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Synthesis, biological evaluation and structure–activity relationships of glycyrrhetinic acid derivatives as novel anti-hepatitis B virus agents

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ABSTRACT

Fifty-seven derivatives of glycyrrhetinic acid (GA) were synthesized, and their anti-hepatitis B virus (HBV) activity was evaluated in HepG 2.2.15 cells. Among them, sixteen compounds showed greater anti-HBV activity than GA, especially, compounds **29**, **32**, **35**, **41** exhibited significantly inhibitory activities against HBV DNA replication with IC_{50} values of 5.71, 5.36, 8.90 and 9.08 μM, respectively. The structure–activity relationships (SARs) of GA derivatives were discussed for exploring novel anti-HBV agents.

Hepatitis B virus (HBV) infection can cause liver disease, such as liver cancer or cirrhosis, which is a significant health problem throughout the world.[1] Currently, therapies for HBV infection including immuno-modulator, interferons (interferon-alpha and pegylated interferon) and nucleoside analogues (lamivudine (3TC), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT) and tenofovir-DF (TDF) are less than satisfactory.[2] For example, interferons have limited effectiveness and serious side effects (influenza-like symptoms, fatigue, myalgia, nausea, headache, etc.); nucleoside analogues result in drug resistance and high recurrence for the single target on the viral DNA polymerase.[3,4] Thus, researchers are continuing to search for new anti-HBV agents with novel antiviral targets and mechanisms.

Natural products and their derivatives by simple functional-group transformations offer many opportunities for finding novel anti-HBV inhibitors.[5–14] Licorice root (*Glycyrrhizae glabra*) has long been used widely as a traditional medicine mainly for the treatment of peptic ulcer, hepatitis C, pulmonary and skin diseases, and several other useful pharmacological properties (antiinflammatory, antiviral, antimicrobial, antioxidative, anticancer activities, etc.).[15] Glycyrrhizin (Fig. 1) and its metabolite and pharmacologically active form glycyrrhetinic acid (GA, Fig. 1) are the main effective constituents of Licorice root.[16] Many derivatives of chemical modified GA were reported, which mainly focused on enhancing the antiinflammatory and antitumor activity.[17–24] Although GA had been used for the treatment of chronic hepatitis B,[25–29] no investigation of GA derivatives had been conducted for their anti-HBV activity. Moreover, GA has been used as a ligand for liver targeting, and GA-modified carriers were shown to be more efficient for liver- or hepatocyte-targeted delivery.[30–32] Therefore, we synthesized a series of GA derivatives in order to develop novel anti-HBV agents. Herein, we report the synthesis of several GA derivatives modified on rings A, C, and E at positions 3, 11, 12, 13 and 30, respectively. Structure–activity relationships (SARs) of these GA analogs with anti-HBV activity are also discussed in this letter.

The syntheses of GA derivatives were summarized in Scheme 1. GA was treated with anhydride and a catalytic amount of 4-dimethylaminopyridine (DMAP) in dry pyridine to afford compounds **1–3**. Derivative **4** was synthesized by the reaction of 3,4,5-trimethoxycinnamic acid with GA in the presence of *N*′,*N*′-dicyclohexylcarbodiimide (DCC) and DMAP.[8] Oxidation derivative 5 was successfully obtained by treatment of GA with pyridinium chlorochromate (PCC) in CH_2Cl_2.[33] Anhydrous K_2CO_3 was added to a solution of GA and alkyl- or benzyl halide in dry DMF to yield the derivatives **6–41**.[34] 11-Deoxo-GA (**42**) was prepared by treatment of GA in glacial acetic acid with catalytic reduction using PtO_2 under the H_2 atmosphere.[35] In order to further evaluation the function of hydroxy at C-3 and carboxyl at C-30 for biological activity, the C-30 esters (**43–46**) and C-3, 30 diesters (**47–56**) of compound **42** were obtained by the method described above for compounds **6–41** and **4**, respectively. Epoxidation of compound **42** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in CH_2Cl_2 at room temperature gave derivative 57.[14] All of the synthesized derivatives were purified by column chromatography and their structures were characterized by

