and character of the substituents, and this position can accommodate some substituents without decreasing the anti-HBV activity. (b) TBDPS substitution is an important feature in the conferring relatively low cytotoxicity. (c) The role of TBDPS at hydroxyethyl moiety for anti-HBV activity is ambiguous.

For 2-O-substituted analogues, etherification of hydroxyl group at C-3 of 4-aryl-6-chloro-quinoline decreased anti-HBV activity. For 2-N-substituted analogues, TBDPS substitution increased activity against HBV DNA replication, but caused the loss of suppressant property on the secretion of HBsAg and HBeAg. The preliminary SAR study provides valuable information for our on-going anti-HBV studies on 4-aryl-6-chloro-quinoline compounds.

5. Experimental

5.1. Chemistry

MS spectra were run on a VG Auto Spec-3000 spectrometer (VG, Manchester, England); NMR spectra were recorded on Bruker AM 400 ($^1H/^{13}C$, 400 MHz/100 MHz) or DRX-500 ($^1H/^{13}C$, 500 MHz/125 MHz) spectrometer (Bruker, Bremerhaven, Germany) and chemical shifts were given in δ with TMS as internal reference; silica gel column chromatography (CC): silica gel (200–300 mesh); Qingdao Makall Group Co., Ltd; Qingdao; China). All reactions were monitored using thin-layer chromatography (TLC) on silica gel plates.

5.1.1. 6-Chloro-4-(2-chlorophenyl)-3-(2-hydroxyethyl) quinolin-2(1*H*)-one (1)

A 100 mL, 2-neck flask was charged with 2-amino-2',5-dichlorobenzo-phenone (1.0 g, 3.76 mmol) and THF (20 mL). The resulting solution was cooled to 0 °C and LiHMDS (28.2 mL, 1 M in THF) was added over 15 min. The internal temperature was controlled 0 °C for 10 min, then γ-valerolactone (1.7 g, 16.90 mmol) was added over 10 min. The reaction solution was allowed to warm up to room temperature and stirred at room temperature for 2 h. Then water (10.2 mL) was added over 10 min, and the reaction mixture was stirred at room temperature for 24 h. The aqueous layer was extracted with ethyl acetate (100 mL) and the organic layer was washed with water (80 mL) and brine (3 × 50 mL) and dried with anhydrous Na_2SO_4. Removal of the solvents gave a residue which was purified by silica gel column chromatography (Si CC) with $CHCl_3/CH_3OH$ (98:2) to obtain compound **1** (1.08 g, yield 86%) as white amorphous powder; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.16 (1H, br s), 7.68 (1H, dd, J = 1.6, 5.2 Hz), 7.59–7.49 (3H, m), 7.41–7.36 (2H, m), 6.56 (1H, s), 4.61 (1H, br s), 3.43 (2H, t, J = 7.2 Hz), 2.56–2.48 (1H, m), 2.31–2.29 (1H, m); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 161.6, 144.5, 136.4, 134.1, 131.9, 131.2, 130.7, 130.5, 129.8, 129.7, 127.9, 125.9, 124.3, 120.4, 117.4, 58.8, 32.3; ESIMS: m/z 334 $[M+H]^+$, HRESIMS: calcd for $C_{17}H_{14}NO_2Cl_2$ $[M+H]^+$ 334.0401, found 334.0409.

5.1.2. 2,6-Dichloro-3-(2-chloroethyl)-4-(2-chlorophenyl) quinoline (2)

To solid compound **1** (50 mg, 0.15 mmol) in a flask was added phenylphosphonic dichloride (2 mL). The mixture was slowly warmed to 100 °C with stirring and kept for 2 h. The resulting mixture was carefully basified with ammonium hydroxide, extracted with EtOAc, washed with brine, dried with anhydrous Na_2SO_4. Removal of the solvents gave a residue which was purified by Si CC with petroleum ether/acetone (100:1) to afford compound **2** (50 mg, yield 91%) as white amorphous powder; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (1H, d, J = 9.0 Hz), 7.66–7.62 (2H, m), 7.56–7.48 (2H, m), 7.25 (1H, dd, J = 7.5, 2.0 Hz), 7.12 (1H, d, J = 2.0 Hz), 3.67–3.63 (2H, m), 3.26–3.20 (1H, m), 3.07–3.01 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.8, 147.4, 145.0, 133.9, 133.5, 133.0, 131.3, 130.9, 130.8, 130.3, 130.2, 129.0, 127.4, 127.3, 124.6, 41.2, 34.5; ESIMS: m/z 370 $[M+H]^+$, HRESIMS: calcd for $C_{17}H_{12}NCl_4$ $[M+H]^+$ 369.9723, found 369.9733.

