Synthesis and trypanocidal activity of salicylhydrazones and p-tosylhydrazones of S-(-)-carvone and arylketones on African trypanosomiasis

Bienvenu GLINMA 1.2.4, Fernand A. GBAGUIDI 1.2.3*, Urbain C. KASSEHIN 3, Salomé D.S. KPOVIESSI 1, Alban HOUNGBEME 2, Horhhus D. HOUNGUE 3, Georges C. ACCROMBESSI 1 and Jacques H. POUPAERT 3

1Laboratoire de Chimie Organique Physique et de Synthèse, Département de Chimie, Faculté des Sciences et Techniques, Université d’Abomey-Calavi, 01 BP 4521 Cotonou, République Bénin. 2Laboratoire de Pharmacognosie/Institut de Recherche et d’Expérimentation en Médecine et Pharmacopée Traditionnelles (IREMPT) / Centre Béninois de la Recherche Scientifique et Technique (CBRST)/ UAC, 01 BP 4521 Cotonou, République Bénin. 3Louvain Drug Research Institute (LDRI), School of Pharmacy, Université Catholique de Louvain, B1 7203 Avenue Emmanuel Mounier 72, B-1200 Brussels, Belgique.

ABSTRACT

Hydrazones are nowadays considered to be good candidates for various pharmaceutical applications. Here, we have synthesized two series of hydrazones: salicylhydrazones (GS1-4) and p-tosylhydrazones (GT1-4) from S-(-)-carvone and three arylketones with good yields (57-91%). Molecules were characterized by elemental analyses; TLC, NMR H, NMR 13C and MS. Submitted, in vitro, to their antiparasitic testing on Trypanosoma brucei brucei, and toxicity on Artemia salina Leach, all compounds except GT2 showed significant antitrypanosomal activity IC50 ranging from 1 to 34 micromolar (µM). Among them, 2-acetynaphthalene salicylhydrazide (GT3, IC50 = 1.97 ± 0.42 µM) exhibited good trypanocidal activity and the other are moderates on parasite; when the compounds GS1, GT3 and GT4 presented toxic activity on larvae. In agreement to their selectivity index, which is greater than 1 (SI > 1), products turn out quite selective on the parasite: a series of salicylhydrazones revealed more selective (SI ≥ 11), especially GT4 (SI = 157) than the series of p-tosylhydrazones showed 1 ≤ SI ≤ 22. The synthesized compounds clearly displayed significant selective pharmaceutical activities on the parasite tested. Compounds developing could open promising route to news drug-candidates.

INTRODUCTION

Hydrazides and hydrazones are nowadays an important class of biologically active compounds (Ali et al., 2012; Narasimhan et al., 2010). They exhibit a wide range of interesting pharmaceutical derivatives and are also important intermediates in organic synthesis (Rollas et al., 2007). In addition, these compounds have shown anti-cancer properties (Wandakhan et al., 2013; El-Sabagh and Rady, 2009; Zhang et al., 2004), anti-HIV (Vicini et al., 2009) and are potential inhibitors for many enzymes (Xu et al., 2008; Hassanien et al., 2008; Singh et Kumar, 2006), DNA synthesis and cell growth (Sreeja et al., 2004) and therefore they acquired an important place in medicinal chemistry.

Some hydrazide-hydrazones derivatives have been commercialized: the nifurtimox is used for the treatment of Chagas’ disease (Melnyk et al., 2006) and nifuroxazide (D) as intestinal antiseptic (Küçükgözü et al., 2003). Hydrazones can act as polydentate ligands, depending on the nature of the substituent attached to the hydrazone unit. We also note that their complexing properties give them the opportunity to be interesting candidates for drugs based on transition metals.

In general, the ligands act synergistically with metals for their biological activity (Badiger et al., 2012). Hydrazides-hydrazones are also used as analytical reagents, a polymer coating of ink, pigments and fluorescent materials (El-Tabl et al., 2008).
These molecules are known possessing several interesting biological properties, among others, antibacterial (Özkay et al., 2010; Bedia et al., 2006), anti-convulsant (Kaushik et al., 2010), antitrypanosomal (Troberg et al., 2000), anti-fungal (Cui et al., 2011, Loncle et al., 2004), antipyretic (Cocco et al., 2006), malaria (Xia et al., 2008).

