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ORIGINAL ARTICLE

Novel thiosemicarbazones derivatives bearing aromatic iodine moiety: Design, synthesis and anti-malarial activity

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Abstract A series of thiosemicarbazones of aromatic iodide derivatives were designed and synthesized. The structures of all the newly synthesized compounds had been identified by elemental analysis, ^{1}H NMR and ^{13}C NMR. Their biological activities were evaluated against *Plasmodium falciparum*. Among these compounds, at concentrations of 3, 9 and 27 mg/kg of mouse per day, **4e** inhibited the growth of the malaria parasite *in vivo* test in mice with the respective percentages: 88.1%, 90.7% and 92.6%. The present work suggest that thiosemicarbazones of aromatic iodide may become a lead compound for anti-malaria medicine.

1. Introduction

Malaria is one of the most significant infectious diseases in the world. It is endemic through the entire tropical region of the Earth, except for high mountain areas, deserts and a few islands (Cox-singh et al., 2008; Guinovart et al., 2006; Plowe, 2005; Newman et al., 2004; Leder et al., 2006). Chloroquine has been the most effective and widely used drug in malaria therapy. Therefore, great hopes have been placed on development of agents, which can reverse resistance to chloroquine (Uhlemann and Krishna, 2005; Nogueira et al., 2010). Recently there were a lot of studies using iron-chelating agents as a possible treatment for malaria (Cabantchik, 1994; Kontoghiorghes et al., 2010). Thiosemicarbazones are known iron-chelating agents by bonding through the sulfur and azomethine nitrogen atoms (Walcourt et al., 2004). Their activity against extracellular protozoan such as *Plasmodiumfalciparum, Trichomonas vaginalis, Trypanosoma cruzi,* and other parasites were demonstrated by several works (Greenbaum et al., 2004; Bharti et al., 2002).

On the other hand, iodine is a trace mineral required for human life. Iodine is important in the developing of the fetus, particularly in the brain. It helps the functioning of the heart, pancreas, liver, kidneys, muscles, and brain. Iodine promotes general growth and development of the body as well as metabolism of nutrients (Azuolas and Caple, 1984; Lamard and Tressol, 1989; Boyages, 1993). The replacement of chlorine atom by iodine atom led to compounds with a less toxicity and better biology activity. These prompted us to explore the biological activities of thiosemicarbazone analogs of aromatic iodide. In this context, we report the preparation of new thio-

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semicarbazones of aromatic iodide analog. These compounds were tested *in vivo* for their ability to inhibit the growth of malaria parasite.

2. Experimental

2.1. Material and reagents

All the reagents and solvents were of the commercial quality and were used without purification. Elemental analysis was performed on a PE-2400 elemental analyzer, the C, H and N analysis were repeated twice. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AM-400 spectrometer with chemical shifts reported as ppm (in DMSO-d_6, TMS as internal standard). Melting points were determined by an X-6 micro-melting point apparatus and were uncorrected.

*2.2. General procedure for the preparation of 4-(p-iodophenyl)-3-thiosemicarbazone derivatives (**4a**–**4e**)*

The synthetic routes of the target compounds **4a**–**4e** were shown in Scheme 1. In a typical procedure (Hodgkins and Reeves, 1964). Aromatic iodine 1 (21.9 g, 0.1 mol) was dissolved in the minimum amount of benzene and treated with 7.0 mL of carbon disulfide and 16 mL of triethylamine in ice bath, then the solution filtered to get the solid, which was then dissolved in 90 mL of chloroform. A mixture of 15 mL of triethylamine and 10.2 mL of ethyl chlorocarbonate was added dropwise, followed by stirring for 1 h. The chloroform solution was washed with 3 mol L^{-1} HCl and water, respectively, and dried over sodium sulfate, then evaporated in vacuum to dryness to get crude solid, which on recrystallization with ethanol gave **2**. Compound **2** (26.1 g, 0.1 mol) was dissolved in minimum amount of ethanol, and then was dropped to hydrazine hydrate (24 g, 0.4 mol) at ambient temperature. A white solid was separated, which was washed and dried to give **3**. Equimolar quantities of thiosemicarbazones **3** and difference aldehydes were mixed in boiling ethanol for about 1–2 h, then solution was concentrated, the solid was filtered and recrystallized with ethanol and dried to give **4a**–**4e**.

All the target compounds were pale yellow solid and stable at room temperature, insoluble in water and readily soluble in DMF and DMSO.