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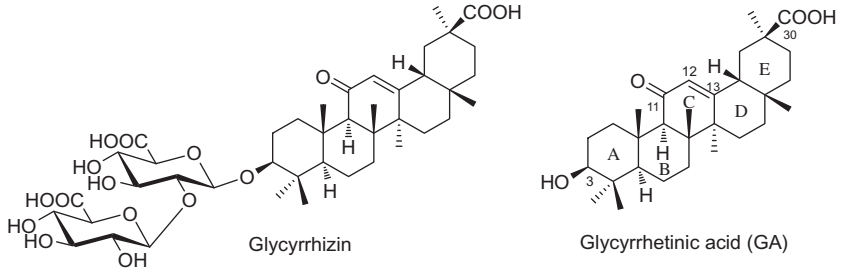
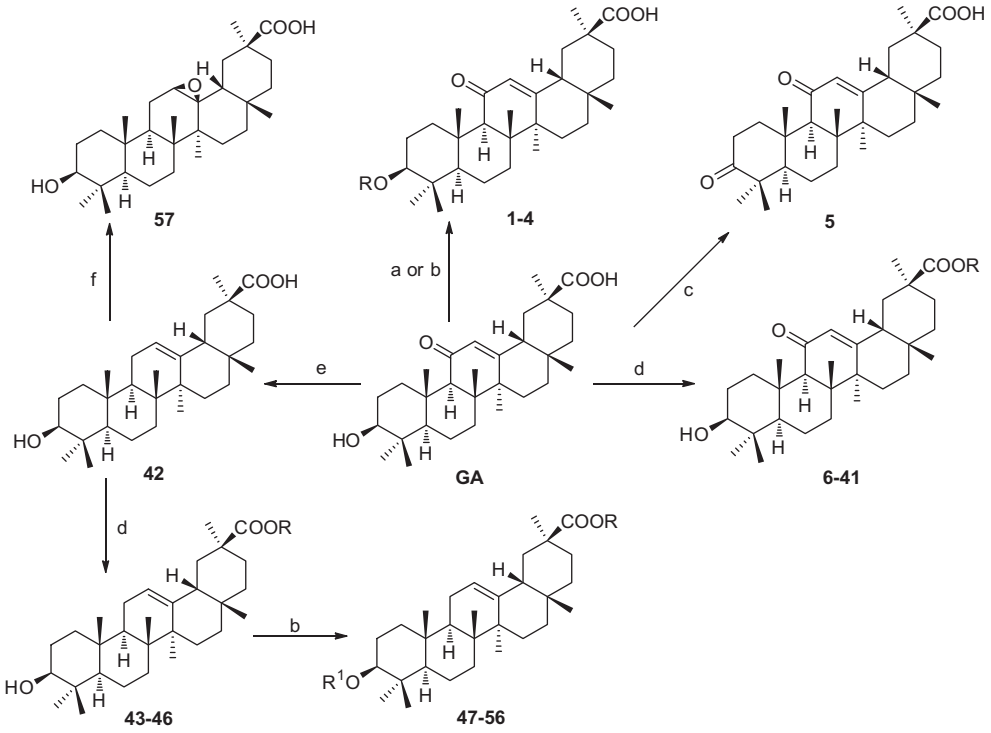


Figure 1. Chemical structure of glycyrrhizin and glycyrrhetinic acid (GA).



Scheme 1. Synthesis of compounds **1–57**. Reagents and conditions: (a) $(RCO)_2O$, DMAP, anhydrous pyridine, reflux; (b) DMAP, DCC, carboxylic acid, CH_2Cl_2, rt; (c) PCC, CH_2Cl_2, rt; (d) RX, K_2CO_3, DMF, rt; (e) H_2, PtO_2, CH_3COOH; (f) *m*-CPBA, CH_2Cl_2, rt.