Based on higher bio-activity, the biological importance of the hydrazone group and its derivatives, it appears important to design, synthesize new derivatives with the pharmacophore hydrazone group and evaluate their pharmacological activities.

In this study we have synthesized two derivatives of hydrazones: the salicylhydrazones (series GS) and the p-tolylhydrazones (series GT) respectively with S-(-)-carvone (GS1, GT1), 4’-methylaceto phenone (GS2, GT2), 7-methoxy-1-tetralone (GS3, GT3) and 2-acetyl naphthalene (GS4, GT4) and then evaluate their parasitic activity on Trypanosoma brucei brucei. The selectivity of each compound was also determined.

MATERIALS AND METHODS

Equipment

All synthesized compounds were characterized by Nuclear Magnetic Resonance spectra using Bruker Avance 400 UltraShield with dimethylsulfoxide (DMSO)-d_{6} or chloroform DCD_{3} and then Mass Spectrophotometer spectra obtained using the method of Atmospheric-pressure chemical ionization and mass is given in m/z of [MH]+.

The frequencies for \(^1{H}\) and \(^{13}{C}\) are 400.130 and 100.612 MHz respectively. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane as internal standard. Multiplicity was designated as singlet (s), doublet, double double (dd) triplet (t), quintuplet (q) and multiplet (m). Melting points (m.p.) were determined on a fusionometer of the type electrothermal 1A 9000 and were not corrected.

Reagents

All reagents were obtained from chemical societies: Sigma-Aldrich, Acros Organic, Janssen Chimica, Prolabo and Riedel-de Haen. Substrates, reagents, catalysts and solvents were used directly for syntheses without any further purification. There are: S-(-)-carvone, 4’-methylaceto phenone, 7-methoxy-1-tetralone, 2-acetyl naphthalene; glacial acetic acid (AA{G}), Technical ethanol (EtOH), tetrahydrofuran (THF); salicyl hydrazine and the para-toluencesulfonylhydrazide (p-tolylhydrazide) is prepared from the hydrazine monohydrate with the p-toluencesulfonyl chloride following the method described in the previous literature (Goldman et al., 1960).

Chemistry

General methods of synthesis

p-tolylhydrazide (p-toluencesulfonylhydrazide)

Into a 1 L round-bottomed three-necked flask fitted with a thermometer, a mechanical stirrer, and a dropping funnel are placed 200 g (1.05 moles) of p-toluencesulfonyl chloride and 350 mL of tetrahydrofuran. The stirred mixture is cooled in an ice bath to 10–15°C; then a solution of hydrazine in water (135 mL of 85% hydrazine hydrate, 2.22 moles) is added at such a rate that the temperature is maintained between 10° and 20°C. Stirring is continued for 15 minutes after the addition is complete. The reaction mixture is transferred to a separatory funnel. The lower layer is drawn off, and discarded. The upper tetrahydrofuran layer is filtered by suction through a bed of Celite to remove suspended particles and foreign matter (if any). The Celite is washed with a little tetrahydrofuran to remove any absorbed tosylhydrazide. The clear, colorless filtrates are stirred vigorously during the slow addition of two volumes of distilled water. p-toluencesulfonylhydrazide separates as fluffy white crystalline needles. The product is filtered through a Büchner funnel; washed several times with distilled water, and air-dried.

p-tolylhydrazones

In a 100 mL flask, we prepare a solution of 0.01 mole of ketone in 10-40 mL of ethanol and 2 mL of glacial acetic acid (GAA) and then we add gradually a solution of p-tolylhydrazide (1.76 g) dissolved in 10 mL ethanol. The mixture is maintained at reflux for 2 hours and the reaction is followed by Thin Layer Chromatography TLC (Hex / AcOEt: 8/2 or 7/3). The crystals formed are filtered, washed with distilled water and dried before being recrystallized with ethanol.

