Synthesis and antileishmanial evaluation of some 2,3-disubstituted-4(3H)-quinazolinone derivatives

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Abstract

Background: Leishmaniasis is a neglected tropical parasitic diseases affecting millions of people around the globe. Quinazolines are a group of compounds with diverse pharmacological activities. Owing to their promising antileishmanial activities, some 3-aryl-2-(substituted styryl)-4(3H)-quinazolinones were synthesized in good yields (65.2% to 86.4%).

Results: The target compounds were synthesized by using cyclization, condensation, and hydrolysis reactions. The structures of the synthesized compounds were determined using elemental microanalysis, infrared (IR), and proton nuclear magnetic resonance (¹H NMR). The in vitro antileishmanial activities of the synthesized compounds were evaluated using Leishmania donovani strain. All the synthesized compounds displayed appreciable antileishmanial activities (IC₅₀ values, 0.0128 to 3.1085 μg/ml) as compared to the standard drug miltefosine (IC₅₀ = 3.1911 μg/ml). (E)-2-(4-chlorostyryl)-3-p-tolyl-4(3H)-quinazolinone (7) is the compound with the most promising antileishmanial activities (IC₅₀ = 0.0128 μg/ml) which is approximately 4 and 250 times more active than the standard drugs amphotericin B deoxycholate (IC₅₀ = 0.0460 μg/ml) and miltefosine (IC₅₀ = 3.1911 μg/ml), respectively.

Conclusions: The results obtained from this investigation indicate that the synthesized and biologically evaluated quinazoline compounds showed promising antileishmanial activities and are good scaffolds for the synthesis of different antileishmanial agents.

Keywords: Quinazolinones; Leishmania; Antileishmanial activities

Background

Leishmaniasis is a neglected tropical disease resulting from infection of macrophages by obligate intracellular parasites of the genus Leishmania [1-3]. It is a public health problem in at least 88 countries with an estimated 350 million people at risk. The estimated global prevalence of all forms of the disease is 12 million. Every year, 1.5 to 2 million new cases and 70,000 deaths occur due to cutaneous leishmaniasis (CL). In addition, 500,000 new cases and 59,000 deaths from visceral leishmaniasis (VL) occur annually [4]. The number of cases of leishmaniasis is increasing globally due to Leishmania/HIV co-infection [5,6], international travel, and migration of immigrants and refugees from endemic regions [7,8].

The prophylactic treatment of leishmaniasis mainly rely on vector and reservoir control [9-11]. Control of reservoir host and vector is difficult due to high cost, operational difficulties, and frequent relapses in the host [12]. Although considerable effort has been made to produce vaccine candidates for the treatment of leishmaniasis, there is no vaccine against any form of human leishmaniasis yet [13-17].

Pentavalent antimonials (Sb⁵⁺) have been used for the treatment of leishmania infections. Unfortunately, in many parts of the world, the parasite has become resistant to Sb⁵⁺ [18]. Treatment failure to sodium stibogluconate (SSG) is observed in Eastern Sudan [19] and in Tigray, Northern Ethiopia [20]. Recent reports showed that pentamidine also developed resistance as well as difficulties in treating patients with Leishmania/HIV co-infection [21].

Combination chemotherapy has improved prospects for decreasing the emergence of drug resistance, increasing activity, and reducing required doses and thereby toxic side effects. In the previous study, WR 279,396 (a topical formulation containing 15% paromomycin and 0.5% gentamicin) was found to be safe and effective against CL...
caused by *Leishmania major* [22]. In addition, AmBisome-paromomycin is the most cost-effective combination among miltefosine-paromomycin and AmBisome-miltefosine [23]. So far, no combination chemotherapy has been used in treatment programs, except paromomycin/SSG [24].

