

N-(4-((*E*)-3-Arylacryloyl)phenyl)acetamide Derivatives and their Antileishmanial Activity

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A atividade leishmanicida de uma série de derivados enônicos (chalconas) sintetizados via reações de condensação de Claisen-Schmidt assistidas por radiação ultrassom foi caracterizada através da análise de suas citotoxicidades contra formas promastigotas de *Leishmania* (*Viannia*) *panamensis*, espécie responsável por mais de 90% dos casos de Leishmania na Colômbia. Dois compostos foram ativos contra Leishmania com índices de seletividade de LC₅₀ EC₅₀⁻¹ (concentração letal média e concentração efetiva média) maiores que 27 e 3, respectivamente. Estes resultados sugerem que a substituição de um dos dois anéis de chalcona (anel A aromático) com oxigênio é apropriada. Um composto deve ser pesquisado quanto à sua atividade leishmanicida, especialmente por ser fácil de obter em elevados rendimentos, tornando possível a produção de medicamentos para o tratamento de leishmaniose cutânea.

The antileishmanial activity of a series of enonic derivatives (chalcones) synthesized via Claisen-Schmidt condensation reactions assisted by ultrasonic radiation was characterized by analyzing their cytotoxicity against *Leishmania* (*Viannia*) *panamensis* promastigotes, a species responsible for over 90% of Leishmania cases in Colombia. Two compounds were active against Leishmania with selectivity indexes of LC₅₀ EC₅₀⁻¹ (lethal concentration 50 and effective concentration 50) higher than 27 and 3, respectively. These results suggest that a substitution on one of the two chalcone rings (aromatic ring A) with oxygen is convenient. Compound **3g** should be further investigated for its antileishmanial activity, especially for being easy to obtain in high yields, making it possible to produce drugs for the treatment of cutaneous leishmaniasis.

Keywords: chalcone, sonochemistry, antileishmanial activity, *Leishmania* (*Viannia*) *panamensis*

Introduction

Leishmania spp is a protozoan parasite of the Trypanosomatidae family that infects approximately 12 million people worldwide. This parasite causes a wide variety of diseases, ranging from cutaneous manifestations to clinical pictures with visceral leishmaniasis.¹ This parasitic infection has become endemic in tropical and

subtropical areas around the world due to the incidence of new cases in which *Leishmania* spp is common among patients with human immunodeficiency virus (HIV).² The administration of pentavalent antimony salts (sodium stibogluconate or meglumine antimoniate), pentamidine, miltefosine and amphotericin B are first and second option treatments to control all leishmanial clinical forms. However, these treatments have severe side effects and have led to the emergence of parasite strains that are resistant to treatment.³⁻⁸ Thus, there is an urgent need for

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new alternatives to control this parasitosis. A large number of natural and synthetic compounds with diverse chemical structures have been analyzed *in vitro*. However, synthetic difficulties and low yields represent the limitations for the development of new antileishmanials. Within the group of compounds with promising antileishmanial activity are nitrogenated heterocycles, such as quinoxalines,⁹⁻¹² benzodiazepines,¹³ indolylglyoxylamides derivatives,¹⁴ pyrimidines and triazines.¹⁵⁻¹⁶ These α,β -unsaturated systems are convenient and easily available as materials or intermediates for the synthesis of a wide variety of heterocyclic compounds.¹⁷ Compounds with α,β -unsaturated-based structures have been reported to exhibit a range of pharmacological activities, including cytotoxicity toward neoplastic,^{18,19} antimetabolic,²⁰ antiviral,²¹ antibacterial^{22,23} and antileishmanial cells.²⁴ With regards to leishmanial activity, many compounds have been studied, but only a few prototypes have made it to preclinical stages, due to, among other reasons, the difficulty of scaling up their production to industrial levels. Strategies that utilize simple syntheses and guarantee the production of sufficient quantities of the compound with the required quality for a pharmaceutical activity are needed to provide new therapeutic alternatives to control infectious diseases, such as leishmaniasis. The synthesis of heterocyclic compounds with enonic fragments can be performed via the non-conventional procedures of green chemistry, in which large amounts of compound can be obtained using methodologies compatible with the environment. In this study, the antileishmanial activity of a series of synthetic chalcones was characterized by screening for the viability of macrophages and promastigotes of *Leishmania (Viannia) panamensis*, the specie responsible for over 90% of cutaneous leishmaniasis cases in Colombia.²⁵

Results and Discussion

Chemistry

An ultrasonic-enhanced synthesis of *N*-(4-((*E*)-3-arylacryloyl)phenyl)acetamides (**3a-k**) was performed under Claisen-Schmidt conditions using the various substituted aromatic aldehydes shown in Figure 1.

