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Bioorganic & Medicinal Chemistry 15 (2007) 7553–7560
Bioorganic & Medicinal Chemistry

Synthesis and in vitro evaluation of leishmanicidal and trypanocidal activities of *N*-quinolin-8-yl-arylsulfonamides

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Received 3 August 2007; revised 2 September 2007; accepted 7 September 2007
Available online 12 September 2007

Abstract—In the present paper 12 *N*-quinolin-8-yl-arylsulfonamides synthesized by coupling 8-aminoquinolines with various arylsulfonylchlorides were assayed in vitro against *Leishmania amazonensis*, *L. chagasi* and *Trypanosoma cruzi* strains. This series of new compounds were found to be selective for *Leishmania* spp. promastigote and amastigote forms. The most active compound was the *N*-(8-quinolyl)-3,5-difluoro-benzenesulfonamide **10** with an IC_{50} against *L. amazonensis* and *L. chagasi* of 2.12 and 0.45 μM, respectively. The less cytotoxic biphenyl derivative **7** was very effective against intracellular *L. amazonensis* with a reduction of macrophage cell infection of 82.1% at 25 μM. In addition, a copper complex **17** of an inactive ligand was readily synthesized and showed high leishmanicidal and trypanocidal activity against both extra and intracellular forms.
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1. Introduction

Diseases caused by protozoan parasites are severe global public health problem, especially in the tropical and subtropical regions of the world. Despite the socioeconomical importance of these tropical infectious diseases, efforts directed towards the discovery of new drugs and/or vaccines are insufficient. In addition, most drugs currently in use were developed several decades ago showing variable efficacy. They promote serious side effects, are expensive, require long-term treatment, show low activity in immunosuppressed patients and parasites may be resistant to the drugs.[1] Thus, the need for developing new, effective, cheap and safe drugs continues to be a major goal in the field of leishmaniasis and trypanosomiases chemotherapy. For the last decade, new potential therapies have been introduced for leishmaniasis. These include Amphotericin B, Miltefosine, Aminosidine and Sitamaquine (Fig. 1). The latter has completed phase II trials in India, Kenya and Brazil.[2] In addition, a great number of both natural and synthetic compounds have been tested in recent years in antileishmanicidal and antitrypanosomal assays.[3]

In this context, the use of quinoline derivatives as antiprotozoal agents is well established.[4] Although there is a large amount of experimental work on this heterocyclic system, it still remains an area of active research.[5] On the other hand, sulfonamides have long been the subject of pharmaceutical interest as a result of their potent biological activities.[6] Indeed, the sulfonamide derivatives have been reported to possess antitrypanosomal and antileishmanial activities.[7] As part of our efforts to develop new compounds aimed at the therapy of parasitic infection,[8] we have synthesized and assayed against leishmania and trypanosome some

Keywords: Quinolinylarylsulfonamides; Quinolinylarylsulfonamide-copper and zinc complexes; Leishmanicidal activity; Trypanocidal activity; Vero cells; Macrophages.
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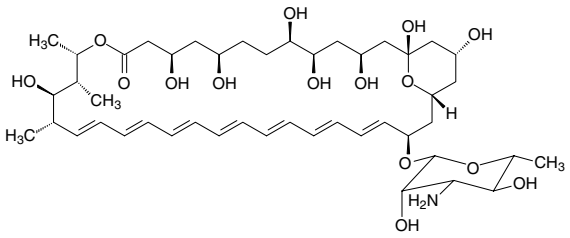
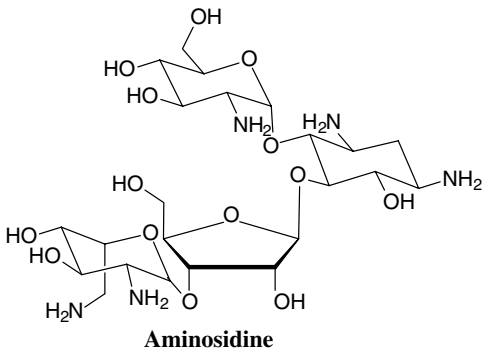
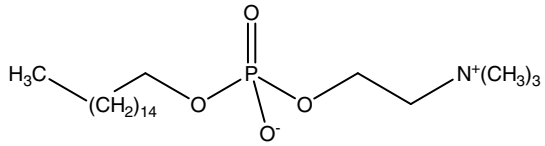
doi:10.1016/j.bmc.2007.09.007



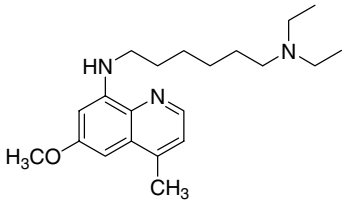
Amphotericin B



Aminosidine



Miltefosine



Sitamaquine

Figure 1. Drugs currently used in the treatment of leishmaniasis.

quinolinylarylsulfonamides and two of their copper and zinc complexes.