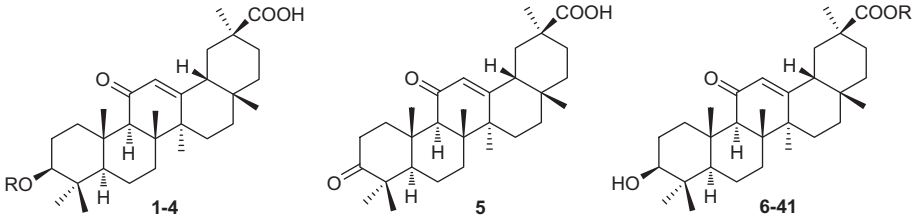
spectroscopic means (^1H, ^{13}C NMR, MS and HRMS), which had a degree of purity >90%, based on the TLC method in three different solvent systems (all compounds exhibited one spot both under UV radiation and when sprayed with H_2SO_4) and NMR spectra (the baseline was smooth without impurity peaks).

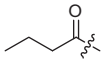
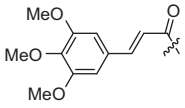
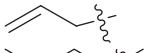
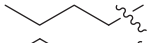
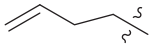
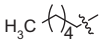
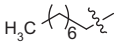
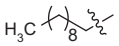
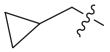
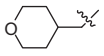
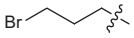
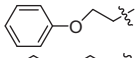
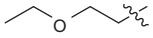
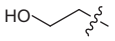
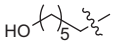
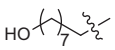
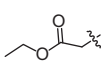
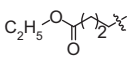
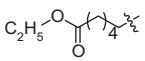
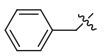
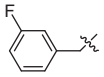
GA and its derivatives were tested for their cytotoxicities and potential anti-HBV activities, namely inhibiting the secretion of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and HBV DNA replication in HepG 2.2.15 cells using tenofovir as a positive control.[36] The results of their anti-HBV activity and cytotoxicity were listed in Tables 1 and 2.

As shown in Table 1, GA showed inhibitory potency to the secretion of HBsAg and HBV DNA replication with the IC_{50} value of 20.86 μM and 39.28 μM, but displayed cytotoxicity (CC_{50} = 55.15 μM), resulting in relatively low selectivity index (SI_{HBsAg} = 2.6, $SI_{HBV\ DNA}$ = 1.4). Tenofovir, the positive control drug, showed significant inhibitory of HBV DNA replication with the IC_{50} value of 0.89 μM (SI > 1973.4) but weak activity of against the secretion of HBsAg and HBeAg. The cytotoxicity of derivatives (**1–4**) decreased with acylation of the hydroxy at C-3 of GA. Among them, compounds **2** and **3** exhibited inhibitory to the secretion of HBeAg and HBV DNA replication, without obvious advantage comparing to GA. Oxidation of the hydroxy at C-3 of GA produced the ketone **5**, which exhibited low anti-HBV activity relative to that of GA. Thus, it could be concluded that the hydroxy group of the C-3 was important for the anti-HBV activity.

Derivatives (**6–12**) with aliphatic groups lost their anti-HBV activity, except that compound **10** (the alkyl chain was six carbon atoms) was observed to possess activity against the HBV DNA replication with the IC_{50} value of 66.15 μM. This result indicated that the chain length could affect the anti-HBV activity of these derivatives. Compounds **13** and **14** with cyclopropyl and cyclobutyl groups exhibited inhibitory activity on HBV DNA replication. Otherwise, derivative **15** lost its anti-HBV activity when the (tetrahydro-2*H*-pyran-4-yl) methyl group was incorporated. Most of the C-30 esters (**16–25**) with substituted alkyl moiety (bromo, hydroxyl, ethoxycarbonyl, etc.) showed potent activity against the HBV DNA replication. The derivatives (**26–37**) yielded from the reaction of GA with various substituted benzylbromide could greatly reduce the cytotoxicity and enhance the anti-HBV activity. Among them, compounds **29**, **32** and **35** exhibited significant efficacy on suppressing the HBV DNA replication with the IC_{50} values of 5.71 μM, 5.36 μM, 8.90 μM, along with the high SI values of more than 172.6, 255.9, 149.2, respectively. Interestingly, the positions