5.1.3. 2-[6-Chloro-4-(2-chlorophenyl)-2-(methylsulfonyloxy) quinolin-3-yl]ethylmethanesulfonate (3)

Methanesulfonyl chloride (372 mg, 3.26 mmol) was added dropwise to a solution of compound **1** (300 mg, 0.90 mmol) and Et_3N (109 mg, 1.08 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was warmed to room temperature and stirred 4 h. The reaction was then quenched with 5% HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give the residue which was purified by Si CC with petroleum ether/acetone (20:1) give compound **3** (36 mg, yield 8%) as yellow amorphous power; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, d, J = 8.9 Hz), 7.65 (2H, m), 7.52 (2H, m), 7.28 (1H, m), 6.86 (1H, d, J = 1.7 Hz), 4.34 (2H, m), 3.78 (3H, s), 3.13 (1H, m), 2.97 (1H, m), 2.92 (3H, m); ^{13}C NMR

($CDCl_3$, 100 MHz) δ 155.2, 149.7, 143.1, 133.3, 133.2, 133.0, 131.4, 131.2, 130.9, 130.3, 129.9, 127.5, 127.4, 124.8, 121.1, 67.2, 41.9, 37.2, 28.0; FABMS: *m/z* 490 $[M+H]^+$, HRESIMS: calcd for $C_{19}H_{18}NO_6S_2Cl_2$ $[M+H]^+$ 489.9953, found 489.9951.

5.1.4. 2-[6-Chloro-4-(2-chlorophenyl)-2-oxo-1,2-dihydroquinolin-3-yl]ethylacetate (4)

To a solution of compound **1** (100 mg, 0.30 mmol), Ac_2O (37 mg, 0.36 mmol) in anhydrous pyridine (5 mL), was stirred until the starting material was not observed by TLC. The reaction mixture was diluted with 50 mL of EtOAc and washed three times with 50 mL of 5% HCl and saturated $NaHCO_3$ (3 × 30 mL). The organic layer was dried with anhydrous Na_2SO_4 and concentrated in vacuo to give the residue which was purified by Si CC with $CHCl_3$/MeOH, (98:2) to afford the product **4** (99 mg, yield 88%) as white amorphous power; ^1H NMR ($CDCl_3$, 500 MHz) δ 13.13 (1H, br s), 7.59 (1H, dd, *J* = 9.5, 2.0 Hz), 7.46 (4H, m), 7.25 (1H, m), 6.86 (1H, d, *J* = 1.8 Hz), 4.30 (2H, t, *J* = 6.8 Hz), 2.95 (1H, m), 2.67 (1H, m), 1.97 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 164.0, 147.1, 136.0, 134.2, 133.0, 130.7, 130.4, 130.3, 130.1, 129.1, 128.1, 127.2, 125.5, 121.1, 117.6, 62.3, 28.1, 21.1; FABMS: *m/z* 376 $[M+H]^+$, HRESIMS: calcd for $C_{19}H_{16}NO_3Cl_2$ $[M+H]^+$ 376.0507, found 376.0497.

5.1.5. 2-(2,6-Dichloro-4-(2-chlorophenyl)quinolin-3-yl)ethyl acetate (5)

To solid compound **4** (20 mg, 0.05 mmol) was added phenylphosphonic dichloride (2 mL). The mixture was slowly warmed to 100 °C with stirring and kept for 2 h. The resulting mixture was carefully basified with ammonium hydroxide, extracted with EtOAc, washed with brine, dried with anhydrous Na_2SO_4, concentrated in vacuo to give the residue which was purified by Si CC with petroleum ether/acetone (97:3) to afford compound **5** (17 mg, yield 81%) as white amorphous power; ^1H NMR ($CDCl_3$, 500 MHz) δ 8.00 (1H, d, *J* = 9.0 Hz), 7.62 (2H, m), 7.54–7.46 (2H, m), 7.25 (1H, d, *J* = 7.5 Hz), 7.12 (1H, d, *J* = 2.1 Hz), 4,24–4.16 (2H, m), 3.16–3.12 (1H, m), 2.93–2.88 (1H, m), 2.16 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.6, 152.1, 147.3, 144.9, 134.0, 133.4, 133.1, 131.1, 131.0, 130.7, 130.2, 130.2, 128.9, 127.3, 127.2, 124.6, 62.2, 30.5, 20.9; ESIMS: *m/z* 416 $[M+Na]^+$, HRESIMS: calcd for $C_{19}H_{15}NO_2Cl_3$ $[M+H]^+$ 394.0168, found 394.0161.

5.1.6. 2-[6-Chloro-4-(2-chlorophenyl)-2-methoxyquinolin-3-yl] ethanol (6)

To a solution of compound **5** (300 mg, 0.76 mmol) in MeOH/H2O (15 ml, 4:1) was added K_2CO_3 (314 mg, 2.28 mmol). The mixture was refluxed and monitored by TLC (petroleum ether/acetone, 4:1), then quenched by 5% HCl, and extracted three times with 50 mL of EtOAc. The EtOAc layer was washed with brine, dried with anhydrous Na_2SO_4. Removal of the solvents gave a residue which was purified by Si CC with petroleum ether/acetone (5:1) to give compound **6** (241 mg, yield 69%) as white amorphous power; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (1H, d, *J* = 8.8 Hz), 7.56–7.37 (4H, m), 7.20 (1H, dd, *J* = 7.2, 2.0 Hz), 7.02 (1H, d, *J* = 2.3 Hz), 4.12 (3H, s), 3.70 (2H, m), 2.88–2.81 (1H, m), 2.71–2.62 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 145.8, 143.7, 134.8, 133.3, 131.1, 130.0, 129.9, 129.5, 128.7, 127.1, 125.4, 124.4, 122.0, 61.4, 53.8, 31.6, 21.6; ESIMS: *m/z* 370 $[M+Na]^+$, HRESIMS: calcd for $C_{18}H_{16}NO_2Cl_2$ $[M+H]^+$ 348.0558, found 348.0554.