Tremendous quinazoline derivatives are synthesized in the past two decades, using different synthetic pathways [25-30], due to their diverse pharmacological activities [31-36] including antileishmanial activities [37-40]. These reports indicate that several quinazolines were synthesized and tested for their antileishmanial activities, with the aim of discovering alternative chemotherapeutic agents for the development of new antileishmanials. Promising antileishmanial activities were observed in some 4-aminoquinazoline [37], indolo[2,1-b]quinazoline-6,12-dione [38], and 2,3-disubstituted-4(3H)-quinazolone derivatives [39,40]. As part of the efforts to discover less toxic and more effective drug analogues for the treatment of leishmaniasis, we synthesized some 2,3-disubstituted-4(3H)-quinazolinones and tested their *in vitro* antileishmanial activities.

**Methods**

**Chemicals and reagents**

Anthranilic acid, acetic anhydride, aniline, *p*-toluidine, *o*-toluidine, acetone, dimethylsulfoxide, anhydrous zinc chloride, *p*-chlorobenzaldehyde, *p*-nitrobenzaldehyde, *p*-hydroxybenzaldehyde, chloroform, absolute ethanol, resazurin sodium salt, anhydrous petroleum ether, distilled water, iodine, HCl, and KOH were used in the study.

**Instruments and apparatuses**

Melting points were determined in open capillaries using electro-thermal 9100 melting point apparatus and were uncorrected. Infrared (IR) spectra in nujol were recorded with the SHIMADZU 8400SP FT-IR spectrophotometer (Shimadzu Corporation, Nakagyo-ku, Kyoto, Japan), and proton nuclear magnetic resonance (1H NMR) spectral data were performed on Bruker Avance DNX400 FT-NMR spectrometer (Bruker, Billerica, MA, USA) using tetramethyl silane (TMS) as internal standard. Silica gel TLC plates of 0.25-mm thickness were used in the study.

**Experimental animals and strains**

Swiss albino male mice of weight 20 to 32 g and age 6 to 8 weeks (for acute toxicity test) were obtained from Biomedical Laboratory, Department of Biology, Faculty of Science, AAU. *Leishmania donovani* isolate used in this study was obtained from Leishmania Diagnosis and Research Laboratory (LDRL) culture bank, School of Medicine, AAU.

**Culture medium and conditions**

RPMI-1640, 10% heat-inactivated fetal calf serum (HIFCS), 1% penicillin-streptomycin, and 1% L-glutamine were supplied to make a complete culture medium. The *L. donovani* isolate was grown first on Novy-MacNeal-Nicolle (NNN) medium and then in tissue culture flasks containing RPMI-1640 medium supplemented with 10% HIFCS and 1% 100 IU penicillin/ml-100 μg/ml streptomycin solution at 22°C for promastigotes.

**Reference drugs**

Miltefosine/hexadecylphosphocholine (AG Scientific, San Diego, CA, USA) and amphotericin B deoxycholate (Fungizone®, ER Squibb, Middlesex, UK) were employed as reference drugs in the *in vitro* antileishmanial activity testing of the synthesized compounds.

**Preparation of stock and working solutions**

Stock solutions of 10 mg/ml of the synthesized compounds were prepared by dissolving each compound in DMSO. Stock solutions were diluted using complete RPMI to obtain aliquots of 10 μg/ml. Then, threefold serial dilution with complete RPMI gave the final six working concentrations (10, 3.33, 1.11, 0.37, 0.12, and 0.04 μg/ml) of each of the synthesized compounds. Amphotericin B deoxycholate and miltefosine, which were used as a positive control for comparison of the antileishmanial activities of the test compounds, were also made in threefold serial dilutions. All the prepared drugs were stored at –20°C and retrieved only during use [41].

**In vitro antileishmanial activity**

In a 96-well microtiter plate, 100 μl of each of the seven threefold serial dilutions of synthesized compounds were added in triplicate wells. Then, 100 μl of suspension of parasites (3.0 × 10^6 promastigotes/ml of *L. donovani*) was added in duplicate. Some of the wells contained only the parasites which served as a positive control. The media and DMSO alone acted as a negative control. The contents of the plates were then maintained in humidified atmosphere at 22°C under 5% CO_2_.