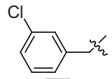
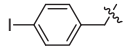
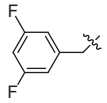
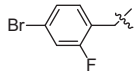
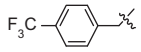
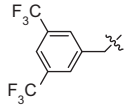
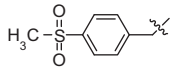
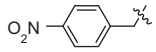
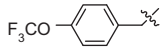
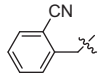
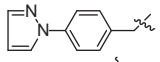
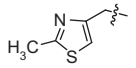
Table 1
Structure, anti-HBV activity and cytotoxicity of GA derivatives **1–41**[a]



Compd	R	CC_{50}[b] (μM)	HBsAg[c]		HBeAg[d]		DNA replication	
			IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]
GA		55.15	20.86	2.6	130.49	—[g]	39.28	1.4
1		517.87	1001.50	—	>517.87	—	121.14	4.3
2		99.58	1357.83	—	49.20	2.0	44.40	2.2
3		118.80	369.65	—	37.03	3.2	48.22	2.5
4		>1164.43	>1164.43	—	232.16	5.0	120.10	>9.7
5		467.14	432.54	1.1	>467.14	—	189.31	2.5
6		>1744.29	>1744.29	—	>1744.29	—	>443.57	—
7		>2310.55	>2310.55	—	>2310.55	—	>577.64	—
8		>986.33	>986.33	—	>986.33	—	>246.58	—
9		>1754.39	>1754.39	—	>1754.39	—	332.04	>5.3
10		175.04	>1696.43	—	>1696.43	—	66.15	2.6
11		>1446.71	>1446.71	—	>1446.71	—	>361.67	—
12		>1027.76	>1027.76	—	>1027.76	—	>256.94	—
13		695.92	678.43	—	>1102.40	—	67.02	10.4
14		742.35	810.05	—	>1813.46	—	89.53	8.3
15		>1914.57	>1914.57	—	>1914.57	—	>478.64	—
16		160.10	>1392.04	—	>1392.04	—	28.59	5.6
17		101.19	57.38	1.8	>1179.00	—	14.17	7.1
18		540.86	835.27	—	>1717.14	—	198.16	2.7
19		55.33	40.00	1.4	>1115.36	—	28.76	1.9
20		380.11	1010.98	—	>1924.57	—	297.86	1.3
21		67.28	129.06	—	>1254.70	—	47.68	1.4
22		157.28	145.46	1.1	>1392.36	—	13.23	11.9
23		>1203.30	>1203.30	—	>1203.30	—	138.54	>8.7
24		53.34	38.22	1.4	56.77	—	30.87	1.7
25		54.74	208.96	—	>1747.22	—	47.16	1.2
26		2007.88	>2007.88	—	>2007.88	—	153.08	13.1
27		>1313.97	587.62	>2.2	>1313.97	—	19.54	>67.2

(*continued on next page*)

Table 1 (*continued*)

Compd	R	CC_{50}[b] (μM)	HBsAg[c]		HBeAg[d]		DNA replication	
			IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]
28		>1850.92	>1850.92	—	>1850.92	—	529.31	>3.5
29		>985.68	>985.68	—	>985.68	—	5.71	>172.6
30		>1233.09	>1233.09	—	>1233.09	—	>307.43	—
31		>1431.23	>805.06	—	>805.06	—	18.12	>79.0
32		>1373.13	>1373.13	—	>1373.13	—	5.36	>255.9
33		>1702.45	>1702.45	—	>1702.45	—	>425.60	—
34		1025.29	54.40	18.8	>1212.24	—	21.24	48.3
35		>1327.92	606.49	>2.2	>1327.92	—	8.90	>149.2
36		>1132.84	>1132.84	—	>1132.84	—	159.71	>7.1
37		>1537.41	>1537.41	—	>1537.41	—	195.17	>7.9
38		>1698.35	>1698.35	—	>1698.35	—	15.30	>111.0
39		320.99	1071.55	—	>1356.43	—	171.30	1.9
40		1985.79	926.80	2.1	>2064.32	—	23.74	83.6
41		37.17	36.34	1.0	>1483.90	—	9.08	4.1
TF[h]		>1756.36	1442.23	>1.2	1248.76	>1.4	0.89	>1973.4