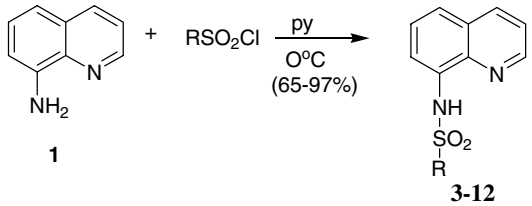
2. Results and discussion

2.1. Chemistry

A series of quinolinylarylsulfonamides were obtained by direct reaction of the corresponding commercial available 8-aminoquinoline **1** and arylsulfonylchlorides in pyridine[9] at 0 °C (Scheme 1). The titled **3**–**12** were obtained in good yields (65–97%) and their corresponding octanol-water partition coefficients (*C*log *P*) were calculated using free software available on the web (Table 1).

8-Aminoquinoline (**1**) was allowed to react with bromine in acetic acid to afford the expected 5,7-dibromo-8-aminoquinoline **13**.[10] Reaction of the 5,7-dibromoderivative **13** with 4-*n*-propylbenzenesulfonylchloride in pyridine at the 0 °C gave the corresponding compound **14** (Scheme 2).

The quinoline **15** containing a quite similar substitution pattern of sitamaquine was prepared as described by Kimber et al.[11] and placed to react with 4-*n*-propylbenzenesulfonylchloride in pyridine at the 0 °C to furnish the *N*-quinolin-8-yl-arylsulfonamide **16** in 70% yield (Scheme 3).



Scheme 1. General structure of synthesized *N*-quinolin-8-yl-arylsulfonamides derivatives **3-12**.

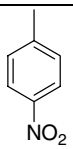
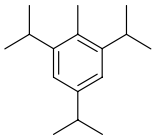
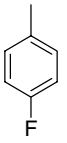
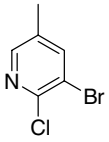
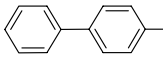
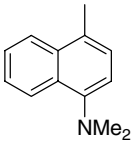
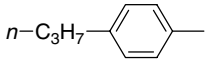
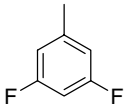
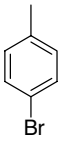
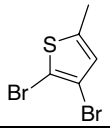
Recent studies have suggested that the leishmanicidal activity of copper complex could be associated with their interaction with the parasite DNA.[12] Furthermore important biological activities have been associated to chelated copper and zinc cations.[13] These prompted us to synthesize the copper and zinc complexes **17** and **18**[14] (Fig. 2). The copper and zinc cations were chelated by two bidendate quinolinylsulfonamides in methanol at room temperature. Their unambiguous structures were established by X-ray analysis.[15]

2.2. Antiprotozoal activity

Due to the facility of cultivation, both promastigotes and epimastigotes forms are largely used for in vitro compounds screening. Therefore, the efficacy of the synthesized quinolinylarylsulfonamides on promastigotes of *L. amazonensis*, *L. chagasi* and epimastigotes of *T. cruzi* was assessed by a previously described method.[8] Results are summarized in Table 2 and show a high selectivity towards *Leishmania* spp. The only exception was observed for compound **6**, which presented a moderate activity against *T. cruzi* (31.75 μM). However, its index of selectivity (IS) defined as the ratio of the CC_{50} value on Vero cells to the IC_{50} value on the epimastigotes *T. cruzi* strains, was only 2.1.

The quinolinylarylsulfonamides **6**, **10**, **11** and **12** were found to be the most active compounds against promastigote forms of *L. amazonensis* and *L. chagasi* with IC_{50} ranging from 2.12 to 2.85 μM and 0.45 to 2.99 μM, respectively. These are outstanding results since the IC_{50} for compounds **6**, **10** and **12** are just two times greater than the IC_{50} of the control Amphotericin B in the *L. chagasi* bioassay. The IS for these three compounds was remarkable, where values ranging from 24

Table 1. *N*-Quinolin-8-yl-arylsulfonamides and the corresponding partition coefficients (*C*log *P*)

Compound	*C*log *P*	R
3	3.19	
4	6.23	
5	2.68	
6	2.92	
7	4.20	
8	3.87	
9	3.85	
10	2.84	
11	3.46	
12	4.18	

to 30 for *L. amazonensis* and 120 to 147 for *L. chagasi* were observed. Structurally three different aryl moieties are associated to these compounds: basic π-deficient in **6**, homocyclic in **10** and π-excessive in **12**, although they have in common dihalide substituents.