5.1.7. 2-[2,6-Dichloro-4-(2-chlorophenyl)quinolin-3-yl] ethanol (7)

To a solution of compound **5** (55 mg, 0.14 mmol) in MeOH/H_2O (5.0 ml, 4:1) was added NH_4OAc (86 mg, 1.11 mmol). The mixture was refluxed and monitored by TLC (petroleum ether/acetone, 4:1), then quenched by 5% HCl, and extracted with EtOAc. The combined EtOAc layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to obtain the residue which was purified by Si CC with petroleum ether/acetone (5:1) to produce compound **7** (41 mg, yield 84%) as white amorphous power; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, d, *J* = 9.0 Hz), 7.61– 7.57 (2H, m), 7.50–7.42 (2H, m), 7.24 (1H, dd, *J* = 7.2, 1.9 Hz), 7.09 (1H, d, *J* = 2.2 Hz), 3.85–3.73 (2H, m), 3.08–3.01 (1H, m), 2.90–2.83 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.3, 147.2, 144.6, 134.3, 133.3, 133.1, 131.0, 131.0, 130.5, 130.2, 130.0, 129.5, 127.4, 127.3, 124.5, 60.9, 34.6; EIMS: *m/z* (%) 351 ($[M]^+$, 24), 286 (65%), 250 (100%), 214 (60%), HREIMS: calcd for $C_{17}H_{12}NOCl_3$ $[M]^+$ 350.9984, found 350.9981.

5.1.8. 2-[2,6-Dichloro-4-(2-chlorophenyl)quinolin-3-yl]ethyl methanesulfonate (8)

A solution of compound **7** (50 mg, 0.14 mmol) and trimethylamine (17 mg, 0.17 mmol) in 3 mL of dichloromethane was cooled to 0 °C. A solution of methanesulfonyl chloride (32 mg, 0.28 mmol) in 1 mL of dichloromethane was added dropwise. The ice was removed and the mixture was stirred at room temperature for 3 h. The mixture was extracted three times with 50 mL of EtOAc. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, and concentrated in vacuo to give the residue which was purified by Si CC with petroleum ether/acetone (6:1) to yield derivative **8** (46 mg, 77%) as white amorphous power; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (1H, d, *J* = 9.0 Hz), 7.64 (2H, m), 7.50 (2H, m), 7.27 (1H, dd, *J* = 7.2, 1.6 Hz), 7.12 (1H, d, *J* = 2.0 Hz), 4.38–4.34 (2H, m), 3.26–3.19 (1H, m), 3.08–3.01 (1H, m), 2.88 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.5, 147.9, 145.0, 133.65, 133.56, 132.8, 131.4, 131.0, 130.8, 130.23, 130.16, 127.5, 127.2, 127.1, 124.6, 66.8, 37.2, 31.1; EIMS: *m/z* (%) 429 ($[M]^+$, 7), 298 (52), 262 (100), 214 (41), HREIMS: calcd for $C_{18}H_{14}NO_3SCl_3$ $[M]^+$ 428.9760, found 428.9754.

5.1.9. 3-(2-Azidoethyl)-2,6-dichloro-4-(2-chlorophenyl)quinoline (9) and 2-azido-3-(2-azidoethyl)-6-chloro-4-(2-chlorophenyl)quinoline (10)

A solution of compound **8** (64 mg, 0.15 mmol) in *N*,*N*-dimethylformamide (3 mL) and sodium azide (20 mg, 0.31 mmol) was heated at 80 °C for 4 h. The mixture was cooled and extracted with EtOAc (100 mL). The organic layer was washed with brine, dried with anhydrous Na_2SO_4, concentrated in vacuo to obtain the residue which was purified by Si CC with petroleum ether/acetone (100:1) to afford derivatives **9** (29 mg, yield 52%) as white amorphous power and **10** (27 mg, yield 47%) as white amorphous power; Compound **9**: ^1H NMR ($CDCl_3$, 400 MHz) δ 8.00 (1H, d, *J* = 8.9 Hz), 7.65–7.61 (2H, m), 7.55–7.47 (2H, m), 7.24 (1H, d, *J* = 1.6 Hz), 7.12 (1H, d, *J* = 2.0 Hz), 3.46–3.42 (2H, m), 3.05–3.00 (1H, m), 2.91–2.85 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8, 147.3, 144.9, 134.0, 133.5, 133.1, 131.2, 130.81, 130.78, 130.3, 130.2, 129.0, 127.5, 127.3, 124.6, 49.4, 30.8; ESIMS: *m/z* 399 $[M+Na]^+$, HRESIMS: calcd for $C_{17}H_{12}N_4Cl_3$ $[M+H]^+$ 377.0127, found 377.0132.; Compound **10**: ^1H NMR ($CDCl_3$, 500 MHz) δ 8.70 (1H, d, *J* = 8.8 Hz), 7.80 (1H, dd, *J* = 8.8, 2.1 Hz), 7.66 (1H, m), 7.60–7.53 (2H, m), 7.36 (1H, dd, *J* = 7.4, 1.7 Hz), 7.24 (1H, d, *J* = 2.2 Hz), 3.09–3.85 (1H, m), 3.74–3.69 (1H, m), 3.27–3.21 (1H, m), 3.07–3.01 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8, 147.4, 140.2, 134.2, 133.7, 132.8, 131.4, 131.1, 130.4, 128.2, 127.7, 126.9, 125.5, 123.5, 118.4, 49.4, 29.4; ESIMS: *m/z* 406 $[M+Na]^+$, HRESIMS: calcd for $C_{17}H_{12}N_7Cl_2$ $[M+H]^+$ 384.0531, found 384.0520.