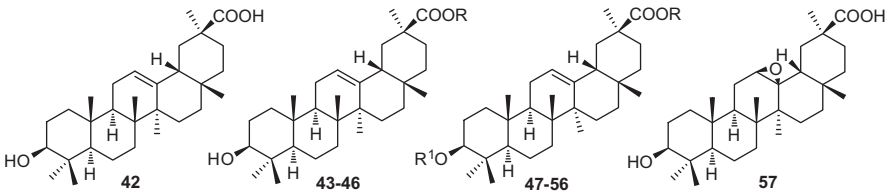
[a] Values are means of two independent experiments.
[b] CC_{50} is 50% cytotoxicity concentration in HepG2 2.2.15 cells.
[c] HBsAg: hepatitis B surface antigen.
[d] HBeAg: hepatitis B e antigen.
[e] IC_{50} is 50% inhibitory concentration.
[f] SI (selectivity index) = CC_{50}/IC_{50}.
[g] No SI can be obtained.
[h] Tenofovir as the positive control.

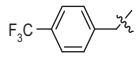
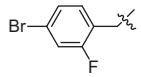
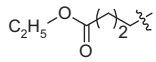
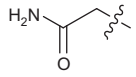
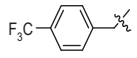
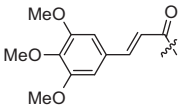
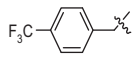
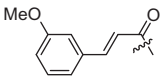
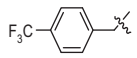
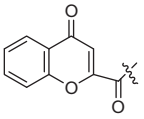
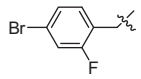
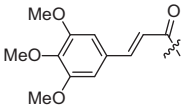
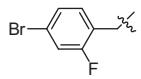
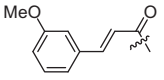
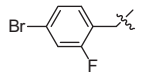
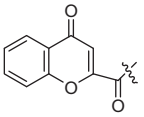
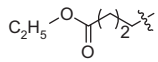
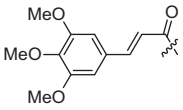
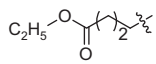
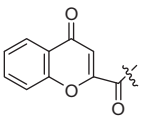
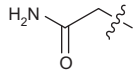
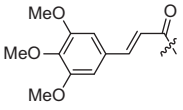
and number of substitution on the benzyl moiety could influence the anti-HBV activity of the C-30 derivatives. Compounds **27** with 3-fluorobenyl moiety and **32** with 4-(trifluoromethyl)benzyl moiety showed potent anti-HBV activity, however, compounds **30** with 3,5-difluorobenzyl moiety and **33** with 3,5-di(trifluromethyl)benzyl moiety lost the anti-HBV activity completely, which may be due to the influence of electron-withdrawing substituents on the aromatic moiety to have a higher activity while much of these groups have a deleterious effect. The derivatives of GA with medium-sized hydrocarbon chains or benzyl on C-30 had potent anti-HBV activity, suggesting that the steric hindrance may also affect their activity. Four derivatives (**38–41**) were synthesized based on the fact that many active anti-HBV agents with nitrogen heterocyclic ring possessed effective anti-HBV activity. The IC_{50} values of compounds **38**, **40**, **41** inhibiting HBV DNA replication were 15.30 μM (SI > 111.0), 23.74 μM (SI = 83.6), 9.08 μM (SI = 4.1), respectively. From the above results, it suggested that the carboxyl group at C-30 of GA might be a good target for further optimization by introducing the suitable substitutions.