With respect to the sulfonamides **7**, **8** and **9**, which can be regarded as the lipophilic members of this series (*C*log *P* from 3.85 to 4.20), their activity was inferior to the previous set of compounds but still very significant, with IC_{50} ranging from 6.27 to 14.47 μM against *L. amazonensis* and from 2.18 to 13.96 μM against *L. chagasi*. The IS for the most active compound **7** within this set was 39 and 112 for *L. amazonensis* and *L. chagasi*, respectively. The IS for compounds **8** and **9** dropped considerably, ranging from 4.4 to 11 for *L. amazonensis* and 4.6 to 23 for *L. chagasi*.

The presence of either a nitro group or fluorine atom at 4-position of the phenyl moiety as in compounds **3** and **5**, respectively, induced total loss of activity (IC_{50} > 100 μM). It is important to notice that bromine at 4-position of the phenyl moiety promoted different effect as described previously for **11**. Similar result to compounds **3** and **5** was observed for compound **4** containing bulky groups on the aryl moiety.

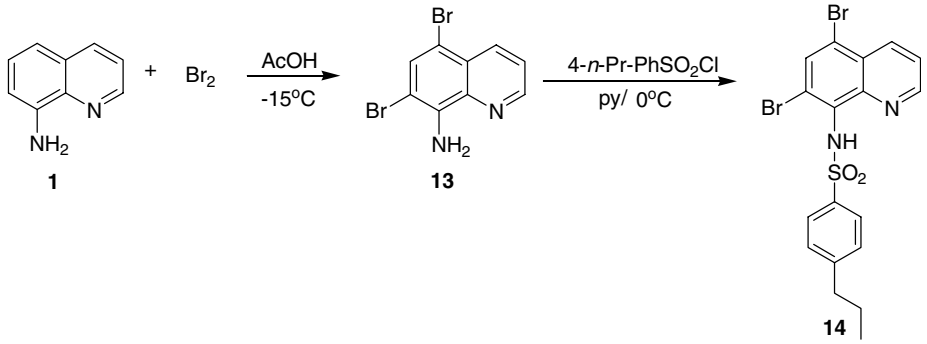
Another interesting finding of the present study is the sensitivity of this series towards the introduction of substituents on the quinoline ring. The presence of dibromine as in compound **14** and methoxy and methyl groups as in **16** led to the loss of activity.

A preliminary study related to metal complex of quinolinylarylsulfonamides was undertaken. The readily made and purified copper **17** and zinc **18** complexes were assayed against *L. amazonensis* and *L. chagasi* promastigote and *T. cruzi* epimastigote forms. The results are summarized in Table 2. A drastically change in the antiprotozoal activity was observed since the corresponding sulfonamide ligands **5** and **3** were inactive. The copper complex showed significant activity against *Leishmania amazonensis* (IC_{50} = 2.28 μM), *L. chagasi* (IC_{50} = 1.10 μM) and *T. cruzi* (IC_{50} = 4.10 μM) whereas the zinc complex was slightly less active against *Leishmania* spp. strains (6.46 μM for *L. amazonensis*, and 3.00 μM for *L. chagasi*). Moreover, compound **17** was found more active than the reference compound benznidazole, although its IS was only 3.3.

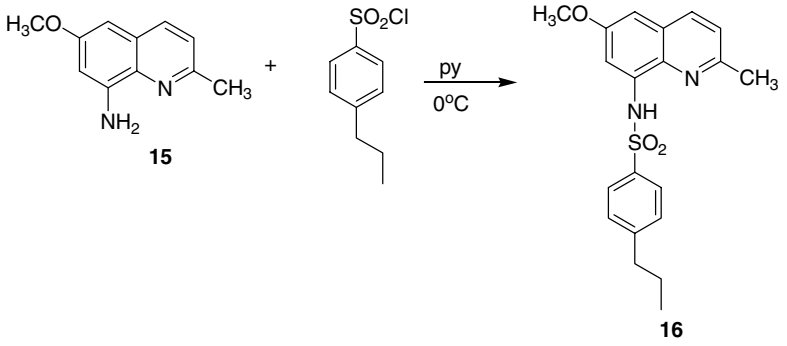
It is well known that extracellular and intracellular forms of these protozoans exhibit metabolic differences and distinct levels of sensitivity to drugs. Amastigote is the relevant clinical form for both diseases and its use on the evaluation of antiparasitic activity of compounds might be very useful.[16]

Limited by the availability of some compounds representatives of the quinolinylarylsulfonamide series were selected and tested against intracellular amastigote forms of *L. amazonensis* (infected macrophages) and *T. cruzi* (infected Vero cells). Three different concentrations of the selected compounds were considered and the results are summarized in Table 3.