After 68 h of incubation, 10 μl of fluorochrome resazurin solution (12.5 mg dissolved in 100 ml of distilled water) was added into each well. The fluorescence intensity was measured after a total incubation period of 72 h using Victor3 Multilabel Counter (PerkinElmer, Waltham, MA, USA), at an excitation wavelength of 530 nm and emission wavelength of 590 nm [42]. The IC_{50} values were evaluated from sigmoidal dose-response curves using GraphPad Prism 5.0 software (GraphPad Software, Inc., San Diego, CA, USA).

**In vivo acute toxicity test**

The oral acute toxicity of compound 7 that exhibited promising antileishmanial activity was investigated using male Swiss albino mice (approximately 20 g each) following reported methods [43]. The experimental animals were
divided into six groups (containing six mice per group) and fasted overnight. Groups 1-5 received compound 7 suspended in a vehicle containing 1% gum acacia, in doses of 10, 50, 100, 200, and 300 mg/kg, respectively. The sixth group received vehicle containing 1% gum acacia (served as a control group) at a maximum dose of 1 ml/100 g of body weight by oral route. The mice were observed closely for 24 h with special attention to the first 4 h. Acute toxicity signs were checked in the test mice.

Statistical analysis
The IC50 values for in vitro promastigotes assay of synthesized compounds were evaluated from sigmoidal dose-response curves using computer software GraphPad Prism 5.0.

Results and discussion
Chemistry of the synthesized compounds
Synthesis of the target compounds involved the formation of 2-5 and 10 as intermediates. It was accomplished using nucleophilic reaction, nucleophilic with ring opening and closing, condensation reaction, and hydrolysis reactions. The target compounds are synthesized in a good yield, which ranged from 65.2% to 86.4% (Table 1). All the synthesized compounds were readily soluble in DMSO and chloroform except compound 12 which is readily soluble in acetone. Spectral data (IR and 1HN NMR) of the synthesized compounds were in full agreement with the proposed structures.

Biological activity testing results
In vitro antileishmanial activity of the synthesized compounds
The antipromastigote activities of the synthesized compounds and the standard antileishmanial drugs (amphotericin B deoxycholate and miltefosine) were evaluated using the clinical isolate of *L. donovani* strain. The IC50 of the synthesized and reference drugs were evaluated from fluorescence characteristic of AlamarBlue® (resazurin) (Trek Diagnostic Systems, Inc., Cleveland, OH, USA) which is soluble, stable in culture medium, non-toxic to cells, and does not affect the secretary abilities of cells [44]. The test works as a cell viability and proliferation indicator through the conversion of resazurin to resorufin via reduction. The amount of fluorescence produced is proportional to the number of living cells [45,46].

The quinazolinone derivatives synthesized were shown to have good antileishmanial activity which was in line with the previous reports [37-40]. All the tested compounds exhibited better antileishmanial activity than the standard drug miltefosine as shown in Table 2. Among them, compound 7 was found to have a very promising antileishmanial activity with an IC50 value of 0.0128 μg/ml which was 250 times superior than miltefosine (3.1911 μg/ml). Compounds 8 and 11 were 30 times more active than miltefosine. Compounds 6 and 12 were 10 times and twice more active than miltefosine, respectively. Compounds 9 and 13 were as active as miltefosine. All the synthesized compounds except compound 7 displayed weak antileishmanial activities as compared to amphotericin B deoxycholate. Better antipromastigote activity was observed for (E)-2-(4-chlorostyryl)-3-<i>p</i>-tolyl-4(<i>3H</i>)-quinazolinone (7) with an IC50 value of 0.0128 μg/ml which is four times higher than the standard drug amphotericin B deoxycholate with an IC50 value of 0.0128 μg/ml. (E)-2-(4-chlorostyryl)-3-<i>p</i>-tolyl-4(<i>3H</i>)-quinazolinone (7) was found to be 4 times more active than amphotericin B deoxycholate and 250 times more active than miltefosine.

Oral acute toxicity study
Compound (E)-2-(4-chlorostyryl)-3-<i>p</i>-tolyl-4(<i>3H</i>)-quinazolinone (7) was observed to be devoid of any inherent acute toxicities at a maximum dose of 300 mg/kg.