Salicylhydrazones

We prepare in a 100 mL flask a salicylhydrazine solution (1.52 g in 10 mL of ethanol) that we gradually add to a solution of ketone (0.01 mole) dissolved in 10-40 mL of ethanol and 2 mL of glacial acetic acid. The mixture is brought to reflux for 2 hours and the reaction is followed by TLC (Hex / AcOEt: 8/2 or 7/3). After cooling, the precipitate is filtered off, washed with distilled water and dried and then is recrystallized from technical ethanol.

The reactions are followed in Thin Layer chromatography (TLC), the product is dissolved in chloroform and the eluent is composed of a mixture of hexane / ethyl acetate (Hex / EtOAc v/v: 7/3; 8/2).

All compounds after synthesis have been submitted to the in vitro anti-trypanosomal testing activity on the bloodstream form of the strain 427 of Trypanosoma brucei brucei and were evaluated for their in vitro cytotoxicity on Artemia salina Leach following standard biological methods.

Pharmacology

Anti-trypanosomal test

The assessment is performed on the bloodstream form of the strain 427 of T. b. brucei by the «LILIT Alamar Blue™» method (Baltz et al., 1985 ; Rüz et al., 1997). The stock solutions of each hydrazone have been prepared from an initial concentration of 10 mg/mL in dimethylsulfoxide (DMSO). The trypanosomes are grown in a medium containing 10% of heat-inactivated fetal calf serum and bloodstream form supporting factor. The trypanosome suspensions were adjusted to 5x10^{4} tryp/mL. In each well, 50 μL of different dilutions of the stock...
solution were added to 50 μL of suspension of trypanosomes. The plates were then incubated at 37°C for 72 hours in an atmosphere with 5% CO₂. 10 μL of dye "Alamar Blue™" is added to each well and then incubated for 4 hours. The dye "Alamar Blue™" is a reagent for detecting enzymatic activity. The wells in which the concentration of compound is insufficient to inhibit the proliferation of trypanosomes are stained. The half-inhibitory concentration is the concentration of unstained wells in which there is the lowest amount of hydrazones. The plate reading is made in comparison with control wells on a fluorescence plate reader using an excitation wavelength of 530 nm and an emission wavelength 590 nm. We carried out the test in triplicate for each compound. All data were expressed as means ± standard deviation of triplicate measurements.

**Cytotoxicity screen**

The cytotoxicity test was performed on larvae of brine shrimp (*Artemia salina* Leach) by the method of Sleet and Brendel (1983). *A. salina* eggs were incubated in seawater until hatching of young larvae (48 hours). Then, series of solutions of test compound at varying concentrations were prepared in DMSO/seawater. A defined number of larvae were introduced into each solution and incubated under rocking condition for 24 h. To evaluate the toxicity of the solution, counting of larvae viability was performed under microscope by determining the number of dead larvae in each solution. In the case where there was death in the control medium, the data was corrected by Abbott’s formula: % death = [(nd test - nd control)/ nd control] × 100 (Abbott, 1925). nd : number of dead larvae.

Data (dose-response) were transformed by logarithm and the half-lethal concentration LC₅₀ was determined by linear regression (Hafner et al., 1977). Tests were carried out in triplicates. All data were expressed as mean ± standard deviation of triplicate measurements.

**RESULTS AND DISCUSSION**

We have synthesized two series of derivatives hydrazones in goods yields (57-91%). There are: S- (+)-carvone salicylhydrazone (GS1), 4'-methylacetophenone salicylhydrazone (GS2), 7-methoxy-1-tetralone salicylhydrazone (GS3) and 2-acetanaphthene salicylhydrazone (GS4); S- (+)-carvone p-tosylhydrazone (GT1), 4'-methylacetophenone p-tosylhydrazone (GT2), 7-methoxy-1-tetralone p-tosylhydrazone (GT3) and 2-acetanaphthene p-tosylhydrazone (GT4).