The synthesis of *N*-(4-((*E*)-3-arylacryloyl)phenyl)acetamide derivatives was performed by dissolving

N-(4-acetylphenyl)acetamide **1** (1.0 mmol) and aromatic aldehydes (1.0 mmol) in ethanol (5.0 mL) with a KOH catalytic amount. The reaction mixture was placed in an ultrasonic bath at room temperature for 5-20 min, cooled to room temperature and then poured onto crushed ice to obtain the products. The precipitate obtained was filtered, washed with distilled water and recrystallized from ethanol. Although the yields are similar to those reported in the literature for conventional method (stirred at room temperature), the reaction times were significantly shorter (Table 1).²⁶ Thus, it was clear from the data that, ultrasound could accelerate the reaction times to obtain chalcones affording more yield than conventional conditions as can be appreciated from Table 1.

After purification, all synthesized chalcones were characterized by spectroscopic methods, such as infrared and nuclear magnetic resonance (NMR) spectroscopies, mass spectrometry and elemental analysis. In the infrared spectra of compounds **3(d, g, h, i)**, absorptions were observed between 1662-1676, 1667-1681 and 1532-1598 cm^{-1} , which were related to HN-C=O , carbonyl and -C=C stretching, respectively. The ^1H NMR spectra for all chalcones displayed signals between 7.45 and 7.52 ppm, corresponding to hydrogens attached to nitrogen. The signals corresponding to aromatic hydrogens were displayed between 6.84 and 8.15 ppm. The ^1H NMR spectra of compounds (**3d, 3g, 3h** and **3i**) showed a doublet between 7.35 and 7.69 ppm, as well as 7.39 and 7.98 ppm, corresponding to $\text{H}\alpha$ and $\text{H}\beta$, respectively. The ^1H NMR spectra indicated that the chalcones were geometrically pure and of the *trans* configuration (J 15.6 Hz), which is in agreement with data previously described.²⁶

Biological activity assays

Recent studies have focused on searching whether modifications as substitutions and additions, located specifically on the ring A of the molecule, differentially modulate chalcones biological activity. In this study, we examined the leishmanicidal activity of various chalcones with structural modifications and identified two compounds with antileishmanial activity against promastigotes. Results of the bioassays with the synthesized compounds are summarized in Table 2. Compounds **3g** and **3h** (selectivity

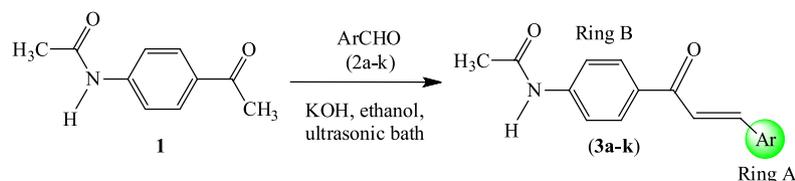


Figure 1. Scheme of synthesis of *N*-(4-((*E*)-3-arylacryloyl)phenyl)acetamide derivatives.

Table 1. Reaction conditions of synthesis of *N*-(4-((*E*)-3-arylacryloyl)phenyl)acetamide derivatives