Experimental
Synthesis of target compounds
The synthesis of target compounds, 3-aryl-2-(substitutedstyryl)-4(<i>3H</i>)-quinazolinones (6-9 and 11-13), was achieved using cyclization, condensation, and hydrolysis reactions. It involved the synthesis of acetanthranil (2-methyl-3,1-benzoxazin-4-one (2)) and 3-aryl-2-methyl-4

Table 1 Physical constants and percent yield of the synthesized compounds

| Test compound | Molecular formula | Molecular weight (g/mol) | % yield | Melting point (°C) | R<sub>f</sub> values [CHCl<sub>3</sub>/C<sub>6</sub>H<sub>6</sub> (9:1)] |
|---------------|------------------|--------------------------|---------|-------------------|----------------------------------|
| 6             | C<sub>22</sub>H<sub>17</sub>CIN<sub>2</sub>O        | 360.85                    | 68.3    | 201 to 203        | 0.520                            |
| 7             | C<sub>23</sub>H<sub>19</sub>CIN<sub>2</sub>O        | 374.87                    | 65.2    | 189 to 191        | 0.577                            |
| 8             | C<sub>23</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>  | 384.41                    | 74.8    | 214 to 216        | 0.422                            |
| 9             | C<sub>23</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>  | 384.41                    | 76.2    | 235 to 237        | 0.642                            |
| 11            | C<sub>26</sub>H<sub>24</sub>N<sub>2</sub>O<sub>4</sub>  | 428.49                    | 86.4    | 151 to 153        | 0.781                            |
| 12            | C<sub>22</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>  | 342.40                    | 80.3    | 298 to 300        | 0.524                            |
| 13            | C<sub>24</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub>  | 386.45                    | 82.2    | 196 to 198        | 0.711                            |
(3H)-quinazolinones (3-5) as intermediates (Scheme 1). The details of each reaction and reaction conditions, the summarized characteristic stretching and bending IR vibration frequencies, the elemental microanalysis, and the $^1$H NMR chemical shift data for each of the synthesized target compounds are given below.

### General procedure for the synthesis of 2-methyl-3,1-benzoxazin-4-one (2)
A solution of anthranillic acid (1) (10 g, 0.073 mol) in acetic anhydride (25 ml) was heated under reflux for 1 h. The precipitate formed on cooling was filtered and the excess acetic anhydride was washed with anhydrous petroleum ether, where upon a solid mass is obtained. This solid mass (2), without purification, was used for subsequent reaction [47].

### General procedure for the synthesis of 3-aryl-2-methyl-4(3H)-quinazolinones (3-5)
A mixture of 2-methyl-3,1-benzoxazin-4-one (2) (3 g, 0.017 mol) and equimolar amounts of aromatic amines (aniline, $p$-toluidine, and $o$-toluidine, respectively) was heated under reflux at 190°C for 5 h. The dark sticky mass formed were cooled and recrystallized from ethanol to yield compounds 3-5, respectively [48].

### General procedure for the synthesis of 3-aryl-2-(4-chlorostyryl)-4(3H)-quinazolinones (6 and 7)
To a solution of 3 or 4 (0.5 g each) in acetic anhydride (10 ml), an equimolar amount of $p$-chlorobenzaldehyde

### Table 2 Antipromastigote activity (IC$_{50}$) of the synthesized compounds

| Test compounds | IC$_{50}$ values (μg/ml) | IC$_{50}$ values (ng/ml) |
|----------------|--------------------------|--------------------------|
| 6              | 0.3014                   | 301.40                   |
| 7              | 0.0128                   | 12.80                    |
| 8              | 0.1085                   | 108.50                   |
| 9              | 2.7017                   | 2,701.70                 |
| 11             | 0.1086                   | 108.60                   |
| 12             | 1.6472                   | 1,647.20                 |
| 13             | 3.1085                   | 3,108.50                 |
| Miltefosine    | 3.1911                   | 3,191.10                 |
| Amphotericin B | 0.0460                   | 46.00                    |

IC$_{50}$: effective concentration required to achieve 50% growth inhibition (in μg/ml).
was added in the presence of 10 mg of anhydrous zinc chloride as a catalyst. The reaction mixture was heated under reflux for 8 h, cooled, and poured into ice-cooled water. The solid products formed (6 or 7) were filtered, dried, and recrystallized from chloroform/ethanol (2:1) [49].