5.1.10. 3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophenyl)quinolin-2(1*H*)-one (11)

Compound **1** (909 mg, 2.72 mmol) was dissolved in 15 mL of DMF, stirred and cooled to 0 °C in an ice bath. *N*-Ethyldiisopropylamine (DIEA, 35 mg, 0.27 mmol) and *tert*-butyldiphenylchlorosilane (TBDPSCl, 1.5 g, 5.45 mmol) were added to the solution and

the resulting mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with 5% HCl and brine, dried with anhydrous $MgSO_4$, filtered. Removal of the solvents gave a residue which was purified by Si CC with $CHCl_3$/MeOH (70:1) to produce compound **11** (1.32 g, yield 86%) as white amorphous power; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 13.1 (1H, s), 7.57 (5H, m), 7.50–7.18 (11H, m), 6.85 (1H, s), 4.10–4.04 (1H, m), 3.98–3.92 (1H, m), 3.07–3.00 (1H, m), 2.79–2.72 (1H, m), 1.04 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1, 146.6, 135.9, 135.42 (C × 2), 135.40 (C × 2), 134.4, 133.9 (C × 2), 133.8, 132.9, 131.1, 130.0, 129.99 (C × 2), 129.96 (C × 2), 129.4, 127.8, 127.7, 127.51 (C × 2), 127.49 (C × 2), 127.1, 125.3, 117.5, 62.1, 32.0, 27.0 (C × 3), 19.3; ESIMS: *m/z* 572 $[M+H]^+$, HRESIMS: calcd for $C_{33}H_{32}NO_2SiCl_2$ $[M+H]^+$ 572.1579, found 572.1585.

5.2. General procedure for the synthesis of compounds 12 and 13

To a solution of compound **11** (200 mg, 0.35 mmol) in acetone (5 mL) were added K_2CO_3 (241 mg, 1.75 mmol), and 2,6-difluorobenzyl bromide or 2,6-dichlorobenzyl bromide (250 mg, 1.05 mmol) at room temperature, The resulting mixture was stirred at room temperature until the starting material disappeared on the TLC. The reaction mixture was filtered, concentrated in vacuo to give the residue which was performed on Si CC to afford the products (**12** and **13**).

5.2.1. 12-(2,6-Difluorobenzyloxy)-3-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophe-nl) quinoline (12)

Colorless oil, yield 54% (after chromatography with petroleum ether/acetone, 20:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (1H, d, *J* = 8.9 Hz), 7.43–7.24 (15H, m), 7.23 (1H, d, *J* = 8.9 Hz), 6.97 (1H, d, *J* = 2.4 Hz), 6.89 (2H, m), 5.58 (2H, s), 3.79–3.74 (2H, m), 2.93–2.86 (1H, m), 2.71–2.64 (1H, m), 0.92 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.3, 160.9, 160.3, 145.9, 143.5, 135.3, 134.8, 133.92, 133.86, 133.3, 131.5, 130.3, 130.2, 129.8, 129.4, 129.3, 128.8, 127.4, 126.9, 125.6, 124.4, 122.2, 111.42, 111.35, 111.2; ESIMS: *m/z* 720 $[M+Na]^+$, HRESIMS: calcd for $C_{40}H_{36}NO_2F_2SiCl_2$ $[M+H]^+$ 698.1860, found 698.1842.

5.2.2. 2-(2,6-Dichlorobenzyloxy)-3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-6-chloro-4-(2-chloroph-enyl)quinoline (13)

Colorless oil, yield 49% (after chromatography with petroleum ether/acetone, 20:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (2H, d, *J* = 8.5 Hz), 7.53 (2H, m), 7.42 (5H, m), 7.35 (4H, m), 7.29–7.21 (6H, m), 7.14 (1H, dd, *J* = 7.6, 1.6 Hz), 7.01 (1H, d, *J* = 7.4 Hz), 5.77 (2H, m), 3.81 (2H, m), 2.92–2.87 (1H, m), 2.73–2.63 (1H, m), 0.91 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.5, 146.1, 143.4, 137.1, 135.3, 134.7 (C × 4), 132.5, 131.6, 130.2, 129.8, 129.7, 129.5, 129.4, 129.3, 128.7, 128.3, 127.5, 127.4, 126.9, 125.7, 124.5, 122.3, 63.5, 62.5, 31.6, 26.8, 19.2; ESIMS: *m/z* 730 $[M+H]^+$, HRESIMS: calcd for $C_{40}H_{36}NO_2Cl_4Si$ $[M+H]^+$ 730.1269, found 730.1271.

