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Synthesis and biological evaluation of ethyl 6-alkoxy-7-phenyl-4-hydroxy-3-quinolinecarboxylates against *Eimeria tenella*

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Abstract

A series of ethyl 6-alkoxy-7-phenyl-4-hydroxy-3-quinolinecarboxylates were designed and synthesized. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR, IR and HRMS. The biological activities were primarily evaluated against *Eimeria tenella* according to Anticoccidial Index (ACI) method *in vivo*. The results showed that compounds **5e**, **5f** and **5i** exhibited anticoccidial activities against *E. tenella* at 27 mg kg^{-1}.

Keywords: Ethyl 6-alkoxy-7-phenyl-4-hydroxy-3-quinolinecarboxylate; Synthesis; Anticoccidial activity; *Eimeria tenella*

Coccidiosis is an infection of intestinal epithelium caused by protozoan parasite of the genus *Eimeria*, which induces production losses, high morbidity (due to acute, bloody enteritis) and mortality rates [1,2]. Anticoccidiostats were used to control this disease, but after using for a period of time, the coccidia were inevitably to develop resistance to the drugs [3]. Nowadays, drug resistance has extended to all of the anticoccidiostats that have been introduced [4]. It was reported that some anticoccidiostats such as Salinomycin, Dinitolmide, Maduramicin and Amprolium had lost anticoccidial activities against many strains in many areas of China [5]. Thus, it is necessary to search and develop new anticoccidial drugs.

Quinolinecarboxylate anticoccidiostats such as buquinolate, nequinate and decoquinate (Fig. 1), possessing 6-alkoxy/alkyl and 7-alkoxy in the structure of quinoline ring, exhibited good anticoccidial activities for chickens in one time. However, the effects of these drugs have been reported to decline because of drug resistance [4]. These current quinolinecarboxylate anticoccidiostats would be certainly invalid one day.

In order to search new anticoccidial compounds, a series of ethyl 6-alkoxy-7-phenyl-4-hydroxy-3-quinolinecarboxylates were designed and synthesized. In the new object molecules, 7-phenyl group was introduced

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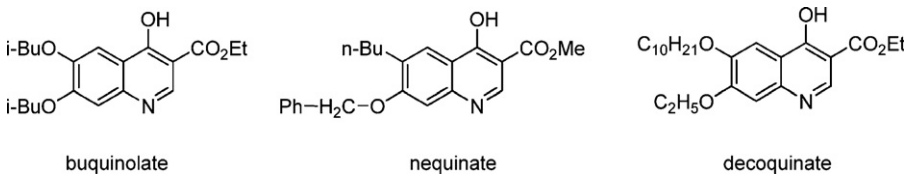
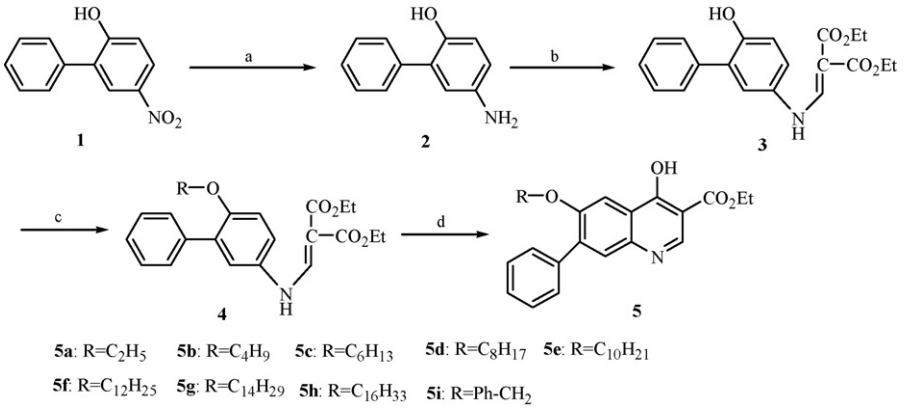


Fig. 1. The structure of buquinolate, nequinate and decoquinate.



Scheme 1. The synthetic route of target compounds. (a) H_2, Pd/C, EtOAc, 45 °C, 6 h; (b) EMME, reflux, 4 h, 75%; (c) R-Br, K_2CO_3, TBAB, DMF, 80 °C, 2–3 h, 70–80%; (d) diphenyl ether, reflux, 10–20 min, 67–78%.

to the quinoline rine and the molecular structures were different from the former quinolinecarboxylate anticoccidiostats. Therefore the drug-resistant strains might be sensitive to the new compounds.