Compounds **6** and **17** were active against both *Leishmania* and *Trypanosoma* as observed in the bioassay against promastigote and epimastigote forms. These compounds presented a significant activity against *L. amazonensis*, promoting at the concentration 5 μM a reduction of cell infection in 67.1% and 88.2%, respectively. A remarkable result was obtained against *T. cruzi* amastigote forms with a reduction of cell infection in 96.4% promoted by **6** at 25 μM concentration, and 98.0% reduction for the complex **17** at 5 μM concentra-



Scheme 2. Synthesis of *N*-(5,7-dibromo-8-quinolyl)-4-*n*-propylbenzenesulfonamide **14**.



Scheme 3. Synthesis of *N*-(6-methoxy-2-methyl-8-quinolyl)-4-*n*-propylbenzenesulfonamide **16**.

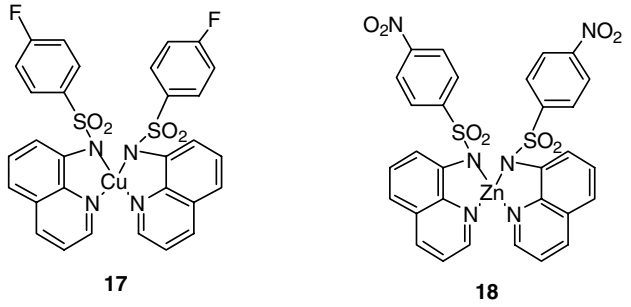


Figure 2. Chemical structures of copper and zinc complexes **17** and **18**.

tion, which was also the most cytotoxic as previously observed. These compounds were more active than the control benznidazol that reduced in 92.0% the cell infection at 25 μM. With respect to the zinc complex **18**, it showed an activity against *L. amazonensis* inferior to compounds **6** and **17**. This result is compatible to the bioassay with *L. amazonensis* culture.

The lipophilic series **7**–**9** was also tested against in vitro *L. amazonensis*. Compound **7**, containing the biphenyl moiety, was found to be the most active, promoting a reduction of cell infection in 82.1% at 25 μM concentration. In fact its activity was similar to compound **6** confirming a trend observed for other classes of antiparasitic compounds where the increase of lipophilicity seems to favor the compound distribution to the intracellular target.[17]

The *C*log *P* observed for compound **12** (4.18) was similar to compound **7** (*C*log *P* = 4.20) and indicates that is necessary to investigate the activity of the former in the cell infected bioassays. Furthermore, the lipophilicity increment associated to the bromine atom could be exploited in the preparation of derivatives of compounds **6**, **10** and **11**.

In conclusion, several new quinolin-8-yl-arylsulfonamides were prepared from the reaction of 8-aminoquinolines with various arylsulfonylchlorides in pyridine. The in vitro bioassay showed the compounds to possess significant antiprotozoal activity against promastigote and amastigote forms of *Leishmania* spp. The only representative of this series active against *T. cruzi* was the sulfonamide containing a pyridine moiety.

The active general molecular structure may embody a variety of features at the aryl moiety, but not at the quinoline ring where the substituents investigated led to the total loss of activity.

Copper and zinc complexes were prepared from the corresponding sulfonamide and copper or zinc salt in methanol. Their activity was investigated against *Leishmania* and *Trypanosoma* strains. The complex increased the sulfonamide activity although its cytotoxicity as well.

No quantitative correlation was carried out and further pharmacological study should be now investigated to determine the target of action. These series has provided leading compounds for further pharmacomodulations.

Table 2. In vitro effect of *N*-quinolin-8-yl-arylsulfonamides and copper and zinc derivatives on the growth of *Leishmania amazonensis* and *Leishmania chagasi* promastigotes, *Trypanosoma cruzi* epimastigotes and toxicity to Vero cells

Compound	*L. amazonensis* (575 strain) IC_{50} (μM)	*L. chagasi* (PP75 strain) IC_{50} (μM)	*T. cruzi* (Y strain) IC_{50} (μM)	Vero cells CC_{50} (μM)
3	>100	>100	>100	ND
4	>100	>100	>100	ND
5	>100	>100	>100	ND
6	2.25 (1.63–3.09)	0.56 (0.51–0.63)	31.75 (26.63–37.85)	67.38 (54.46–83.36)
7	6.27 (4.46–8.82)	2.18 (1.65–2.88)	>100	244.93 (189.04–317.36)
8	7.18 (6.91–7.47)	3.53 (2.28–5.46)	>100	84.22 (60.52–117.21)
9	14.47 (14.14–14.81)	13.96 (12.09–16.13)	>100	64.36 (58.15–71.24)
10	2.12 (1.88–2.40)	0.45 (0.14–1.45)	>100	66.33 (45.80–96.06)
11	4.94 (4.73–5.17)	2.99 (2.73–3.26)	>100	88.70 (74.35–105.83)
12	2.85 (2.59–3.14)	0.53 (0.51–0.55)	>100	68.73 (41.72–113.23)
14	>100	>100	>100	ND
16	>100	>100	>100	ND
17	2.28 (1.41–3.67)	1.10 (0.57–2.11)	4.10 (2.79–6.03)	13.76 (9.59–19.75)
18	6.46 (6.04–6.89)	3.00 (2.81–3.21)	>100	11.43 (11.33–11.53)
Amphotericin B	0.31 (0.25–0.35)	0.25 (0.21–0.26)	—	98.35 (78.85–115.06)
Benznidazole	—	—	14.58 (13.10–16.24)	>1000

IC_{50} with their respective 95% confidence limit; CC_{50} with their respective 95% confidence limit; ND, not determined.