The hydrazine or hydrazide having the same radical H₂N—NH—R reacts with a carbonyl compound according to the same mechanism. Steric and electronic effects of the various substituents of the carbonyl are responsible for the difference in reactivity and yields when the same hydrazine derivative is reacted with various substrates and vice versa.

In the literature, it was described in 1976 the synthesis of acetophenone p-tosylhydrazone without catalyst for 5.5 hours with 68% yield (Ashraf, 1976); the synthesis using benzaldehyde salicylic acid hydrazide and 4-dimethylaminobenzaldehyde or 4-nitrobenzaldehyde for 4 hours (Al-Ajrawy, 2011). To enhance the reaction, we used during our work in the synthesis of the salicylhydrazones (GSn) and p-tosylhydrazones (GTn) the glacial acetic acid and technical ethanol. The mixture is heated to reflux for 2 hours and the reaction followed by TLC with yields ranging from 57 to 90%. The low yield 57% obtained of S- (+)-carvone p-tosylhydrazone (GT1) is due to the nature of this α-β unsaturated ketone. We note well the presence of adduct 1-4 minority (Michael addition) which was removed after purification.

The scaffold has advantageous properties: low molecular weight, reasonable Clog P, good hydrogen bond donating and accepting capabilities (table 1), easy, and economical synthetic routes (Lipinski et al., 1997).

The structures of synthesized compounds were characterized with the TLC frontal rapport (Rₜ) and spectrometrical analysis MS, especially with NMR ¹H & ¹³C.

![Fig. 1: S- (+)-carvone salicylhydrazone (GS1).](image-url)

**Characterization of synthesized compounds**

*S- (+)-carvone salicylhydrazone (GS1) (Figure 1)*

Yield : 78% ; m.p. : 189-190°C; Rₜ (Hex/AcOEt, v/v, 7/3) : 0.57 ; NMR ¹H (DMSO-d₆, δ in ppm) : 161.78 (N-CO-Ar); 147.53 (C=N); 156.36 (C=OH phenolic); 133.87, 130.45, 119.59, 117.95, 116.77 (other C-Ar); 153.99, 133.16, 132.28, 110.32, 40.10, 29.57, 24.95, 20.44, 17.85 (C-carbone). NMR ¹H (DMSO-d₆, δ in ppm) : 11.75 (s, 1H, OH); 11.20 (s, 1H, NH); 7.97-6.95 (m, 4H, H-Ar); 6.25 (t, 1H, C=CH–); 4.84 (d, 2H, C=CH₃); 2.75 (q, 1H, CH₂-CH₃); 2.45 (t, 2H, C=CH₂-CH₂); 2.25 (d, 2H, HC-CH₂-C=N); 1.90 (s, 3H, CH₃); 1.78 (s, 3H, CH₃).

MS m/z [MH]+ found : 285.37 ; [M]theoretical : 284.35 ; Molecular formula : C₁₇H₂₀N₂O₂

<table>
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<td>4.790</td>
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</table>

![Table 1 : Properties Compatible with Reasonable Pharmacokinetics and Drug Availability, Rules of Lipinski et al., (1997) applied to hydrazones.](image-url)
4'-methylacetophenone salicylhydrazone (GS2) (Figure 2)

Yield: 79%; m.p.: 237-238°C; Rf (Hex/AcOEt, v/v, 7/3): 0.63; NMR 13C (DMSO-d6, δ in ppm): 163.14 (N-CO-Ar); 153.51 (C=N); 157.67 (C–OH phenolic); 140.18, 136.27, 134.47, 131.69, 130.12, 127.52, 120.82, 119.02, 118.01 (other C-Ar); 21.99 (H,C-Ar); 14.93 (CH3).

NMR 1H (DMSO-d6, δ in ppm): 11.80 (s, 1H, OH); 11.30 (s, 1H, NH); 8.00-6.97 (m, 8H, H-Ar); 2.45 (s, 3H, H3-C-Ar), 2.31 (s, 3H, CH3).