5.3. General procedure for the synthesis of compounds 14 and 15

To a solution of compounds (**12** and **13**) (0.14 mmol) in THF (3 mL) at 0 °C was added tetrabutylammonium fluoride (0.28 mmol, 280 μL) in one portion. After stirring at room temperature for 12 h, the solvent was evaporated in vacuo to give the residue which was performed on Si CC to afford the products (**14** and **15**).

5.3.1. 2-[2-(2,6-Difluorobenzyloxy)-6-chloro-4-(2-chlorophenyl) quinolin-3-yl]ethanol (14)

White amorphous power, yield 90% (after chromatography with petroleum ether/acetone, 80:20); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (1H, d, *J* = 8.8 Hz), 7.56–7.22 (6H, m), 7.04 (1H, d, *J* = 2.2 Hz), 6.96 (2H, m), 5.68 (2H, m), 3.70 (2H, t, *J* = 6.8 Hz), 2.86–2.79 (1H, m), 2.69–2.62 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.4, 160.8, 160.2, 146.1, 143.5, 134.8, 133.4, 131.2, 130.6, 130.03, 129.98, 129.9, 129.6, 128.8, 127.1, 125.6, 124.4, 122.1, 112.8, 111.5, 111.3, 61.5, 56.3, 31.6; ESIMS: *m/z* 482 $[M+Na]^+$, HRESIMS: calcd for $C_{24}H_{18}NO_2F_2Cl_2$ $[M+H]^+$ 460.0682, found 460.0679.

5.3.2. 2-[2-(2,6-Dichlorobenzyloxy)-6-chloro-4-(2-chlorophenyl) quinolin-3-yl] ethanol (15)

White amorphous power, yield 91% (after chromatography with petroleum ether/acetone, 80:20); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (1H, d, *J* = 8.8 Hz), 7.57–7.52 (2H, m), 7.46–7.39 (4H, m), 7.24 (2H, m), 7.06 (1H, d, *J* = 2.2 Hz), 5.86 (1H, d, *J* = 11.5 Hz), 5.81 (1H, d, *J* = 11.5 Hz), 3.69 (2H, t, *J* = 7.0 Hz), 2.84–2.78 (1H, m), 2.68–2.62 (1H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.4, 146.1, 143.6, 137.1, 134.8, 133.4, 132.4, 131.2, 130.4, 130.0, 130.0, 129.9, 129.6, 128.8, 128.5, 127.1, 125.7, 124.4, 122.0, 63.5, 61.5, 31.6; ESIMS: *m/z* 514 $[M+Na]^+$, HRESIMS: calcd for $C_{24}H_{18}NO_2Cl_4$ $[M+H]^+$ 492.0091, found 492.0105.

5.3.3. 3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophenyl) quinolin-2-yltrifluoro-methanesulfonate (16)

To a solution of compound **11** (57 mg, 0.01 mmol), pyridine (0.25 mmol, 20 mg), and diisopropylethylamine (29 mg, 0.22 mmol) in dichloromethane (5 mL) trifluoromethanesulfonic anhydride (57 mg, 0.02 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and evaporated in vacuo to produce the residue which was purified by Si CC with petroleum ether/acetone (100:1) to obtain compound **18** (60 mg, yield 86%) as yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99 (1H, d, *J* = 8.8 Hz), 7.57 (9H, m), 7.31–7.24 (5H, m), 7.13 (1H, d, *J* = 2.2 Hz), 7.01 (1H, d, *J* = 7.6 Hz), 3.80–3.68 (2H, m), 3.06–2.99 (1H, m), 2.86–2.79 (1H, m), 0.97 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 149.8, 142.8, 135.6, 135.42 (C × 2), 135.40 (C × 2), 133.8, 133.5, 133.42, 133.38, 133.2, 131.3, 131.1, 130.6, 130.4, 130.2, 129.6 (C × 2), 128.1, 127.7 (C × 2), 127.6 (C × 2), 127.2, 124.6, 122.9, 62.2, 31.3, 26.8 (C × 3), 19.1; ESIMS: *m/z* 726 $[M+Na]^+$, HRESIMS: calcd for $C_{34}H_{31}NO_4F_3SCl_2Si$ $[M+H]^+$ 704.1072, found 704.1054.

5.4. General procedure for the synthesis of compounds 17–20

Compound **16** (58 mg, 0.082 mmol), amines (0.16 mmol) and diisopropylamine (22 mg, 0.16 mmol) in acetonitrile (5 mL) was refluxed for 5 h. The solvent was removed in vacuo to provide a residue which was followed by Si CC to yield the products (**17–20**).