(E)-2-(4-chlorostyryl)-3-phenylquinazolin-4(3H)-one (6)

IR (Nujol) (cm⁻¹): 1,682 (C = O), 1,597 (C = N), and 1,224 (C-Cl). ¹H NMR (CDCl₃) δ (ppm): 6.33 (d, 1H, J = 15.49 Hz, vinyl-C₂ H), 7.23 (d, 2H, J = 8.53 Hz, 4-chlorophenyl C₃,5 H), 7.28 (d, 2H, J = 8.47 Hz, 4-chlorophenyl C₂,6 H), 7.34 (d, 2H, J = 6.82 Hz, phenyl C₂,6 H), 7.45 to 7.49 (m, 1H, quina-C₆ H), 7.58 to 7.63 (m, 3H, phenyl C₃,4,5 H), 7.75 to 7.79 (m, 2H, quina-C₇,₈ H), 7.89 (d, 1H, J = 15.47 Hz, vinyl-C₁ H), 8.29 (d, 1H, J = 7.95 Hz, quina-C₆ H). Anal. calcld. for C₂2H₁₇ClN₂O: C, 73.23; H, 4.75; Cl, 9.83; N, 9.51. Found: C, 73.11; H, 5.89; N, 6.42.

General procedure for the synthesis of 3-aryl-2-(4-acetylatedstyryl)-4(3H)-quinazolinones (11)

to a solution of 5 (0.5 g) in acetic anhydride (10 ml), an equimolar amount of p-hydroxybenzaldehyde was added. Anhydrous zinc chloride (10 mg) is added as a catalyst. The reaction mixture is heated under reflux for 8 h, cooled, and poured into ice-cooled water. The solid product formed (11) was filtered, dried, and recrystallized from ethanol [49].

(E)-2-(4-chlorostyryl)-3-p-tolylquinazolin-4(3H)-one (7)

IR (Nujol) (cm⁻¹): 1,682 (C = O), 1,597 (C = N), and 1,224 (C-Cl). ¹H NMR (CDCl₃) δ (ppm): 2.15 (s, 3H, p-tolyl CH₃), 6.42 (d, 1H, J = 15.70 Hz, vinyl-C₂ H), 7.21 (d, 2H, 4-chlorophenyl C₃,5 H), 7.26 to 7.32 (m, 4H, p-tolyl C₃,5,6,7 H), 7.40 (d, 2H, 4-chlorophenyl C₂,6 H), 7.47 to 7.51 (m, 1H, quina-C₆ H), 7.79 to 7.83 (m, 2H, quina-C₇,₈ H), 7.93 (d, 1H, vinyl-C₁ H), 8.32 (d, 1H, quina-C₆ H). Anal. calcld. for C₂₃H₂₁N₃O₃: C, 73.79; H, 6.12; Cl, 9.46; N, 7.47. Found: C, 73.98; H, 5.38; Cl, 9.35; N, 7.21.

General procedure for the synthesis of 3-aryl-2-(4-acetylatedstyryl)-4(3H)-quinazolinones (10)

To a solution of 3 (0.5 g) in acetic anhydride (10 ml), an equimolar amount of p-hydroxybenzaldehyde was added. Anhydrous zinc chloride (10 mg) is added as a catalyst. The reaction mixture is heated under reflux for 8 h, cooled, and poured into ice-cooled water. The solid product formed (10) was filtered, dried, and recrystallized from ethanol [49].