Table 3. Activity of synthesized compounds against intracellular amastigotes of *L. amazonensis* in mice peritoneal macrophages and *Trypanosoma cruzi* in Vero cells after a 48 h treatment

Compound	Concentration (μM)	*L. amazonensis* (575 strain) Reduction of cell infection (%)	*T. cruzi* (Y strain) Reduction of cell infection (%)
6	25	84.8	96.4
	5	67.1	85.2
	1	52.0	78.6
7	25	82.1	NT
	5	72.3	NT
	1	60.0	NT
8	25	Citotoxic	NT
	5	48.2	NT
	1	25.7	NT
9	25	63.7	NT
	5	52.2	NT
	1	18.7	NT
17	25	Citotoxic	Citotoxic
	5	88.2	98.0
	1	76.0	84.1
18	25	Citotoxic	NT
	5	65.7	NT
	1	42.0	NT
Amphotericin B	10	97.0	NT
Benznidazol	25	NT	92.0

The results represent the mean of two experiments. The infection rate was determined evaluating 500 Giemsa stained cells chosen randomly in each slide. NT, not tested.

3. Experimental

3.1. Biological assays

3.1.1. In vitro *L. amazonensis* promastigotes and *T. cruzi* epimastigotes culture and drug assays. *L. amazonensis* (strain 575) promastigotes and *T. cruzi* (Y strain) epimastigotes were grown at 28 °C in Schneider's and LIT media containing 5% and 10% of heat inactivated (56 °C for 30 min) fetal bovine serum (FBS), respectively, and 200 U/ml penicillin and 100 μg/ml of streptomycin (Gibco, UK). Parasites were harvested from 4 days old culture and washed twice in phosphate-buffered saline by centrifugation at 1000*g* for 10 min at 4 °C. Parasite concentration was adjusted to 1×10^6 cells/ml in Schneider's or LIT medium supplemented with 5% or 10% of FBS. For leishmanicidal and trypanocidal activity assays, 150 μl of the parasite suspension was added to 96-well microplates and incubated at 28 °C for 72 h in the presence or absence of the *N*-quinolin-8-yl-arylsulfonamides (0.2–100 μM) and the standard drugs Amphotericin B (0.1–10 μM) and benznidazole (10–100 μM) were used as controls. For each compound three experiments were carried out in triplicate and the number of surviving parasites was determined in Neubauer chambers.[8]

3.1.2. Cell toxicity tests. Cytotoxic effects of *N*-quinolin-8-yl-arylsulfonamides were evaluated in Vero cells using the MTT (tetrazolium-dye) assay.[18] Briefly, cells cultivated in the presence of different compounds for 72 h at 37 °C were incubated with MTT (2 mM/ml) for 4 h. Thereafter supernatant was removed and 100 μl of DMSO was added to solubilize the formazan crystals from viable cells. The samples were read at a wavelength of 540 nm using an ELISA plate reader.[19] Benznidazole and Amphotericin B were used as control drugs. Variance analysis followed by Dunnett's multiple comparison tests were used for data analysis. The 50% inhibitory concentration (IC_{50}) for parasites and 50% cell cytotoxicity (CC_{50}) was determined by linear regression analysis using (GraphPad Software, San Diego, California).

Macrophages were collected from the peritoneal cavity of normal female albino Swiss mice and cultivated on sterile 13 mm glass slides in DMEM supplemented with 20% of heat inactivated FBS at 37 °C, 5% CO_2 as described previously.[20] Vero cells (ATCC CCL81) were cultivated on 13 mm glass slides in DMEM supplemented with 5% of FBS at 37 °C, 5% CO_2.[20] Macrophages

were infected with *L. amazonensis* promastigotes, using a 1:10 cell:parasite ratio and after 4 h period of infection cells were incubated at 37 °C, 5% CO_2 with different concentrations of the compounds for 48 h. Slides were washed with PBS, methanol fixed and stained with Giemsa.[21] Vero cells were incubated with cell culture derived trypomastigotes at 1:10 cell:parasite ratio and after 6 h of infection cells were washed for removing the non-adherent parasites and the cell monolayer incubated for 48 h with different concentrations of the compounds.[20] Slides were methanol fixed and Giemsa stained and 500 random cells were microscopically examined (1000×). The cell infection rate and the number of infected cells as well as the number of parasite/cell were determined.

