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ARTICLE

Design and synthesis of pyridine-pyrazole-sulfonate derivatives as potential anti-HBV agents†

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Hepatits B virus (HBV) is an infectious disease, which can cause acute and chronic infections. Every year, an over 7.5 million person dies due to HBV. No effective drug exists for the treatment of HBV. Thus, we designed and synthesized 16 new pyridine-pyrazole-sulfonate compounds containing pyridine-SCH_2-pyrazole and pyridine-pyrazole derivatives. Their structures were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, mass spectroscopy, and high performance liquid chromatography. All the compounds were evaluated for their anti-HBV activities and established the structure-activity relationship (SAR) in HepG2 2.2.15 cells. We found the pyridine-pyrazole derivatives could inhibit the HBV gene expression and viral DNA replication. Among these compounds, 2-[3-(2-nitrophenylsulfonyl)oxy-5-pyrazol-yl]pyridine **19d** shown the most potent inhibitory activity with IC_{50} value of 9.19 μM, and high selectivity index, SI (TC_{50}/IC_{50}) 35.46. Hence, we believe our compounds could serve as reservoir for anti-HBV drug development.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third cancer-related cause of death. The hepatitis B virus (HBV), a member of the family *Hepadnaviridae*, is a causative agent that frequently leads to acute and chronic infections in humans.[1] Despite the development of a recombinant vaccine against HBV, over 400 million people are chronic carriers worldwide.[2,3] Liver cirrhosis and HCC occur in approximately 80% of chronic HBV carriers.[4] Although interferons and nucleotide analogs have been widely used to treat chronically infected patients, the rapid development of drug resistance is an emerging clinical problem.[5–8] Therefore, the improvement of novel antiviral agents to eradicate HBV in chronic carriers is instantly needed. After HBV infection, four viral transcripts are transcribed from four different viral promoters (Core, X, S, and PreS), which are 3.5, 2.4, 2.1, and 0.8 kb, respectively. The 3.5-kb transcript is translated to produce core, precore, and viral polymerase proteins. It also serves as a pregenomic RNA template for viral genome synthesis. The 2.4- and 2.1-kb transcripts encode small, medium, and large surface (envelope) proteins; the 0.8-kb transcript is translated to produce the X protein, a potent transactivator for both viral and host gene promoters.[9] Instead of viral replication, recent studies showed that how to regulate viral gene expression is a crucial step for antiviral strategies.[10,11] The discovery of novel and effective antiviral agents is usually the result of understanding the viral lifecycle[12] and performing molecular modeling by using the coordinates of the crystal structures of viral proteins, including helicases, proteases, and polymerases.[13] Such targeted drug development has been lacking for HBV, and the most common strategy has been compound screening by using in vitro replication models.[10,11,14,15] Once a new compound has been identified to inhibit HBV, the next step is to determine its mode of antiviral action. Currently, several antiviral compounds have been reported to target cellular signaling factors and disturb the viral gene regulation and genome replication.[10,11] The regulation of HBV viral gene expression is a highly complex issue in molecular virology. Accordingly, understanding how viral proteins regulate the host-signaling network can help us to control the HBV-induced liver cancer.

It had been reported that some anti-HBV agents were nucleoside, nucleotide, or derivatives from botanical origin.[16–18] Pyrazole (**1**, **Figure 1**), a five membered heterocyclic ring with two nitrogen atoms in the adjacent position, is an essential core structure had been widely used in agro-chemicals, building blocks, catalysis, and in medicines.[19] Pyrazole derivatives have been reported and used as antitumor, anti-inflammatory, antiviral, and anti-microbial agents.[20] Many pyrazole containing drugs approved by FDA such as AS-19 (**2**), Lonazolac (**3**), Mavacoxib (**4**), and Fezolamine (**5**). Recently, Kasımogulları et al. reported that