In an effort to gain more information of the SARs of GA derivatives, we probed additional structural change. As shown in Table 2, the anti-HBV activity of 11-deoxo-GA (**42**) was equivalent to GA, whereas compound **42** had less cytotoxicity than GA, indicating that elimination of the carbonyl on C-11 of GA is an important feature in the conferring relatively low cytotoxicity. The importance of the functional group at the position of C-11 for maintaining anti-HBV activity was further demonstrated through comparing the activity of compounds (**43** vs **32**, **44** vs **31**, **45** vs **24**, **46** vs **19**). Most of derivatives (**43–56**) lost the cytotoxicity. But unfortunately, their anti-HBV activity also disappeared except that compound **46** maintained suppressant properties on the HBV DNA replication with IC_{50} value of 64.91 μM. These results further

proved that the functional groups at C-3 and C-30 of GA were the factors not only for the anti-HBV activity, but also for generating cytotoxicity. Compound **57**, the epoxide of C-12(13) double bond of compound **42**, enhanced the inhibiting HBV DNA replication with IC_{50} value of 18.37 μM, whereas an increase in cytotoxicity was also noted (CC_{50} = 35.71 μM) which may be due to an alkylating effect of the epoxide. The HBsAg and HBeAg, playing the role in HBV infection, seroconversion was suggested that was an impor-

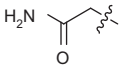
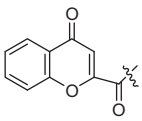
Table 2
Structure, anti-HBV activity and cytotoxicity of GA derivatives **42–57**[a]



Compd	R	R[1]	CC_{50}[b] (μM)	HBsAg[c]		HBeAg[d]		DNA replication	
				IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]
42			161.68	48.66	3.3	>1374.78	—[g]	47.00	3.4
43			>1499.93	>1499.93	—	>1499.93	—	>374.98	—
44			1152.16	>1526.37	—	>1526.37	—	>381.60	—
45			530.03	637.80	—	>1168.76	—	>292.18	—
46			471.74	346.51	1.4	>1107.56	—	64.91	7.3
47			>986.85	>986.85	—	>986.85	—	>246.71	—
48			>898.86	>898.86	—	>898.86	—	>224.72	—
49			>1171.87	>1171.87	—	>1171.87	—	>292.97	—
50			935.05	>1034.51	—	>1034.51	—	>258.63	—
51			>1001.89	>1001.89	—	>1001.89	—	>250.47	—
52			>1083.57	>1083.57	—	>1083.57	—	>270.88	—
53			>1227.81	>1227.81	—	>1227.81	—	>306.94	—
54			>1175.31	>1175.31	—	>1175.31	—	>293.83	—
55			>481.17	229.67	>2.1	251.59	>1.9	>120.31	—

(*continued on next page*)

Table 2 (*continued*)

Compd	R	R[1]	CC_{50}[b] (μM)	HBsAg[c]		HBeAg[d]		DNA replication	
				IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]	IC_{50}[e] (μM)	SI[f]
56			>944.06	>944.06	—	>944.06	—	>236.04	—
57			35.71	43.31	—	>1805.55	—	18.37	1.9
TF[h]			>1756.36	1442.23	>1.2	1248.76	>1.4	0.89	>1973.4

[a] Values are means of two independent experiments.
[b] CC_{50} is 50% cytotoxicity concentration in HepG2 2.2.15 cells.
[c] HBsAg: hepatitis B surface antigen.
[d] HBeAg: hepatitis B e antigen.
[e] IC_{50} is 50% inhibitory concentration.
[f] SI (selectivity index) = CC_{50}/IC_{50}.
[g] No SI can be obtained.
[h] Tenofovir as the positive control.

tant end point in the treatment of chronic hepatitis B.[37–39] Some of derivatives had greater activity against the secretion of HBsAg or HBeAg than that of the tenofovir (positive control, nucleoside drug), which suggested that they might had different mechanisms from the nucleoside analogs. The pharmacokinetic properties (T_{max}, C_{max}, $t_{1/2}$, etc.) of GA has been extensively investigated in the previous reports,[40,41] which might be useful for GA derivatives to be explored and developed as novel anti-HBV agents.