(E)-2-(4-chlorostyryl)-3-p-tolylquinazolin-4(3H)-one (8)

IR (Nujol) (cm⁻¹): 1,682 (C = O), 1,597 (C = N), and 1,224 (C-Cl). ¹H NMR (CDCl₃) δ (ppm): 2.15 (s, 3H, p-tolyl CH₃), 6.56 (d, 1H, J = 8.19 Hz, vinyl-C₂ H), 7.21 (d, 2H, J = 7.97 Hz, p-tolyl C₂,6 H), 7.46 to 7.53 (m, 3H, 4-nitrophenyl C₂,6 and quina-C₆ H), 7.77 to 7.81 (m, 2H, quina-C₇,₈ H), 8.00 (d, 1H, J = 15.52 Hz, vinyl-C₁ H), 8.19 (d, 2H, J = 8.74 Hz, 4-nitrophenyl C₃,5), 8.30 (d, 1H, J = 8.01 Hz, quina-C₆ H). Anal. calcld. for C₂₃H₂₁N₃O₃: C, 73.69; H, 7.25; N, 7.01. Found: C, 73.72; H, 4.35; N, 11.10.

(E)-2-(4-nitrostyryl)-3-p-tolylquinazolin-4(3H)-one (9)

IR (Nujol) (cm⁻¹): 1,682 (C = O), 1,593 (C = N), 1,556 and 1,377 (NO₂). ¹H NMR (CDCl₃) δ (ppm): 2.17 (s, 3H, o-tolyl CH₃), 6.47 (d, 1H, J = 15.66 Hz, vinyl-C₂ H), 7.25 (d, 1H, J = 7.91 Hz, o-tolyl C₃ H), 7.44 to 7.46 (m, 3H, 4-nitrophenyl C₂,6 and o-tolyl C₆ H), 7.47 to 7.58 (m, 3H, o-tolyl C₄,₅ and quina-C₆ H), 7.82 to 7.89 (m, 2H, quina-C₇,₈ H), 8.05 (d, 1H, J = 15.56 Hz, vinyl-C₁ H), 8.19 (d, 2H, J = 8.73 Hz, 4-nitrophenyl C₄,₆ H), 8.36 (d, 1H, J = 8.25 Hz, quina-C₆ H). Anal. calcld. for C₂₃H₂₁N₃O₃: C, 71.86; H, 4.72; N, 10.93. Found: C, 71.68; H, 4.93; N, 11.24.

General procedure for the synthesis of 3-aryl-2-(4-acetylatedstyryl)-4(3H)-quinazolinones (10)

To a solution of 3 (0.5 g) in acetic anhydride (10 ml), an equimolar amount of p-hydroxybenzaldehyde was added. Anhydrous zinc chloride (10 mg) is added as a catalyst. The reaction mixture is heated under reflux for 8 h, cooled, and poured into ice-cooled water. The solid product formed (10) was filtered, dried, and recrystallized from ethanol [49].

(E)-2-(4-nitrostyryl)-3-p-tolylquinazolin-4(3H)-one (8)

IR (Nujol) (cm⁻¹): 1,682 (C = O), 1,597 (C = N), and 1,224 (C-Cl). ¹H NMR (CDCl₃) δ (ppm): 2.15 (s, 3H, phenylacetate CH₃), 2.33 (s, 3H, o-tolyl CH₃), 3.80 (s, 3H, methoxy -O-CH₃), 6.27 (d, 1H, J = 15.44 Hz, vinyl-C₂ H), 6.88 to 6.93 (m, 2H, 2-methoxyphenyl C₃,5 H), 6.98 (d, 1H, J = 8.12 Hz, 2-methoxyphenyl C₆ H), 7.24 (d, 1H, J = 7.52 Hz, o-tolyl C₃ H), 7.42 to 7.53 (m, 4H, o-tolyl C₄,₅,₆,7 H and quina-C₆ H), 7.82 to 7.83 (m, 2H, quina-C₇,₈ H), 7.96 (d, 1H, J = 15.48 Hz, vinyl-C₁ H), 8.34 (d, 1H, J = 7.88 Hz, quina-C₆ H). Anal. calcld. for C₂₆H₂₃N₂O₅: C, 72.88; H, 5.65; N, 6.54. Found: C, 73.11; H, 5.89; N, 6.42.