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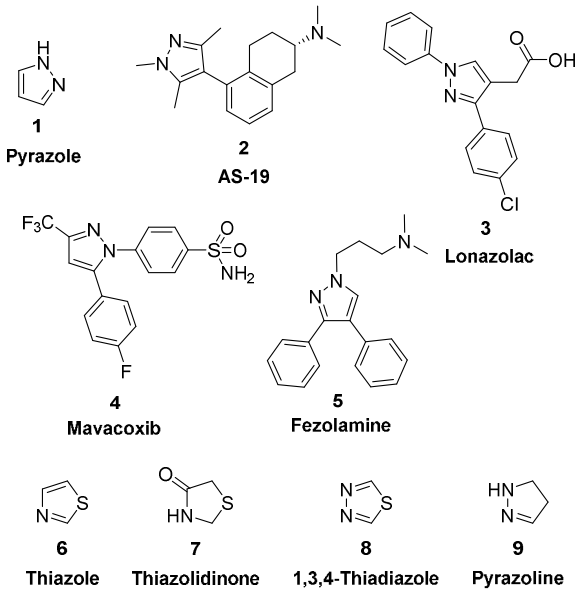


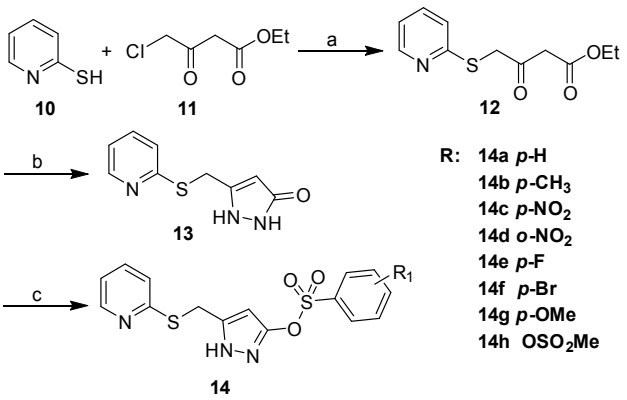
Figure 1. The structures of pyrazole, AS-19, Lonazolac, Macacoxib, Fezolamine, thiazole, thiazolidinone, 1,3,4-thiadiazole, and pyrazoline.

pyrazole-3-carboxylic acid derivatives exhibit antiproliferative activity against tumor cells.[21] Moreover, Bekhit et al. revealed pyrazole derivatives conjugated with five-member heterocyclic moieties such as thiazoles (**6**), thiazolidinones (**7**), 1,3,4-thiadiazoles (**8**) and pyrazolines (**9**), shows dual function for antimalarial activity against Plasmodium berghei infected mice in vivo and against chloroquine resistant (RKL9) strain of Plasmodium falciparum in vitro.[22] Yang et al. published the inhibition of succinate-ubiquinone oxidoreductase (SQR, EC 1.3.5.1, complex II), an essential component of cellular chain and tricarboxylic acid (or Krebs) cycle, using pyrazole-4-carboxamides with K_i = 11 nM (porcine SQR).[23] Herein, we report a novel series of pyrazole derivatives conjugated with pyridine and arenesulfonyl moiety as a new class of anti-HBV agents. Phenylsulfonyl group plays an important role in increasing the solubility of the molecules and triggering antiviral activity.[24,25] The pyrazole core structure was attached to pyridine ring on 3-position and phenylsulfonyl group on 5-position. These new classes of pyrazole derivatives were evaluated for antiviral activity, and they exhibited valuable anti-HBV effects in HepG2 2.2.15 cells. The designed compounds are potential structural templates for developing new anti-HBV agents.

2. Results and discussion

2.1 Chemistry

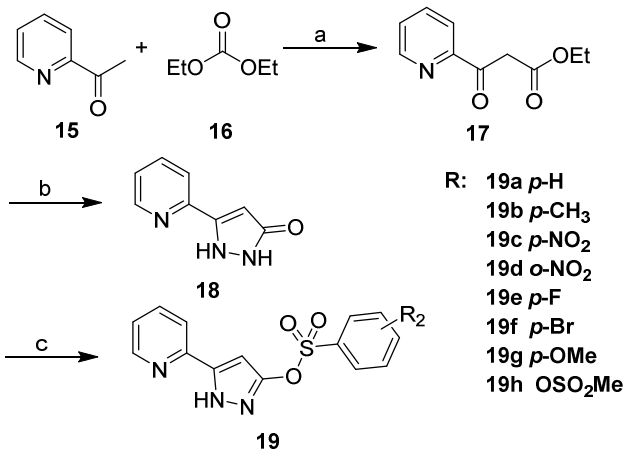
The synthetic route of pyridine-SCH_2-pyrazole derivatives is shown in **Scheme 1**. 2-Mercaptopyridine **10** and ethyl 4-chloroacetoacetate **11** were conjugated by using potassium carbonate as a base at room temperature to get ethyl 4-(pyridin-2-ylthio)acetoacetate **12**.[26] The pyrazole scaffold was