3.2. Chemistry

The compounds were characterized by ^{1}H NMR. The purity of the compounds was determined by TLC using several solvent systems of different polarity. Nuclear magnetic resonance spectra were recorded with on a Bruker AC-300 spectrometer using tetramethylsilane as internal standard. Infrared spectra were determined with a Perkin-Elmer 16PC spectrophotometer. Mass spectra were obtained with on a Bruker-Franzen Esquire LC instrument.

3.2.1. General Procedure for the synthesis of the sulfonamides derivatives. To an ice-cooled solution of the aminoquinoline (1 equiv) in pyridine were added the corresponding sulfonylchloride derivative (1.1 equiv). The mixture was stirred at 0 °C for 90 min and overnight at room temperature. The reaction mixture was quenched with ice water and the precipitated product filtered off. The sulfonamide was recrystallized from MeOH:CH_2Cl_2 solution.

3.2.2. 4-Nitro-*N*-(8-quinolyl)benzenesulfonamide (3). Crystalline solid: 84%. Mp:170 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.54 (m, Ar-H); 7.93 (dd, J = 1.6 and 8 Hz, 1H-H7); 8.08 (d, J = 8 Hz, 2H-H2′-H6′) 8.14 (d, J = 8 Hz, 2H-H3′-H5′); 8.78 (dd, J = 1.6 and 6 Hz, 1H-H2); 11.45 (s, 1H-NH).

Mass spectrometry: m/z = 329 (M^+; 100); 202 (80).

IR (KBr): 3218 (*NH*), 1573, 1383, 1359 (SO_2N), 1169 (SO_2N), 926, 686, 585, 559 cm^{-1}.

3.2.3. 2,4,6-Triisopropyl-*N*-(8-quinolyl)benzenesulfonamide (4). Crystalline solid: 65%. Mp:141 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 18H-CH_3); 2.82 (m, 1H-C*H*); 4.37 (m, 2H-C*H*); 7.09 (s, 2H-C*H*-H3′-H5′); 7.25–7.46 (m, 4H-Ar-H); 7.68 (dd, J = 2 and 6.7 Hz, 1H-H7); 8.09 (dd, J = 1.6 and 6 Hz, 1H-H5); 8.74 (dd, J = 1.6 and 6 Hz, 1H-H2); 9.31 (s, 1H-N*H*).

Mass spectrometry: m/z = 433 (M^+; 100).

IR (KBr): 3245 (*NH*), 1375 (SO_2N), 1164 (SO_2N), 918, 679, 558, 546 cm^{-1}.

3.2.4. 4-Fluoro-*N*-(8-quinolyl)benzenesulfonamide (5). Crystalline solid: 79%. Mp: 140 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (t, J = 6 Hz, 2H-H3-H6); 7.42–7.48 (m, 3H-H3′-H4′); 7.88 (dd, J = 2 and 7 Hz, 1H-H7); 7.90 (dd, J = 2 and 7 Hz, 2H-H3-H6); 8.12 (dd, J = 1,6 and 8 Hz, 1H-H5); 8.76 (dd, J = 2 and 6 Hz, 1H-H2); 9.24 (s, 1H-N*H*).

Mass spectrometry: m/z = 302 (M^+; 35); 238 (90); 143 (100); 116 (60).

IR (KBr): 3260 (*NH*), 1307 (SO_2N), 1160 (SO_2N), 922, 666, 570, 545 cm^{-1}.

3.2.5. *N*-(8-Quinolyl)-5-bromo-6-chloropyridine-3-sulfonamide (6). Yellow solid: 89%. Mp: 155–157 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ (m, 3H-Ar-H); 7.94 (dd, J = 1.6 and 6 Hz, 1H-H5); 8.19 (dd, J = .6 and 6.7 Hz, 1H-H4); 8.41 (s,1H-H1′); 8.79 (s, 1H-H2′); 8.8 (dd, J = 1.6 and 6 Hz, 1H, H2); 9.43 (s, 1H-N*H*).

Mass spectrometry: m/z = 399 (M^+; 25); 334 (55); 143 (100); 116 (65).

IR (KBr): 3192 (*NH*), 1612,1584, 1368 (SO_2N), 1173 (SO_2N), 941, 776, 679, 587, 545 cm^{-1}.

3.2.6. *N*-(8-Quinolyl)-*n*-biphenylsulfonamide (7). White solid: 95%. Mp: 158–159 °C.