5.4.1. 3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophenyl)-2-(piperidin-1-yl) quinoline (17)

Choroless oil, yield 56% (after chromatography with petroleun ethher/EtOAc, 100:1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 (1H, d, *J* = 11.0 Hz), 7.44–7.15 (14H, m), 6.95 (1H, dd, *J* = 9.4, 2.0 Hz), 6.88 (1H, d, *J* = 2.8 Hz), 3.66–3.56 (2H, m), 3.12–3.05 (4H, m) 2.99–2.92 (1H, m), 2.78–2.71 (1H, m), 1.68–1.54 (6H, m), 0.86 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.0, 145.6, 144.4, 135.6, 135.34 (C × 4), 135.33, 133.73, 133.69, 133.4, 131.6, 129.9, 129.7, 129.5, 129.4 (C × 2), 129.2, 127.5 (C × 4), 126.8, 126.5, 125.8, 124.1, 62.8, 52.3 (C × 2), 33.1, 26.8 (C × 3), 26.1 (C × 2), 24.6, 19.1; ESIMS: *m/z* 639 $[M+H]^+$, HRESIMS: calcd for $C_{38}H_{41}N_2OCl_2Si$ $[M+H]^+$ 639.2365, found 639.2357.

5.4.2. 4-{3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophenyl)quinolin-2-yl}mor-ph-oline (18)

Choroless oil, yield 82% (after chromatography with petroleum ether/EtOAc, 30:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.84 (1H, d, *J* = 8.6 Hz), 7.54–7.36 (9H, m), 7.30–7.26 (5H, m), 7.03 (1H, d,

J = 7.6 Hz), 6.98 (1H, d, J = 2.0 Hz), 3.89–3.79 (4H, m), 3.75–3.63 (2H, m), 3.35–3.31 (2H, m), 3.22–3.18 (2H, m), 3.07–3.00 (1H, m), 2.87–2.80 (1H, m), 0.94 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 145.0, 144.4, 135.3, 133.5, 133.3, 131.5, 130.4, 129.9, 129.8, 129.6, 129.53, 129.48, 127.5, 126.9, 125.98, 125.96, 124.1, 67.0, 62.6, 51.3, 32.9, 26.7, 19.1; EIMS: m/z (%) 640 ([M]$^+$, 5), 583 (100), 327 (50), 199 (93), HREIMS: calcd for $C_{37}H_{38}N_2O_2Cl_2Si$ [M]$^+$ 640.2080, found 640.2069.

5.4.3. 3-[2-(*tert*-Butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2-chlorophenyl)-2-(piperazin-1-yl) quinoline (19)

White amorphous power, yield 89% (after chromatography with petroleum ether/EtOAc/Et_2NH (200:1:0.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (1H, d, J = 8.9 Hz), 7.51–7.39 (9H, m), 7.38–7.28 (5H, m), 7.03 (1H, dd, J = 7.5, 1.4 Hz), 6.97 (1H, d, J = 2.2 Hz), 3.73–3.65 (2H, m), 3.35–3.25 (2H, m), 3.22–3.12 (2H, m), 3.08–3.00 (5H, m), 2.90–2.80 (1H, m), 0.94 (9H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.1, 145.8, 144.4, 135.4, 135.3, 133.6, 133.3, 131.5, 130.2, 129.9, 129.8, 129.5, 129.4, 127.5, 126.8, 126.2, 126.0, 124.1, 62.7, 52.1, 45.9, 32.9, 26.7, 19.1; EIMS: m/z 639 ([M]$^+$, 33), 571 (82), 535 (82), 327 (100), 199 (93), 135 (65), HREIMS: calcd for $C_{37}H_{39}N_3OCl_2Si$ [M+H]$^+$ 639.2239, found 639.2206.

5.4.4. *N*-(1*H*-Benzo[*d*][1,2,3]triazol-1-yl)-3-[2-(*tert*-butyldiphenylsilyloxy)ethyl]-6-chloro-4-(2chlorophenyl) quinolin-2-amine (20)

White amorphous power, yield 42% (after chromatography with petroleum ether/EtOAc/Et_2NH (50:50:0.1); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.65 (1H, d, J = 6.0 Hz), 7.61 (1H, d, J = 6.4 Hz), 7.46–7.16 (17H, m), 7.03 (1H, d, J = 7.4 Hz), 6.70 (1H, d, J = 2.0 Hz), 3.84–3.73 (2H, m), 2.88–2.83 (1H, m), 2.61–2.55 (1H, m), 0.90 (9H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.1, 146.9, 135.6, 135.4, 135.3, 134.7, 134.0, 133.3, 132.7, 130.4, 130.3, 130.1, 129.5, 129.3, 128.3, 125.4, 121.3, 117.1, 61.9, 31.8, 26.7, 26.6, 26.4; ESI: m/z 688 [M+H]$^+$, HREIMS: calcd for $C_{39}H_{36}N_5OCl_2Si$ [M+H]$^+$ 688.2066, found 688.2063.

5.5. General procedure for the synthesis of compounds 21–24

To a solution of compound **17–20** (0.078 mmol) in THF (3 mL) at 0 °C was added tetrabutylammonium fluoride (0.16 mmol, 160 μL) in one portion. After stirring at room temperature for 12 h, the solvent was evaporated in vacuo and the residue was performed on Si CC to give compounds **21–24**.