*2.2.1. Salicylaldehyde, 4-(p-iodophenyl)-3-thiosemicarbazone (**4a**)*

Yield 87%, m.p. 191–192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.71 (s, 1H, NH), 9.97 (s, 1H, NH), 9.91 (s, 1H, OH), 8.07 (s, 1H, CH=N), 7.73–6.80 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.24, 140.18, 139.19, 134.62, 133.95, 126.41, 124.70, 113.63, 112.27, 109.28, 105.78, 103.44, 103.27, 90.29; Anal. calcd for $C_{14}H_{12}IN_3OS$ (397.2): C 42.33, H 3.04, N 10.58; found C 42.56, H 3.04, N 10.68.

*2.2.2. Salicylaldehyde, 4-(p-iodophenyl)-3-thiosemicarbazone (**4b**)*

Yield 90%, m.p. 202–203 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.63 (s, 1H, NH), 9.91 (s, 1H, NH), 8.04 (s, 1H, CH=N), 7.68–6.73 (m, 8H, Ar-H), 2.97 (s, 6H, N(CH_3)$_2$); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.20, 149.21, 147.83, 142.89, 138.89, 137.77, 128.82, 126.18, 123.52, 123.49, 117.35, 112.30, 89.37, 40.94; Anal. calcd for $C_{16}H_{17}IN_4S$ (424.3): C 45.29, H 4.04, N 13.20; found C 45.34, H 4.14, N 13.18.

*2.2.3. Salicylaldehyde, 4-(p-iodophenyl)-3-thiosemicarbazone (**4c**)*

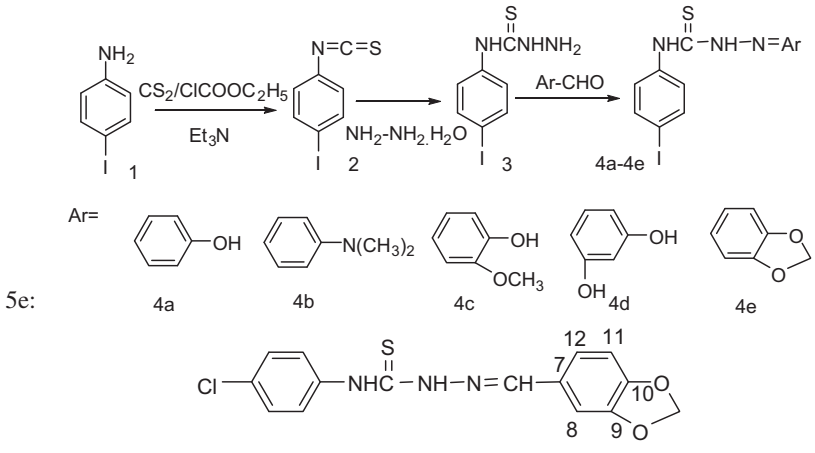
Yield 82%, m.p. 195–196 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.73 (s, 1H, NH), 9.97 (s, 1H, NH), 9.51 (s, 1H, OH),8.06 (s, 1H, CH=N), 7.71–6.80 (m, 8H, Ar-H), 3.83 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.18, 149.10, 147.94, 143.88, 139.04, 136.66, 127.81, 125.16, 122.50, 122.48, 115.33, 110.29, 89.64, 55.83; Anal. calcd for $C_{15}H_{14}IN_3O_2S$ (427.2): C 42.17, H 3.30, N 9.83; found C 42.10, H 3.37, N 9.96.

*2.2.4. Salicylaldehyde, 4-(p-iodophenyl)-3-thiosemicarbazone (**4d**)*

Yield 88%, m.p. 175–176 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.63 (s, 1H, NH), 10.17 (s, 1H, NH), 9.94 (s, 1H, OH), 9.83 (s, 1H, OH), 8.36 (s, 1H, CH=N), 7.85–6.39 (m, 8H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 168.04, 139.16, 137.09, 136.60, 132.90, 127.40, 125.69, 111.62, 110.26, 108.18, 107.75, 102.44, 102.24, 89.29; Anal. calcd for $C_{14}H_{12}IN_3O_2S$ (413.2): C 40.69, H 2.93, N 10.17; found C 41.00, H 3.08, N 9.98.

*2.2.5. Salicylaldehyde, 4-(p-iodophenyl)-3-thiosemicarbazone (**4e**)*

Yield 85%, m.p. 201–202 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 11.78 (s, 1H, NH), 10.07 (s, 1H, NH), 8.06 (s, 1H, CH=N),



Scheme 1 The synthetic routes of the target compounds.