Scheme 1 Reagents and conditions: (a) K_2CO_3, THF, r.t., 4.0 h, 89%; (b) hydrazine hydrate, EtOH/THF (1:1), r.t., 2.0 h, 86%; (c) substituted phenylsulfonyl chloride or methylsulfonyl chloride, K_2CO_3, THF, 40 °C, 4.0-5.0 h, 76-87%.

introduced by treating **12** with hydrazine hydrate in ethanol/THF co-solvent to give key intermediate 1,2-dihydro-5-[(2-pyridinylthio)methyl]-3H-Pyrazol-3-one **13**. By treating various substituted phenylsulfonyl chloride with the intermediate **13** under mild condition, the desired pyrazole-phenylsulfonyl conjugates **14** were obtained.

The synthetic route of pyridine-pyrazole derivatives is shown in **Scheme 2**. 2-Acetylpyridine **15** and diethyl carbonate **16** were conjugated by using sodium hydride under refluxing in toluene to give ethyl picolinoylacetate **17**.[27] The compound **17** was treated with hydrazine to build up the heterocyclic core of the essential intermediate 1,2-dihydro-5-(2-pyridinyl)-3H-Pyrazol-3-one **18**. The final desired pyrazole products **19** were synthesized by treating **18** with various substituted phenylsulfonyl chloride in THF at room temperature. All these products were obtained in good yields and purified to more than 95% by chromatography and recrystallization for bioactivity assays.



Scheme 2. Reagents and conditions: (a) NaH, toluene, 110 °C, 3.0 h, 72%; (b) hydrazine hydrate, EtOH, r.t., 2.0 h, 79%; (c) substituted phenylsulfonyl chloride or methylsulfonyl chloride, K_2CO_3, THF, 40°C, 4.0-5.0 h, 74-88%.

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The structures of all new compounds were determined according to their spectroscopic characteristics. For example, the mass spectrum of **14d** from ESI analysis exhibited 392.0248, which indicates a molecular formula of $C_{15}H_{12}N_4O_5S_2$ with a theoretical value of 392.0249. Its ^{13}C NMR spectrum showed 15 signals, which is in accordance with the theoretical number. Resonance at δ 24.31 and 96.08 was assigned to SCH_2 and pyrazole CH carbons respectively. Also resonance at δ 153.35 ppm was assigned to the N=C−O carbon. Furthermore, the ^1H NMR spectrum of **14d** displayed two characteristic singlets at δ 4.38 and 6.51 for the SCH_2 and H-4' proton respectively. Its IR spectrum showed one strong absorption band at 1376 cm^{-1}, which were attributed to the S=O stretching vibration. Similarly, in case of **19d**, ESI analysis exhibited 346.0376, which indicates a molecular formula of $C_{14}H_{10}N_4O_5S$ with a theoretical value of 346.0372. Its ^{13}C NMR spectrum showed 14 signals, which is in accordance with the theoretical number.

Table 1 Effect and selectivity index (SI) of compounds **13**, **14a–14h**, **18**, and **19a–19h** on cytotoxicity of HepG2 2.2.15 cells, inhibition potential of HBV viral antigen and DNA replication