In summary, fifty-seven derivatives of GA were designed, synthesized, and evaluated for their anti-HBV activity in vitro. The preliminary SAR analysis reveals that (i) the free hydroxy (C-3), carbonyl (C-11) and carboxyl (C-30) group of GA could affect the anti-HBV activity and cytotoxicity; (ii) esterification of the hydroxy on C-3 or carboxyl group on C-30 could decrease the cytotoxicity, but esterifying at both the position C-3 and C-30 would make the anti-HBV activity disappear; (iii) introduction of suitable substituent at the 30-position could significantly enhance the activity; (iv) epoxide functionality at C-12(13) would cause the enhancement of suppressant properties on anti-HBV activity. Among the synthesized analogs, sixteen compounds showed greater anti-HBV activity than GA, particularly compounds **29**, **32**, **35** and **41** exhibited significant inhibitions against HBV DNA replication with IC_{50} values less than 10 μM. The active derivatives may have similar liver targeting properties as GA, which needs to be further investigated. Potentially, this finding may aid in the design of novel agents for the intervention of HBV infection.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.03.081.

References and notes

1. Chemin, I.; Zoulim, F. *Cancer Lett.* **2009**, *286*, 52.
2. Sato, K.; Mori, M. *Mini. Rev. Med. Chem.* **2010**, *10*, 20.
3. Locarnini, S.; Mason, W. S. *J. Hepatol.* **2006**, *44*, 422.
4. Zoulim, F.; Locarnini, S. *Gastroenterology* **2009**, *137*, 1593.
5. Cheng, Y. C.; Ying, C. X.; Leung, C. H.; Li, Y. *J. Clin. Virol.* **2005**, *34*, S147.
6. Ying, C. X.; Li, Y.; Leung, C. H.; Robek, M. D.; Cheng, Y. C. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 8526.
7. 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.
8. 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.
9. 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.
10. Zhang, Q.; Jiang, Z. Y.; Luo, J.; Cheng, P.; Ma, Y. B.; Zhang, X. M.; Zhang, F. X.; Zhou, J.; Niu, W.; Du, F. F.; Li, L.; Li, C.; Chen, J. *J. Bioorg. Med. Chem. Lett.* **2009**, *19*, 6659.
11. Gao, L. M.; Han, Y. X.; Wang, Y. P.; Li, Y. H.; Shan, Y. Q.; Li, X.; Peng, Z. G.; Bi, C. W.; Zhang, T.; Du, N. N.; Jiang, J. D.; Song, D. Q. *J. Med. Chem.* **2011**, *54*, 869.
12. Du, N. N.; Li, X.; Wang, Y. P.; Liu, F.; Liu, Y. X.; Li, C. X.; Peng, Z. G.; Gao, L. M.; Jiang, J. D.; Song, D. Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4732.
13. Crosby, I. T.; Bourke, D. G.; Jones, E. D.; Jeynes, T. P.; Cox, S.; Coates, J. A. V.; Robertson, A. D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1644.
14. Wang, L. J.; Geng, C. A.; Ma, Y. B.; Huang, X. Y.; Luo, J.; Chen, H.; Guo, R. H.; Zhang, X. M.; Chen, J. *J. Bioorg. Med. Chem.* **2012**. http://dx.doi.org/10.1016/j.bmc.2012.03.023.
15. Obolentseva, G. V.; Litvinenko, V. I.; Ammosov, A. S.; Popova, T. P.; Sampiev, A. M. *Pharm. Chem. J.* **1999**, *33*, 427.
16. Li, H. Y.; Xu, W.; Su, J.; Zhang, X.; Hu, L. W.; Zhang, W. D. *Pharmacology* **2010**, *86*, 287.