^{1}H RMN ($CDCl_3$, 300 MHz) δ 7.40–7.44 (m, 6H-Ar-H); 7.57 (s, 2H-H2″-H6″); 7.89 (dd, J = 9 Hz, 1H-H3′-H5′); 7.90 (s, 4H-H3′-H5′-H2′-H6′); 8.07 (d, J = 9 Hz, 1H-H5); 8.71 (dd, J = 2 and 9 Hz, 1H-H2); 9.29 (s, 1H-N*H*).

Mass spectrometry: m/z = 360 (M^+); 296 (100); 143 (35); 116 (20).

IR (KBr): 3250 (*NH*), 1317 (SO_2N), 1123 (SO_2N), 959, 664, 567, 552 cm^{-1}.

3.2.7. *N*-(8-Quinolyl)-5-(dimethylamino)naphthalenesulfonamide (8). Green solid: 90%. Mp: 155–156 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.79 (s, 6H-CH_3); 7.10 (d, J = 7.5 Hz, 1H-H6); 7.32 (dd, J = 4,2 and 7 Hz, 2H-H6′-H7′); 7.44 (t, J = 7.5 Hz, 2H-H3-H6); 7.58 (t, J = 7.8 Hz, 2H-H7-H3′); 8.01 (d, J = 8.1 Hz, 1H-H5); 8.37 (d, J = 7.2 Hz, 1H-H4′); 8.46 (d, J = 8.7, 1H-H8′); 8.50 (d, J = 8.7,1H-H2′); 8.69 (d, J = 4.2 Hz, 1H-H2); 9.45 (s, 1H-N*H*).

Mass spectrometry: m/z = 377 (M^+; 75); 313 (100); 170 (40).

IR (KBr): 3248 (*NH*), 1314 (SO_2N), 1139 (SO_2N), 936, 678, 573, 551 cm^{-1}.

3.2.8. *N*-(8-Quinolyl)-4-*n*-propylbenzenesulfonamide (9). White solid: 77%. Mp: 105 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (t, J = 7.3 Hz, 3H-CH_3); 1.48 (q, J = 7.5 Hz, 2H-CH_2); 2.10 (t, J = 7.2 Hz, 2H-CH_2); 7.06 (d, J = 9 Hz, 2H-H3′-H5′); 7.36 (dd, J = 2 and 7 Hz, 1H, H5); 7.38 (t, J = 6 Hz, 1H, H6); 7.40 (d, J = 7 Hz, 1H, H7); 7.69 (t, J = 6 Hz, 1H, H3); 7.75 (d, J = 9 Hz, 2H-H2′-H6′); 8.02 (dd, J = 2 and 6 Hz, 1H-H2); 8.69 (dd, J = 2 and 6 Hz-H4); 9.17 (s, 1H-NH).

Mass spectrometry: m/z = 326 (M^+; 18); 262 (50); 233 (100); 143 (60); 116 (45).

IR (KBr): 3218 (NH), 1359 (SO_2N), 1169 (SO_2N), 926, 686, 585, 559 cm^{-1}.

3.2.9. *N*-(8-Quinolyl)-3,5-difluoro-benzenesulfonamide (10). White solid: 96%. Mp: 120–121 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82 (t, J = 9 Hz, 1H-H4′); 7.21 (s, 2H-H2′-H6′); 7.36–7.50 (m, 3H-Ar-H); 7.79 (d, J = 6 Hz, 1H-H7); 8.06 (d, J = 6 Hz, 1H-H5); 8.70 (dd, J = 2 and 6 Hz, 1H-H2); 9.23 (s, 1H-NH).

Mass spectrometry: m/z = 320 (M^+; 45); 256 (70); 143 (100); 116 (55).

IR (KBr): 3245 (NH), 1375 (SO_2N), 1164 (SO_2N), 952, 692, 596, 584 cm^{-1}.

3.2.10. *N*-(8-Quinolyl)-4-bromobenzenesulfonamide (11). White solid: 56%. Mp: 160–162 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.33 (m, 3H); 7.40 (d, J = 8 Hz, 2H-H3′-H5′) 7.68 (d, J = 8 Hz, 2H-H2′-H6′); 7.75 (d, J = 7.2 Hz, 1H); 8.01 (d, J = 8 Hz, 1H); 8.66 (d, J = 7.2 Hz, 1H); 9.18 (s, 1H-NH).

IR (KBr): 3250 (NH), 1320 (SO_2N), 1169 (SO_2N), 961, 655, 570, 550 cm^{-1}.

3.2.11. 4,5-Dibromo-*N*-(8-quinolyl)tiophene-2-sulfonamide (12). White solid: 57%. Mp: 143 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.19 (s, 1H-H5′); 7.44–7.53 (m, 3H-Ar-H); 7.83 (dd, J = 2 and 6 Hz, 1H-H7); 8.10 (d, J = 9 Hz, 1H-H5); 8.73 (dd, J = 2 and 6 Hz, 1H-H2); 9.12 (s, 1H-NH).