MS m/z [MH]+ found: 269.27; [M]theoretical: 268.31

Molecular formula: C10H10N2O2

Fig. 2: 4'-methylacetophenone salicylhydrazone (GS2)

7-methoxy-1-tetralone salicylhydrazone (GS3) (Figure 3)

Yield: 85%; m.p.: 223-224°C; Rf (Hex/AcOEt, v/v, 7/3): 0.47; NMR 13C (DMSO-d6, δ in ppm): 161.82 (N-CO-Ar); 151.75 (C=N); 157.64 (C–OH phenolic); 156.42 (Cα-OCH3); 133.31, 133.04, 132.56, 130.57, 129.62, 119.69, 117.90, 116.83, 116.35, 108.18 (other C-Ar); 55.10 (O-CH3); 27.92, 25.55, 21.53 (3s, 6H, 3"-CH2-3").

NMR 1H (DMSO-d6, δ in ppm): 11.80 (s, 1H, OH); 11.33 (s, 1H, NH); 8.00-6.90 (m, 7H, H-Ar); 3.80 (s, 3H, O-CH3); 3.35, 2.69, 1.89 (s, 6H, 3CH3).

MS m/z [MH]+found: 311.33; [M]theoretical: 310.34

Molecular formula: C19H16N2O3

Fig. 3: 7-methoxy-1-tetralone salicylhydrazone (GS3)

2-acetynaphthalene salicylhydrazone (GS4) (Figure 4)

Yield: 91%; m.p.: 241-242°C; Rf (Hex/AcOEt, v/v, 7/3): 0.33; NMR 13C (DMSO-d6, δ in ppm): 162.01 (N-CO-Ar); 151.83 (C=N); 156.47 (C–OH phenolic); 135.26, 133.39, 133.28, 133.05, 132.74, 130.66, 128.54, 127.73, 127.48, 126.89, 123.63, 119.72, 117.92, 116.87 (other C-Ar); 13.60 (CH3).

NMR 1H (DMSO-d6, δ in ppm): 11.80 (s, 1H, OH); 11.42 (s, 1H, NH); 8.36-7.05 (m, 11H, H-Ar); 2.33 (s, 3H, CH3).

MS m/z [MH]+found: 305.32; [M]theoretical: 304.34

Molecular formula: C19H16N2O2

Fig. 4: 2-acetynaphthalene salicylhydrazone (GS4)

S-(-)-carvone p-tosylhydrazone (GT1) (Figure 5)

Yield: 57%; m.p.: 167-168°C; Rf (Hex/AcOEt, v/v, 8/2): 0.46; NMR 13C (CDCl3, δ in ppm): 154.80 (C=N); 144.02, 132.46, 129.38, 128.26 (C-Ar); 147.11, 135.17, 133.59, 110.40, 40.36, 29.96, 29.09, 21.64, 17.65 (C-carvone); 20.65 (H,C-Ar).

NMR 1H (CDCl3, δ in ppm): 7.90 (s, 1H, NH); 7.65 & 7.30 (2s, 4H, H-Ar); 6.05 (t, 1H, C=CH–); 4.75 (dd, 2H, C=CH2); 2.60 (m, 1H, CH2–CH2); 2.45 (t, 2H, C=CH–CH2); 2.25 (d, 2H, HC=CH2–C=N); 1.95 (m, 3H, CH3); 1.77 (s, 3H, CH3); 1.70 (s, 3H, CH3).

MS m/z [MH]+found: 319.33; [M]theoretical: 318.43

Molecular formula: C17H22N2O5S

Fig. 5: S-(-)-carvone p-tosylhydrazone (GT1)

4'-methylacetophenone p-tosylhydrazone (GT2) (Figure 6)

Yield: 81%; m.p.: 190-191°C; Rf (Hex/AcOEt, v/v, 7/3): 0.51; NMR 13C (DMSO-d6, δ in ppm): 153.17 (C=N); 143.26, 138.98, 136.21, 134.62, 129.40, 128.90, 127.57, 125.86 (C-Ar); 20.97, 20.75 (H,C-Ar); 14.17 (CH3).