Compound	TC_{50} (μM)	HBsAg IC_{50} (μM)	HBsAg SI (TC_{50}/IC_{50})	HBeAg IC_{50} (μM)	HBeAg SI(TC_{50}/IC_{50})	Inhibition of HBV DNA replication IC_{50} (μM)	HBV DNA replication SI(TC_{50}/IC_{50})
13	1117.4	814.65	1.37	590.40	1.89	524.13	2.13
14a	103.30	151.94	0.68	20.31	5.09	18.93	5.46
14b	86.39	19.83	4.36	19.42	4.45	14.29	6.04
14c	38.24	4.80	7.97	5.97	6.41	5.56	6.88
14d	66.25	6.25	10.6	9.92	6.68	6.30	10.51
14e	116.22	26.19	4.44	249.98	0.46	197.49	0.59
14f	52.38	114.93	0.46	9.20	5.69	6.07	8.63
14g	90.25	14.53	6.21	44.61	2.02	38.14	2.37
14h	830.46	160.51	5.17	679.38	1.22	738.95	1.12
18	1063.96	1377.26	0.77	1368.31	0.78	1349.82	0.79
19a	135.13	136.79	0.99	69.49	1.94	65.34	2.07
19b	216.72	23.17	9.35	32.31	6.71	31.33	6.92
19c	786.54	125.34	6.28	-	-	-	-
19d	325.89	7.48	43.54	12.02	27.11	9.19	35.46
19e	253.94	45.91	5.53	82.85	3.06	92.07	2.76
19f	809.20	210.07	3.85	-	-	-	-
19g	87.53	15.37	5.69	23.09	3.79	22.17	3.95
19h	1058.08	287.19	3.68	-	-	-	-
5-FU	21.68	-	-	-	-	-	-
Lamivudine (3TC)	352.03	-	-	-	-	2.09	46.13

TC_{50} : The concentration of the compound at which cell viability was reduced to 50%.; IC_{50}: The concentration of the compound on anti-HBV effect was reached to 50%; 5-FU (Fluorouracil) is the positive control for cytotoxic analysis; Lamivudine (3TC) is the positive control for anti-HBV analysis.

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Resonance at δ 94.46 and 153.35 ppm were assigned to the pyrazole CH carbons and N=C–O carbon respectively. Furthermore, the ^{1}H NMR spectrum of **19d** displayed one characteristic singlet at δ 6.51 for the H-4' proton. Its IR spectrum showed one strong absorption band at 1375 cm^{-1}, which were attributed to the S=O stretching vibration.

2.2 Cytotoxic Effect of the Compounds on HepG2 2.2.15 Hepatoma Cells

To evaluate the structure-activity relationship (SAR) and determine the cytotoxic effects of compounds **13**, **14a–14h**, **18**, and **19a–19h** on HepG2 2.2.15 cells, the cells were subjected to twofold serial dilution with each compound for 72 h, and the viability of the cells was measured according to the manufacturer's protocol. All measurements were performed in four replicates, and the results were presented as a relative percentage of the results of the control group. The results are shown in **Table 1**; a decrease in the cell viability in a dose-dependent manner was observed for all compounds. To explore the SAR of conjugates in this new compound library, two new series derivatives, containing pyridine-SCH$_2$-pyrazole and pyridine-pyrazole as core structure, were synthesized and conjugated with different sulfonyl groups. According to their TC_{50}, 9 compounds displayed potent inhibition tendency towards cell viability. (**Table 1**)

Compared with **13** and **18**, conjugation of phenylsulfonate with two scaffolds increase the cytotoxicity, but doesn't for methylsulfonate derivatives. Such phenomena can be observed in compound **13** vs **14c**, **14d** and **14f** with TC_{50} value of, 1117.4 vs 38.24, 66.25, and 52.38 μM, and also in compound **18** vs **19a** and **19g** of 1063.96 vs 135.13, and 87.53 μM. Pyridine-SCH$_2$-pyrazole conjugates are more cytotoxic than pyridine-pyrazole. Thiomethyl linker between pyridine and pyrazole increases the cytotoxicity in all derivatives except **14g** and **19g**. In case of pyridine-pyrazole conjugates, *p*-nitro derivative **19c** is less cytotoxic (786.54 μM) than *o*-nitro benzene sulfonate derivative **19d** (325.89 μM). Furthermore, in case of pyridine-SCH$_2$-pyrazole scaffold, the substituent of phenylsulfonate barely affects the cytotoxicity (cf. **14a** vs **14b** vs **14c** vs **14d** vs **14e** vs **14f** vs **14g**). Among pyridine-pyrazole scaffold, the phenylsulfonate was found more cytotoxic than alkyl sulfonate in compound **19b** (216.72 μM) and **19h** (1058.08 μM). Also *p*-bromo derivative **19f** (809.20 μM) shows less cytotoxicity than *p*-fluoro derivative **19e** (253.94 μM).