Compounds **5a–i** were prepared as shown in Scheme 1. Compound **1** [6] was reduced by Pd/C catalyzed hydrogenation in EtOAc at normal pressure for 6 h. The obtained mixture was directly used to react with proper amount of diethylethoxymethylenemalonate (EMME) for 4 h to form **3**, which was purified through recrystallization in ethanol. Then, **3** was treated with bromoalkane (R-Br), TBAB and potassium carbonate in DMF for 2–3 h to give compounds **4a–i**. Target compounds **5a–i** were obtained by cyclization reaction in diphenyl ether for 10–20 min, and purified by washing with petroleum ether and EtOAc. The data of yields, melting points, ^{1}H NMR, ^{13}C NMR, IR and HRMS spectra of the target compounds were shown in Ref. [8].

The anticoccidial activities of **5c–5i** were evaluated according to ACI method [7] *in vivo*, using diclazuril as reference drug (Table 1). Compared with Infected-untreated group (ACI 60.9), **5e**, **5f** and **5i** showed obvious anticoccidial activities against *Eimeria tenella*, with ACI 122.4, 138.5 and 133.3, respectively. At the same time, **5f** and **5i** showed better anticoccidial activities than diclazuril (ACI 127) against the tested *E. tenella* strain.

Table 1
Anticoccidial activity of target compounds **5c–5i** against *Eimeria tenella* at 27 mg kg^{-1}.

Group	Test compounds	No. of chicken	Relative rate of weight gain (%)	Rate of survival (%)	Lesion value	Oocyst value	ACI
1	**5c**	10	73.9	80	38	40	75.9
2	**5d**	10	65.7	90	25	30	100.7
3	**5e**	10	68.8	90	16.4	20	122.4
4	**5f**	10	87.6	90	19.1	20	138.5
5	**5g**	10	47.9	70	33	40	44.9
6	**5h**	10	62.1	70	24	30	78.1
7	**5i**	10	85.1	90	21.8	20	133.3
8	Diclazuril[a]	10	87	90	30	20	127
9	Infected-untreated	10	78.9	60	38	40	60.9
10	Uninfected-untreated	10	100	100	0	0	200

[a] The concentration of diclazuril is 1 mg kg^{-1}, which is the standard concentration of this drug for chickens.

From the results of **5c**–**5h**, it was clear that the number of carbon atoms in 6-alkyoxy played an important role in determining the activities. Anticoccidial activity was exhibited by the introduction of decyloxy (C_{10}) or dodecyloxy (C_{12}) group in 6-position, while compounds with more or less number of carbon atoms displayed no anticoccidial activity. **5i** with 6-benzyloxy also showed anticoccidial activity against *E. tenella*.

In summary, nine ethyl 6-alkoxy-7-phenyl-4-hydroxy-3-quinolinecarboxylates were designed and synthesized. Evaluation of the anticoccidial activity of new compounds revealed that compounds **5e**, **5f** and **5i** had anticoccidial activities against *E. tenella* at 27 mg kg^{-1}.