General procedure for the synthesis of 3-aryl-2-(4-acetylatedstyryl)-4(3H)-quinazolinones (12 and 13)

Subsequent treatment of 10 and 11 with 0.1 M alcoholic KOH (5 ml) in the presence of ethanol followed by 0.1 M HCl (6 ml) gave the corresponding 4-hydroxyl containing compounds 12 and 13 after recrystallization from ethanol [49].

(E)-2-(4-hydroxy styryl)-3-p-tolylquinazolin-4(3H)-one (12)

IR (Nujol) (cm⁻¹): 3,290 (OH), 1,652 (C = O), and 1,604 (C = N). ¹H NMR (acetone-d₆) δ (ppm): 6.24 (d, 1H, J = 15.39 Hz, vinyl-C₂ H), 6.80 (d, 2H, J = 8.64 Hz, 4-
hydroxyphenyl C₃,₅ H), 7.24 (d, 2H, J = 8.62 Hz, 4-hydroxyphenyl C₂,₈ H), 7.46 to 7.50 (m, 3H, phenyl C₃,₄,₅ H), 7.60 to 7.66 (m, 3H, quina-C₉, phenyl C₂,₆ H), 7.73 (d, 1H, J = 8.07 Hz, quina-C₉ H), 7.81 to 7.85 (m, 1H, quina-C₇ H), 7.92 (d, 1H, J = 15.43 Hz, vinyl-C₁₁), 8.02 (s, 1H, 4-hydroxyphenyl -OH), 8.17 (d, 1H, J = 9.18 Hz, quina-C₅ H). Anal. calcd. for C₂₉H₂₃N₂O₇: C, 71.7%; H, 5.23; N, 8.18. Found: C, 76.86; H, 5.02; N, 8.38.

(E)-2-(4-hydroxy-3-methoxy styryl)-3-o tolyquinazolin-4(3H)-one (13)

IR (Nujol) (cm⁻¹): 3,400 (OH), 1,683 (C = O), 1,634 (C = N), 1,211 and 1,148 (C-O-C). ¹H NMR (CDCl₃ δ (ppm): 2.15 (s, 3H, o-tolyl CH₃), 3.80 (s, 3H, 4-hydroxy-2-methoxyphenyl -O-CH₃), 6.10 (s, 1H, 4-hydroxy-2-methoxyphenyl -OH), 6.27 (d, 1H, J = 15.44 Hz, vinyl-C₁₁ H), 6.88 to 6.93 (m, 2H, 4-hydroxy-2-methoxyphenyl C₃,₅ H), 6.98 (d, 1H, J = 8.12 Hz, 4-hydroxy-2-methoxyphenyl C₆ H), 7.24 (d, 1H, J = 7.52 Hz, o-tolyl C₁₀ H), 7.42 to 7.53 (m, 4H, o-tolyl C₄,₅,₆ H and quina-C₆ H), 7.82 (m, 2H, quina-C₇,₈ H), 7.96 (d, 1H, J = 15.48 Hz, vinyl-C₁₁ H), 8.34 (d, 1H, J = 7.884 Hz, quina-C₅ H). Anal. calcd. for C₂₉H₂₃N₂O₇: C, 74.59; H, 5.74; N, 7.23. Found: C, 74.28; H, 5.96; N, 7.56.

Conclusions

Some 3-aryl-2-(substitutedstyryl)-4(3H)-quinazoline derivatives were synthesized and tested for their antileishmanial activities. Most of the synthesized compounds displayed better antileishmanial activities as compared to the standard drug miltefosine and lower antileishmanial activity as compared to amphotericin B deoxycholate except (E)-2-(4-chlorostyryl)-3-p-tolyl-4(3H)-quinazoline (7). Compound 7 showed pronounced antileishmanial activities as compared to miltefosine and amphotericin B deoxycholate. Thus, 2,3-disubstituted-4(3H)-quinazolines containing an aromatic substitution at 3-position and substituted styril moiety at 2-position represent a promising matrix for the development of antileishmanial agents.

Competing interests

The authors declare that they have no competing interests.

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