17. Asl, M. N.; Hosseinzadeh, H. *Phytother. Res.* **2008**, *22*, 709.
18. Lai, Y. S.; Shen, L. H.; Zhang, Z. Z.; Liu, W. Q.; Zhang, Y. H.; Ji, H.; Tian, J. D. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6416.
19. Chadalapaka, G.; Jutooru, I.; McAlees, A.; Stefanacb, T.; Safe, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2633.
20. Nakagawa-Goto, K.; Nakamura, S.; Bastow, K. F.; Nyarko, A.; Peng, C. Y.; Lee, F. Y.; Lee, F. C.; Lee, K. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2894.
21. Csuk, R.; Schwarz, S.; Siewert, B.; Kluge, R.; Ströhl, D. *Eur. J. Med. Chem.* **2011**, *46*, 5356.
22. Lallemand, B.; Gelbcke, M.; Dubois, J.; Prévost, M.; Jabin, I.; Kiss, R. *Mini- Rev. Med. Chem.* **2011**, *11*, 881.
23. Xiao, Y. C.; Xu, J. W.; Mao, C. M.; Jin, M.; Wu, Q.; Zou, J.; Gu, Q. L.; Zhang, Y.; Zhang, Y. Y. *J. Biol. Chem.* **2010**, *285*, 1128.
24. Maitraie, D.; Hung, C. F.; Tu, H. Y.; Liou, Y. T.; Wei, B. L.; Yang, S. C.; Wang, J. P.; Lin, C. N. *Bioorg. Med. Chem.* **2009**, *17*, 2785.
25. Van Rossum, T. G. J.; Vulto, A. G.; Hop, W. C. J.; Brouwer, J. T.; Niesters, H. G. M.; Schalm, S. W. *J. Gastroenterol Hepatol.* **1999**, *14*, 1093.
26. Iino, S.; Tango, T.; Matsushima, T.; Toda, G.; Miyake, K.; Hino, K.; Kumada, H.; Yasuda, K.; Kuroki, T.; Hirayama, C.; Suzuki, H. *Hepatol. Res.* **2001**, *19*, 31.
27. Zhang, L.; Wang, B. *Hepatol. Res.* **2002**, *24*, 220.
28. Hayashi, J.; Noguchi, A.; Nakashima, K.; Hayashi, S.; Kashiwagi, S.; Mayumi, T.; Motomura, M. *Clin. Ther.* **1990**, *12*, 12.
29. Sato, H.; Goto, W.; Yamamura, J.; Kurokawa, M.; Kageyama, S.; Takahara, T.; Watanabe, A.; Shiraki, K. *Antiviral Res.* **1996**, *30*, 171.
30. Negishi, M.; Irie, A.; Nagata, N.; Ichikawa, A. *Biochim. Biophys. Acta Biomembr.* **1991**, *1066*, 77.
31. Huang, W.; Wang, W.; Wang, P.; Zhang, C. N.; Tian, Q.; Zhang, Y.; Wang, X. H.; Cha, R. T.; Wang, C. H.; Yuan, Z. *J. Mater. Sci.-Mater. Med.* **2011**, *22*, 853.
32. Tian, Q.; Wang, X. H.; Wang, W.; Zhang, C. N.; Liu, Y.; Yuan, Z. *Int. J. Pharmaceut.* **2010**, *400*, 153.
33. Wei, Y.; Ma, C. M.; Hattori, M. *Bioorg. Med. Chem.* **2009**, *17*, 3003.
34. Um, S. J.; Park, M. S.; Park, S. H.; Han, H. S.; Kwon, Y. J.; Sin, H. S. *Bioorg. Med. Chem.* **2003**, *11*, 5345.

35. Dean, P. D. G.; Halsall, T. G.; Whitehouse, M. W. J. *Pharm. Pharmac.* **1967**, *19*, 682.
36. Geng, C. A.; Wang, L. J.; Zhang, X. M.; Ma, Y. B.; Huang, X. Y.; Luo, J.; Guo, R. H.; Zhou, J.; Shen, Y.; Zuo, A. X.; Jiang, Z. Y.; Chen, J. *J. Chem-Eur J.* **2011**, *17*, 3893.
37. Milich, D.; Liang, T. *J. Hepatology* **2003**, *38*, 1075.
38. Liaw, Y. F. *Hepatol. Int.* **2009**, *3*, 425.
39. den Brouw, M. L. O.; Binda, R. S.; Geijtenbeek, T. B. H.; Janssen, H. L. A.; Woltman, A. M. *Virology* **2009**, *393*, 84.
40. Heilmann, P.; Heide, J.; Schöneshöfer, M. *Eur. J. Clin. Chem. Clin. Biochem.* **1997**, *35*, 539.
41. Krähenbühl, S.; Hasler, F.; Krapf, R. *Steroids* **1994**, *59*, 121.