5.5.1. 2-[6-Chloro-4-(2-chlorophenyl)-2-(piperidin-1-yl)quinolin-3-yl]ethanol (21)

White amorphous power, yield 81% (after chromatography with petroleum ether/acetone, 80:20); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.90 (1H, d, J = 8.9 Hz), 7.58–7.52 (2H, m), 7.45–7.41 (2H, m), 7.19 (1H, d, J = 7.3 Hz), 7.04 (1H, d, J = 1.8 Hz), 3.76 (1H, m), 3.59 (1H, m), 3.30 (2H, m), 3.18 (2H, m), 2.80 (1H, m), 2.51 (1H, m), 1.80 (4H, m), 1.67 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.8, 145.4, 144.3, 135.2, 134.7, 133.2, 131.1, 130.0, 129.9, 129.8, 129.6, 128.9, 127.1, 126.5, 124.2, 63.2, 52.5 (C × 2), 32.4, 25.7 (C × 2), 24.0; EIMS: m/z (%) 400 ([M]$^+$, 55), 366 (100), 251 (63), 214 (70), 84 (87), HREIMS: calcd for $C_{22}H_{22}N_2OCl_2$ [M]$^+$ 400.1109, found 400.1119.

5.5.2. 2-[6-Chloro-4-(2-chlorophenyl)-2-morpholinoquinolin-3-yl]ethanol (22)

White amorphous power, yield 62% (after chromatography with with $CHCl_3/CH_3OH$, 50:1); ^{1}H NMR (CD_3OD, 400 MHz) δ 7.77 (1H, d, J = 8.9 Hz), 7.48–7.30 (4H, m), 7.11 (1H, dd, J = 8.9, 2.2 Hz), 6.90 (1H, d, J = 2.2 Hz), 3.90–3.80 (4H, m), 3.58–3.46 (2H, m), 3.28–3.22 (2H, m), 3.18–3.12 (2H, m), 2.85–2.78 (1H, m), 2.69–2.62 (1H, m); ^{13}C NMR (CD_3OD, 125 MHz) δ 161.3, 146.1, 144.0, 134.9, 133.0, 131.0, 130.9, 129.9, 129.8, 129.6, 129.3, 127.0, 126.6, 126.1, 124.0, 66.6 (C × 2), 61.5, 51.2 (C × 2), 32.4; EIMS: m/z 402 ([M]+, 85), 367 (100), 282 (83), 199 (75), 86 (100), HREIMS: calcd for $C_{21}H_{20}N_2O_2Cl_2$ [M]$^+$ 402.0902, found 402.0904.

5.5.3. 2-(6-Chloro-4-(2-chlorophenyl)-2-(piperazin-1-yl)quinolin-3-yl)ethanol (23)

White amorphous power, yield 76% (after chromatography with $CHCl_3/CH_3OH/Et_2NH$, 500:50:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.88 (1H, d, J = 8.9 Hz), 7.59–7.52 (2H, m), 7.48–7.40 (2H, m), 7.19 (1H, dd, J = 7.2, 1.8 Hz), 7.02 (1H, d, J = 2.2 Hz), 3.77–3.71 (1H, m), 3.62–5.57 (1H, m), 3.38–3.13 (8H, m), 3.00–2.92 (1H, m), 2.83–2.75 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.9, 145.8, 144.4, 135.2, 133.3, 131.3, 131.2, 130.1, 130.0, 129.9, 129.8, 128.1, 127.2, 126.5, 124.3, 63.0, 52.3 (C × 2), 45.8 (C × 2), 32.5; EIMS: m/z 401 ([M]$^+$, 15), 333 (100), 297 (85), 83 (25), HRESIMS: calcd for $C_{21}H_{21}N_3OCl_2$ [M]$^+$ 401.1062, found 401.1062.

5.5.4. 2-[2-(1*H*-Benzo[*d*][1,2,3]triazol-1-ylamino)-6-chloro-4-(2-chlorophenyl)quinolin-3-yl]ethan-nol (24)

Colorless oil, yield 50% (after chromatography with petroleum ether/acetone, 50:50); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (1H, d, J = 7.5 Hz), 7.40–7.23 (7H, m), 7.13 (1H, d, J = 6.8 Hz), 6.75 (2H, m), 3.29 (2H, m), 2.69–2.64 (1H, m), 2.52–2.48 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 146.7, 135.4, 134.1, 132.7, 130.7, 130.3, 130.2, 130.0, 128.3, 128.2, 127.72, 127.67, 127.4, 127.3, 127.2, 125.4, 121.2, 116.9, 115.9, 115.7, 61.2, 31.4; ESI: m/z 450 [M+H]$^+$, HREIMS: calcd for $C_{23}H_{18}N_5OCl_2$ [M+H]$^+$ 450.0888, found 450.0879.

5.6. Determination of HBV replication[23]

HepG 2.2.15 cells were seeded in 24 well culture plates at a density of 5 × 10^5 cells per well. Every 2 days, medium was changed. After 6 days, compounds were added to the cell cultures, and fresh medium was fed every other day for another 6 days. Cells were collected and total DNA was isolated by using TIANamp Gemomic DNA Kit (TIANGEN, Biotech Co., Ltd, China) following the manufacturer's instructions. For detection of HBV DNA, a real-time PCR assay was used.

5.7. Analysis of secreted HBV antigens[24,25]

Medium from HepG 2.2.15 cells was collected, centrifuged at 6000g to remove cellular debris, transferred to clean tubes. The levels of HBsAg and HBeAg were determined utilizing commercially available quantitative ELISA test kits (Autobio diagnostics Co., LTD, China.) and measured with a microplate reader (model 680, Bio-Rad, USA).