2.3 Antiviral Effect of Compounds on HBV Viral Antigen Expression in HepG2 2.2.15

Table 1 also shows the secretion of HBsAg and HBeAg in treated HepG2 2.2.15 cell culture media. Phenylsulfonyl group was found significant affect the activity of HBsAg inhibition. For the inhibition of HBsAg, the conjugation of phenylsulfonyl side chains onto the pyridine-SCH2-pyrazole increased the overall inhibitory effect (**13** vs **14a–14h**). Compound **14c** and **14d** displayed potent inhibitory effect with IC_{50} of 4.80, 6.25 μM and high selectivity index, SI (TC_{50}/IC_{50}) of 7.97 and 10.6 respectively. Similar effect of increasing HBsAg inhibitory activity was also observed when the pyridine-pyrazole scaffold conjugated with phenylsulfonyl side chain (**18** vs **19a–19h**). Among halogen substituents, the *p*-fluoro derivatives showed better inhibition activity than the *p*-bromo derivatives (**14e** vs **14f**, and **19e** vs **19f**). In the case of electron releasing group on the phenylsulfonyl side chain, the methoxy group exhibited better activity than methyl group in both core structures (**14b** vs **14g**, and **19b** vs **19g**). Furthermore, we found the *ortho*- and *para*-position of nitro group shown no significant different of the activity in the pyridine-SCH$_2$-pyrazole scaffold **14**. However, in the pyridine-pyrazole derivatives **19**, *ortho*-nitro derivative **19d** was much more active than *para*-nitro derivative **19c**. The compound **19d** was found the most potent lead molecule in this family with IC_{50} of 7.48 μM and high selectivity index of 43.5.

In the inhibition of HBeAg, the conjugation of phenylsulfonyl side chains increased the inhibitory effect in pyridine-SCH$_2$-pyrazole scaffold (cf. **13** vs **14a–14h**). Compound **14c**, **14d**, and **14f** showed potent inhibitory effect with IC_{50} of 5.97, 9.92, 9.20 μM and SI of 6.41, 6.68, 5.69 respectively. Also, the pyridine-pyrazole derivatives (**18** and **19a–19h**) were displayed similar effect when conjugated with phenylsulfonyl groups. In case of pyridine-pyrazole scaffold, *o*-nitro derivative **19d** demonstrated potential to be a lead molecule in this family with IC_{50} of 12.02 μM and high SI of 27.11.

2.4 Antiviral Effect of Compounds on HBV DNA Replication in HepG2 2.2.15

To investigate the antiviral activity of compounds in HBV DNA replication, HepG2 2.2.15 cells were treated with three noncytotoxic concentrations of compounds for 48 h. As shown in **Table 1**, phenylsulfonate derivatives with two scaffolds increase the inhibition effect on HBV replication, but the phenomenon doesn't exist on methylsulfonate compound **14h**. In addition, *p*-bromophenylsulfonate derivative **19d** shows great effect with IC_{50} of 6.07 μM. Moreover, nitro-phenylsulfonate on both scaffolds enhances inhibition effect whether on *ortho*- or *para*-positon. (i.e. **14c**, **14d** and **19d**) 5-(Pyridin-2-yl)-1H-pyrazol-3-yl-2-nitrobenzenesulfonate **19d** also exhibits the highest selectivity index of 35.46 in these two series compounds.

3. Conclusions

In summary, we design and synthesized two new series pyrazole core structure conjugated with sulfonyl groups. One series derivatives were pyridine-SCH$_2$-pyrazole derivatives **14**, the other were pyridine-pyrazole derivatives **19**. All the synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectroscopy. All the compounds were evaluated for their anti-HBV activities and established the structure-activity relationship (SAR) between these two series compounds. We found our new pyrazole derivatives could inhibit the HBV gene expression and viral DNA replication. The results displayed that 5-(Pyridin-2-yl)-1H-pyrazol-3-yl-2-nitrobenzenesulfonate **19d** exhibited potent activity against HBV in HepG2 2.2.15 cells with IC_{50} values of 9.19 μM, especially for the high selectivity index (TC_{50}/IC_{50}) of 35.46,

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the compound could be a potential lead compound for anti-HBV therapy.

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Graphic Abstract