Mass spectrometry: m/z = 448 (M^+; 25); 384 (35); 303 (100); 223 (75); 143 (85); 116 (77).

IR (KBr): 3249 (NH), 1443, 1376 (SO_2N), 1164 (SO_2N), 920, 758, 685, 662, 585, 559 cm^{-1}.

3.2.12. 5,7-Dibromoquinolin-8-amine (13). Brow solid. mp: 119–122 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.36 (s, 2H-NH_2); 7.40 (dd, J = 4.2 and 8.7 Hz, 1H-H3); 7.72 (s, 1H-H6); 8.32 (dd, J = 1.5 and 8.4 Hz, 1H-H4); 8.70 (dd, J = 1.8 and 4.2 Hz, 1H-H2).

3.2.13. *N*-(5,7-Dibromo-8-quinolyl)-4-*n*-propylbenzenesulfonamide (14). Crystalline solid: 50%. Mp: 150 °C.

^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.12 (t, J = 7.3 Hz, 3H-CH_3); 1.25 (q, J = 7.5 Hz, 2H-CH_2); 2.95 (t, J = 7.2 Hz, 2H-CH_2); 6.31 (s, 1H-NH); 6.83 (d, J = 9 Hz, 2H, H3′–H5′); 7.08 (t, J = 6 Hz, 1H, H3); 7.34 (s, 1H-H6); 7.56 (d, J = 7.5 Hz, 1H-H4); 7.90 (d, J = 7.5 Hz, 2H-H2′–H6′); 8.25 (d, J = 6 Hz, 1H, H2).

Mass spectrometry: m/z = 484 (M^+; 10); 420 (100); 391 (85); 301 (90); 220 (50); 141 (25).

IR (KBr): 3240 (NH), 1357 (SO_2N), 1163 (SO_2N), 929, 667, 557, 545 cm^{-1}.

3.2.14. *N*-(6-Methoxy-2-methyl-8-quinolyl)-4-*n*-propylbenzenesulfonamide (16). Crystalline solid: 70%. Mp: 111–113 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82 (t, J = 7.3 Hz, 3H-CH_3); 1.46 (q, J = 7.5 Hz, 2H-CH_2); 2.45 (t, J= 7.2 Hz, 2H-CH_2); 2.65 (s, 3H-CH_3); 3.73 (s, 3H-OCH_3); 6.48 (s, 1H-H7); 7.15 (d, J = 8.5 Hz, 2H, H3′–H5′); 7.18 (d, J = 6 Hz, 1H, H3); 7.8 (d, J = 6 Hz, 1H, H4); 7.36 (s, 1H, H7); 7.76 (d, J = 8.5 Hz, 2H, H2′–H6′); 9.34 (s, 1H-NH).

Mass spectrometry: m/z = 370 (M^+; 90); 277 (30); 187 (75); 172 (100); 144 (30).

IR (KBr): 3325 (NH), 1610,1600, 1317 (SO_2N), 1166 (SO_2N), 925, 686, 569, 554 cm^{-1}.

3.2.15. Synthesis of the complexes. The copper complex **17** prepared according to a procedure given in the literature.[22] Into 50 ml of a methanolic solution of copper (II) acetate (0.1996 g, 1 mmol), 100 ml of a methanolic solution containing 0.5965 g (2 mmol) of the ligand was slowly added under stirring. The solution became dark and after one day the crystals appeared.

3.2.16. Bis[4-Fluoro-*N*-(quinolin-8-yl)benzenesulfonamidate-κ_2N,N']copper(II) (17).[15] Green dark solid: 80%. Mp: 278 °C.

IR (KBr): 1322, 1139, 580, 555, 948, 665 cm^{-1}.

Mass spectrometry: m/z = 665 (M^+-1; 48); 347 (25); 237(75); 143 (100).

The zinc complex **18** was prepared according to a procedure found in the literature.[23] About 1.5 mmol of the sulfonamide was dissolved in 75 ml methanol and 2 ml 2 M NH_4OH were added. While this solution was magnetically stirred, 0.75 mmol of $ZnCl_2$ dissolved in 50 ml methanol were added dropwise. When addition was completed a green yellow precipitate was formed which was separated by filtration.

3.2.17. Bis[4-Nitro-*N*-(quinolin-8-yl)benzenesulfonamidate-κ_2N,N']zinc(II) (18).[15] Green/yellow crystalline solid: 88%. Mp: >300 °C.

IR (KBr): 1324, 1284, 1142, 1120, 569, 554, 962, 656 cm^{-1}.

Mass spectrometry: $m/z = 720$ (M^+; 10); 329 (40); 265 (75); 143 (100).

Acknowledgments

The authors are grateful to the Brazilian agencies CNPq and CAPES for financial support.

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