Acknowledgments

The work was supported by grants from National Natural Science Foundation of China for Distinguished Young Scholars (No. 81025023), Xibu Zhiguang Joint-Scholarship of Chinese Academy of Sciences, the External Cooperation Program of Chinese Academy of Sciences (No. GJHI200818), and CAS–Croucher Fund (CAS-CF07/08.SC03). The authors are grateful to the staff of the analytical group of the State Key Laboratory of Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Sciences, for measurements of all spectra.

References and notes

1. Wu, G. Y.; Chen, H. S. *World J. Gastroenterol.* **2007**, *13*, 830.
2. Park, N. H.; Song, I. H.; Chung, Y. H. *Postgrad. Med. J.* **2006**, *82*, 507.
3. Kumar, R.; Nath, M.; Tyrrell, D. L. *J. Med. Chem.* **2002**, *45*, 2032.
4. Lim, Y. S.; Suh, D. J. *J. Korean Med. Sci.* **2004**, *19*, 489.
5. Fattovich, G.; Brollo, L.; Alberti, A.; Pontisso, P.; Giustina, G.; Realdi, G. *Hepatology* **1988**, *8*, 1651.
6. Yeo, H.; Li, Y.; Fu, L.; Zhu, J. L.; Gullen, E. A.; Dutschman, G. E.; Lee, Y.; Chung, R.; Huang, E. S.; Austin, D. J.; Cheng, Y. C. *J. Med. Chem.* **2005**, *48*, 534.
7. Guo, R. H.; Zhang, Q.; Ma, Y. B.; Luo, J.; Geng, C. A.; Wang, L. J.; Zhang, X. M.; Zhou, J.; Jiang, Z. Y.; Chen, J. J. *Eur. J. Med. Chem.* **2011**, *46*, 307.
8. Perni, R. B.; Conway, S. C.; Ladner, S. K.; Zaifert, K.; Otto, M. J.; King, R. W. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2687.
9. Jiang, Z. Y.; Zhang, X. M.; Zhang, F. X.; Liu, N.; Zhao, F.; Zhou, J.; Chen, J. J. *Planta Med.* **2006**, *72*, 951.
10. Lin, Y. M.; Zembower, D. E.; Flavin, M.; Schure, R.; Anderson, H.; Koeba, B.; Chen, F. C. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2325.
11. Zhao, W. G.; Wang, J. G.; Li, Z. M.; Yang, Z. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6107.
12. Ying, C. X.; Li, Y.; Leung, C. H.; Robek, M. D.; Cheng, Y. C. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 8526.
13. Zhang, Q.; Jiang, Z. Y.; Luo, J.; Cheng, P.; Ma, Y. B.; Zhang, X. M.; Zhang, F. X.; Zhou, J.; Chen, J. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4647.
14. Zhang, Q.; Jiang, Z. Y.; Luo, J.; Liu, J. F.; Ma, Y. B.; Guo, R. H.; Zhang, X. M.; Zhou, J.; Chen, J. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2148.
15. Zhang, Q.; Jiang, Z. Y.; Luo, J.; Ma, Y. B.; Liu, J. F.; Guo, R. H.; Zhang, X. M.; Zhou, J.; Niu, W.; Du, F. F.; Li, L.; Li, C.; Chen, J. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6659.
16. Zhan, P.; Jiang, X. M.; Liu, X. Y. *Mini-Rev. Med. Chem.* **2010**, *10*, 162.
17. Chen, H. J.; Wang, W. L.; Wang, G. F.; Shi, L. P.; Gu, M.; Ren, Y. D.; Hou, L. F.; He, P. L.; Zhu, F. H.; Zhong, X. G.; Tang, W.; Zuo, J. P.; Nan, F. J. *ChemMedChem* **2008**, *3*, 1316.
18. Dong, W. L.; Liu, Z. X.; Liu, X. H.; Li, Z. M.; Zhao, W. G. *Eur. J. Med. Chem.* **2010**, *45*, 1919.
19. Cheng, P.; Zhang, Q.; Ma, Y. B.; Jiang, Z. Y.; Zhang, X. M.; Zhang, F. X.; Chen, J. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3787.
20. Robison, M. M. *J. Am. Chem. Soc.* **1958**, *80*, 5481.
21. Abato, P.; Yuen, C. M.; Cubanski, J. Y.; Seto, C. T. *J. Org. Chem.* **2002**, *67*, 1184.
22. McCarthy, O.; Musso-Buendia, A.; Kaiser, M.; Brun, R.; Ruiz-Perez, L. M.; Johansson, N. G.; Pacanowska, D. G.; Gilbert, I. H. *Eur. J. Med. Chem.* **2009**, *44*, 678.
23. Mazet-Wagner, A. A.; Baclet, M. C.; Loustaud-Ratti, V.; Denis, F.; Alain, S. *J. Virol. Methods* **2006**, *138*, 70.
24. Lupberger, J.; Mund, A.; Kock, J.; Hildt, E. *J. Hepatol.* **2006**, *45*, 547.
25. Jiang, Z. Y.; Zhang, X. M.; Zhang, F. X.; Liu, N.; Zhao, F.; Zhou, J.; Chen, J. J. *Planta Med.* **2006**, *72*, 951.