7.81–6.94 (m, 7H, Ar-H); 6.08 (s, 2H, OCH_2O); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 175.50, 149.09, 148.02, 138.98,138.81, 136.63, 135.14, 128.41, 128.03, 127.32, 124.36, 108.13, 105.58, 101.45, 89.80; Anal. calcd for $C_{15}H_{12}IN_3O_2S$ (425.2): C 42.37, H 2.84, N 9.88; found C 42.13, H 2.74, N 9.91.

2.3. In vivo in mice anti-malarial study

The biology activities of the target compounds were evaluated against malaria parasite according with the standard test procedures (WHO standard).

3. Results and discussion

3.1. Synthesis of 4-(*p*-iodophenyl)-3-thiosemicarbazone derivatives and characterization

Firstly, aromatic iodine **1** was treated with carbon disulfide and chloroform to obtain isothiocyanate **2**, and coupling reactions with hydrazine hydrate to give thiosemicarbazones **3**. Then the title compounds **4a**–**4e** were successfully obtained using difference aldehydes as reagent. Compounds **4a**–**4e** were characterized by ^1H NMR, ^{13}C NMR and elemental analysis. All results are in full agreement with the proposed structures. For example, the singlet signal at 8.06 ppm (CH=N) and the signal at 6.08 ppm (OCH_2O) of ^1H NMR spectra suggest that compound **4e** is consistent with its structure. The results of elemental analyses are in good agreement with those calculated for the suggested formula. The melting points are sharp indicating the purity of these compounds.

3.2. Anti-malarial activity

The biology activities of the target compounds were evaluated against malaria according to the standard bioactivity test procedures (WHO standard). The results were summarized in Table 1. From Table 1, we could find that these compounds showed significant anti-malarial activities in the four-day suppressive *in vivo* test in mice. At concentrations of 3, 9 and 27 mg/kg of mouse per day, in contrast, compound **4e** produced the highest activity against malaria. For anti-malarial activity, structural variation between compounds **4a** and **4b** results in remarkably different activity. The only structural differences between **4a** and **4b** are the types of substituents at C-10. Compound **4a** contain hydroxyl group moiety at C-10, while **4b** has a $N(CH_3)_2$ group moiety at C-10. This hydroxyl group appears to be particularly responsible for anti-malarial activity. Compounds **4a**, 4c and **4d**, which contain hydroxyl group moiety at C-10, while 5 has 1,3-dioxolane ring on C-9/C-10 seemed to be much more effective in terms of anti-malarial activity. Furthermore, Compound **4e** inhibited the growth of the malaria parasite with the respective percentages: 88.1%, 90.7% and 92.6%. The corresponding values for **5e** at the same concentrations were 58.0%, 74.8% and 77.0%, respectively. It was worth noting that the thiosemicarbazones of aromatic iodide analog showed improved biology activities to some extent over aromatic chloride counterparts against malaria, which might be contributed by the introduction of iodine atom in benzene.

Table 1 The inhibition percentage of the target compounds against *Plasmodium falciparum*.

Compound	Concentrations (mg/kg)	Percentages of suppression of *Plasmodium falciparum*
4-(*p*-Iodophenyl)-3-thiosemicarbazone (**4a**)	3	60.2
	9	78.2
	27	80.0
4-(*p*-Iodophenyl)-3-thiosemicarbazone (**4b**)	3	54.3
	9	60.2
	27	65.3
4-(*p*-Iodophenyl)-3-thiosemicarbazone (**4c**)	3	62.3
	9	79.1
	27	80.2
4-(*p*-Iodophenyl)-3-thiosemicarbazone (**4d**)	3	64.3
	9	80.4
	27	82.1
4-(*p*-Iodophenyl)-3-thiosemicarbazone (**4e**)	3	88.1
	9	90.7
	27	92.6
4-(*p*-Chlorophenyl)-3-thiosemicarbazone (**5e**)	3	58.0
	9	74.8
	27	77.0

Chloroquine (3 mg/kg of mouse, positive control) had a suppressive activity of 100%.

4. Conclusions

In summary, various types of thiosemicarbazones of aromatic iodide were synthesized and their varying biology activities towards the malaria was demonstrated. The present work suggest that thiosemicarbazones of aromatic iodide may become a lead compound for anti-malaria medicine. Further structure–biology activity relationships about the designed compounds were under the way.

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