NMR 1H (DMSO-d6, δ in ppm): 10.45 (s, 1H, NH); 7.82-7.15 (m, 8H, H-Ar); 2.37 (s, 3H, H3-C-Ar); 2.30 (s, 3H, H3-C-Ar); 2.17 (s, 3H, CH3).

MS m/z [MH]+found: 303.37; [M]theoretical: 302.39

Molecular formula: C16H15N2O3S
In this series of compounds, $^{13}$C NMR spectral analyses presented the group C=N characteristic of the formation of products between 154 and 152 ppm. Aromatic carbons are in the region 144-108 ppm, depending on the structure of the test compound. We remark in $^1$H NMR, the single proton of the internal nitrogen NH is in the form of a singlet at 10.45 ppm for the 4'-methylacetophenone p-tosylhydrazone (GT2) in DMSO-d$_6$ and 8.10 ppm (GT3 & GT4) and 7.90 ppm (GT1) ppm in CDCl$_3$. This difference is due to the effect of DMSO solvent which generates a strong hydrogen bond between oxygen and the NH proton (Silverstein et al., 2007) causing a chemical shift of hydrogen downfield. Aromatic protons are observed as bedding from 7.93 to 6.84 ppm. The molar mass of each synthesized molecule given by mass spectrometry is consistent with theoretical mass found. Various spectrometrical analyses done on each compound have really confirmed the presence of functional groups and different types of protons and carbons in each structure. The spectrometric data are in conformity with the structures suggested for the products.

**Pharmacology**

Anti-parasitic activity of compounds was evaluated in vitro on the bloodstream form of the strain 427 of *Trypanosoma brucei brucei* and their toxicity on larvae of *Artemia salina* L. The half-inhibitory concentration (IC$_{50}$) and half-lethal concentration (LC$_{50}$) were respectively determined and expressed in micromolar (µM) to be compared with the scales of trypanocidal and toxic activities. And then, the selectivity index (SI) of each compound was calculated. The results are reported in table 2.

According to the works of Du et al., 2002 and Fujii et al., 2005 studying thiosemicarbazones, compounds that have IC$_{50}$ values below 10 µM can be considered as trypanocidal molecules, when IC$_{50}$ values are between 10 and 100 µM, they are considered as moderate antitrypanosomal. The compounds which have their IC$_{50}$ higher than 100 µM showed little or no activity.

In our work, we note that compounds 2-acetylcantharidinol salicylhydrazones GS4 and 7-methoxy-1-tetralone p-tosylhydrazone GT3 exhibited a trypanocidal activity (IC$_{50}$ = 1.97 ± 0.42 and 7.98 ± 1.65 µM respectively) when other GT2 (IC$_{50}$ > 100 µM, low activity) showed moderate trypanocidal activity (11 < IC$_{50}$ < 34 µM) (table 2).

Indeed, Du et al. found that macrophage cells are generally sensitive to concentrations above 10 µM of thiosemicarbazones.