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[8] The data for representative compounds: **5a**: yellow solid; yield: 72%; melting point: 252–254 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.29 (s, 1H), 8.53 (s, 1H), 7.67 (s, 1H), 7.58 (d, 2H, *J* = 7.2 Hz), 7.55 (s, 1H), 7.48 (t, 2H, *J* = 7.2 Hz, *J* = 7.6 Hz), 7.42–7.40 (m, 1H), 4.22 (q, 2H, *J* = 7.2 Hz), 4.14 (q, 2H, *J* = 6.8 Hz), 1.32 (t, 3H, *J* = 6.8 Hz), 1.29 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 173.84, 167.83, 152.86, 151.58, 145.02, 138.25, 133.86, 129.45, 129.16, 128.74, 128.08, 127.17, 105.83, 63.88, 58.44, 14.68; IR (KBr, cm^{-1}): 3440, 2979, 2930, 1700, 1613, 1582, 1502, 1469, 1443, 1188; HRMS(ESI): Calcd. for $C_{20}H_{19}NO_4$: 337.1314; Found: 338.1351 (M+H^+), 360.1204 (M+Na^+); **5b**: yellow solid; yield: 75%; melting point: 248–250 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.26 (d, 1H, *J* = 6.0 Hz), 8.51 (d, 1H, *J* = 6.4 Hz), 7.65 (s, 1H), 7.54 (d, 2H, *J* = 8.0 Hz), 7.52 (s, 1H), 7.45 (t, 2H, *J* = 7.2 Hz, *J* = 8.0 Hz), 7.40–7.38 (m, 1H), 4.20 (q, 2H, *J* = 7.2 Hz), 4.06 (t, 2H, *J* = 6.4 Hz), 1.66 (m, 2H), 1.37 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz), 0.89 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 173.99, 167.82, 152.80, 151.79, 144.95, 138.19, 133.75, 129.44, 129.08, 128.72, 128.01, 127.20, 105.54, 67.69, 58.47, 30.62, 18.91, 14.85, 13.71; IR (KBr, cm^{-1}: 3417, 2958, 2926, 2871, 1698, 1614,1581, 1501, 1444, 1384, 1185; HRMS(ESI): Calcd. for $C_{22}H_{23}NO_4$: 365.1627; Found: 366.1709 (M+H^+), 388.1724 (M+Na^+); **5c**: yellow solid; yield: 75%; melting point: 244–245 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.47 (s, 1H), 8.51 (d, 1H, *J* = 4.8 Hz), 7.67 (s, 1H), 7.56 (d, 2H, *J* = 8.0 Hz), 7.55 (s, 1H), 7.47 (t, 2H, *J* = 6.8 Hz, *J* = 7.2 Hz), 7.42–7.40 (m, 1H), 4.22 (q, 2H, *J* = 7.2 Hz), 4.07 (t, 2H, *J* = 6.4 Hz), 1.68 (m, 2H), 1.37 (m, 2H), 1.28 (m, 7H), 0.84 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 173.99, 167.82, 152.83, 151.79, 145.01, 138.22, 133.70, 129.49, 129.11, 128.96, 127.97, 127.17, 105.52, 67.96, 58.43, 30.84, 28.88, 25.33, 22.12, 14.86, 13.91; IR (KBr, cm^{-1}): 3422, 2930, 2861, 1697, 1614, 1580, 1502, 1465, 1444, 1383, 1186, 720; HRMS(ESI): Calcd. for $C_{24}H_{27}NO_4$: 393.1940; Found: 394.2016 (M+H^+), 416.1632 (M+Na^+); **5d**: white solid; yield: 78%; melting point: 236–238 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.25 (d, 1H, *J* = 6.4 Hz), 8.51 (d, 1H, *J* = 7.2 Hz), 7.65 (s, 1H), 7.54 (d, 2H, *J* = 8.0 Hz), 7.56 (s, 1H), 7.45–7.41 (m, 3H), 4.20 (q, 2H, *J* = 7.2 Hz), 4.06 (t, 2H, *J* = 6.4 Hz), 1.67 (m, 2H), 1.35 (m, 2H), 1.26 (m, 11H), 0.84 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 174.03, 167.88, 152.68, 151.83, 145.03, 138.24, 133.78, 129.51, 129.14, 128.97, 128.02, 127.23, 105.57, 68.01, 58.52, 31.27, 28.75, 25.71, 22.21, 14.71, 14.09; IR (KBr, cm^{-1}): 3424, 2960, 2945, 2855, 1698, 1614, 1581, 1502, 1467, 1444, 1384, 1186, 724; HRMS(ESI): Calcd. for $C_{26}H_{31}NO_4$: 421.2253; Found: 422.2290 (M+H^+), 444.2105 (M+Na^+); **5e**: white solid; yield: 75%; melting point: 237–239 °C; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 12.27 (d, 1H, *J* = 6.4 Hz), 8.53 (d, 1H, *J* = 6.8 Hz), 7.67 (s, 1H), 7.57 (d, 2H, *J* = 8.0 Hz), 7.56 (s, 1H), 7.49 (t, 2H, *J* = 6.8 Hz, *J* = 6.8 Hz), 7.42–7.40 (m, 1H), 4.22 (q, 2H, *J* = 7.2 Hz), 4.07 (t, 2H, *J* = 6.4 Hz), 1.66 (m, 2H), 1.32 (m, 2H), 1.26 (m, 15H), 0.86 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (400 MHz, DMSO-*d6*): δ 173.84, 167.83, 152.86, 151.54, 145.07, 138.28, 133.86, 129.49, 129.12, 128.74, 128.08, 127.17, 105.86, 63.86, 58.44, 31.33, 29.10, 28.68, 25.75, 22.12, 18.48, 14.88, 14.01; IR (KBr, cm^{-1}): 3434, 2957, 2925, 2854, 1700, 1614, 1581, 1502, 1467, 1444, 1383, 1186, 725; HRMS(ESI): Calcd. for $C_{28}H_{35}NO_4$: 449.2566; Found: 450.2599 (M+H^+), 472.2419 (M+Na^+). The data left were conserved by the editorial department of Chinese Chemical letters.