### Table 2: Trypanocidal, toxic activity and selectivity index of synthesized hydrazones.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC$_{50}$ (µM)</th>
<th>Activity</th>
<th>LC$_{50}$ (µM)</th>
<th>Toxicity</th>
<th>Selectivity index (SI = LC$<em>{50}$ / IC$</em>{50}$)</th>
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<tbody>
<tr>
<td>GS1</td>
<td>18.42 ± 0.80</td>
<td>Moderate</td>
<td>219.44 ± 2.17</td>
<td>toxic</td>
<td>11.91</td>
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<td>GS2</td>
<td>20.53 ± 0.74</td>
<td>Moderate</td>
<td>352.57 ± 1.32</td>
<td>no toxic</td>
<td>17.17</td>
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<tr>
<td>GS3</td>
<td>11.11 ± 1.77</td>
<td>Moderate</td>
<td>731.13 ± 3.27</td>
<td>no toxic</td>
<td>65.80</td>
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<tr>
<td>GS4</td>
<td>1.97 ± 0.42</td>
<td>Trypanocidal</td>
<td>310.50 ± 1.93</td>
<td>no toxic</td>
<td>157.61</td>
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<tr>
<td>GT1</td>
<td>23.99 ± 5.11</td>
<td>Moderate</td>
<td>536.38 ± 2.35</td>
<td>no toxic</td>
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<tr>
<td>GT2</td>
<td>IC$_{50}$ &gt; 100</td>
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<td>368.06 ± 1.87</td>
<td>no toxic</td>
<td>&lt; 3.68</td>
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<tr>
<td>GT3</td>
<td>7.98 ± 1.65</td>
<td>Trypanocidal</td>
<td>137.32 ± 0.77</td>
<td>toxic</td>
<td>17.20</td>
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<tr>
<td>GT4</td>
<td>33.62 ± 7.29</td>
<td>Moderate</td>
<td>35.45 ± 1.41</td>
<td>toxic</td>
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*All compounds were selective*
Thus, in addition to inhibiting property of the parasite, they would preserve the human macrophage host cell (Du et al., 2002; Fujii et al., 2005). On this basis, hydrazones GS4 (1.97 ± 0.42 μM) and GT3 (7.98 ± 1.65 μM) were selected as good trypanocidal compounds. It remarks in this study that salicylhydrazones synthesized GS1-4, IC₅₀ ranging from 1 to 21 μM, were more trypanocidal than their analogues p-tosylhydrazones GT1-4 (IC₅₀ = 7 to > 100 μM).

The toxicity study showed that only compounds GS1, GT3 and GT4 (LC₅₀ = 219.44, 137.32 and 35.45 μM respectively) exerted a toxic activity whereas the other presented no effect (LC₅₀ > 281 μM) on larvae of Artemia salina. To assess the toxicity with the LC₅₀ values of compounds (table 2), we have referred to the LC₅₀ value of lapachol (LC₅₀ = 281 μM) which is known as reference compound (Graminha et al., 2008; Santos et al., 2003). These tests that are a summary assessment of the toxicity of products reflects the sensitivity of shrimp larvae to the synthesized compounds and by extension that of the human species. Indeed, there is a correlation between toxicity on shrimp larvae and cytotoxicity on cells 9KB and 9PS (human carcinoma nasopharygien) a part (Pelka et al., 2000), cells A549 lung carcinoma and HT-29 cells of carcinoma of the colon on the other (Carballo et al., 2002). Thus, the three toxic products would exert activity on the cells.

From the analyses of their selectivity index (1 < SI < 140), we note that all products turn out quite selective on the parasite Trypanosoma brucei brucei. These results are in perfect agreement with the work of Tiuman et al., (2005) in which if the SI value obtained is greater than unity, the test compound is considered to be selective on the parasite and if SI value is less than unity, the test compound is more cytotoxic than anti-parasitic. Especially, some of the group: the salicylhydrazones of 2-acetyl-naphthalene GS4, 7-methoxy-1-tetralone GS3 (SI = 157, 65 respectively), S- (+)-carvone p-tosylhydrazone GT1 (SI = 22) were the most selective. Based on the different tests values, it appears that the S- (+)-carvone p-tosylhydrazone GT1 and the salicylhydrazones obtained from 4’-methylicacetophenone GS2, 7-methoxy-1-tetralone GS3 and 2-acetyl-naphthalene GS4 exhibited significant trypanocidal activity without effect on Artemia salina L. and selective would be able to be used at higher doses for trypanosomiasis treatment.

CONCLUSION

In this study, eight hydrazones derivatives were synthesized and characterized. Their biological activities were evaluated and products showed interesting trypanocidal activity on the parasite studied and were selective. To our knowledge, this is the first time these molecules are synthesized and their antiparasitic evaluated on Trypanosoma brucei brucei and then they could open an interesting opportunity to the treatment of trypanosome.

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