entry	Ar	Reaction condition		
		time / min	Yield / %	mp / °C
3a	C ₆ H ₅	20/overnight ^a	71/80 ^a	161-163/161.7-162.2 ^a
3b	4-H ₃ CC ₆ H ₄	8/overnight ^a	84/79 ^a	198-201/197.5-199 ^a
3c	4-ClC ₆ H ₄	17/overnight ^a	75/83 ^a	215-217/ 215-215.7 ^a
3d	4-FC ₆ H ₄	10	80	119-121
3e	4-O ₂ NC ₆ H ₄	7/overnight ^a	87/89 ^a	228-230/239.7-241.0 ^a
3f	4-H ₃ COC ₆ H ₄	5/overnight ^a	85/84 ^a	198-200/206.5-207.0 ^a
3g	3,4-OCH ₂ OC ₆ H ₂	6	92	175 (dec)
3h	3,4,5- <i>tri</i> -H ₃ COC ₆ H ₂	5	83	150 (dec)
3i	2-pirryl	17	90	216-218
3j	2-furyl	20/overnight ^a	87/95 ^a	99-103/118.1-119.0 ^a
3k	2-thienyl	20/overnight ^a	90/90 ^a	143-147/147.8-149.3 ^a

^aData to *N*-(4-((*E*)-3-arylacryloyl)phenyl)acetamide derivatives reported in the literature.²⁶

index of ca. 27 and ca. 3, respectively) were the most active against *Leishmania* parasites with respect to other derivatives. Notably, compound **3g** exhibited superior parasitocidal activity compared to pentamidine isethionate (positive control). These compounds are substituted with oxygen on the ring A, enhancing their leishmanicidal capacity over flagellate forms. Similar findings have been reported for other synthetic chalcones with antileishmanial activity, demonstrating that chalcone molecules acting as growth inhibitors of promastigotes and amastigotes are preferable if they contain oxygenated substitution patterns and are hydrophilic in character.²⁷

The pharmacophore for antileishmanial chalcones has been proposed to be composed of two aromatic rings and a spacing chain (propanone). In addition, the importance

of the substituents on the ring A has been demonstrated, as well as the low impact of the ring B substitution pattern on the antileishmanial activity.²⁸ It has been reported the notable influence of the hydrophilic/lipophilic radius of substituents on both aromatic rings.²⁹ In the present study, all compounds have the *p*-acetamide substituent on the ring B. Thus, the differences in cytotoxic activity are strictly a result of the influence of the substituent on the ring A. Due to the presence of the α,β -unsaturated carbonyl system, molecules could possibly react with nucleophilic species through a Michael addition, which has already been reported for chalcones with antimalarial activity.³⁰ However, a study has demonstrated the low influence of this system on antiparasitic activity, indicating that propanone only functions as a spacer between the aromatic rings.²⁹ None of the synthesized analogs, such as the 4-halogenated and heteroaromatic rings, exhibited significant cytotoxic activity against promastigotes. Notably, the **3f** analog (4-H₃CO), although oxygenated, does not show significant inhibitory activity, which may be due to the lack of a more voluminous substituent which is present in compounds **3g** and **3h**. Finally, with our data and the number of compounds synthesized, it is premature to conclude appropriately about the influence of electron-donating or -withdrawing substituents in the activity.

Our results also show that the methylenedioxy derivative exhibits strong inhibitory activity on promastigote growth with an appreciable selectivity index. The fact that compound **3g** does not show cytotoxicity is probably consequence that the methylenedioxy bridge prevents its oxidation to a reactive quinone molecule, being in that way less cytotoxic.³¹ Thus, this molecule acts on some molecular target of the parasite. However, it is necessary to complement this data with biological activity studies on amastigotes, as well as *in vivo* studies, to determine

Table 2. *In vitro* cytotoxic activity against Phagocyte J774 cell lines and leishmanicidal activity against *Leishmania panamensis* promastigotes

Compound	<i>In vitro</i> activity against		Selectivity index
	Phagocyte J774 cell line	<i>Leishmania panamensis</i> Promastigote	
	LC ₅₀ / μ mol	EC ₅₀ / μ mol	LC ₅₀ EC ₅₀ ⁻¹
3a	23.8 \pm 1.8	55.7 \pm 3.5	ca. 0
3b	58.1 \pm 1.0	> 715.99 \pm 0	ca. 0
3c	8.0 \pm 0.9	49.7 \pm 0.77	ca. 0
3d	> 705.97 \pm 0	> 706 \pm 0	ca. 1
3e	> 644.5 \pm 0	> 644.5 \pm 0	ca. 1
3f	> 677.2 \pm 0	> 677.2 \pm 0	ca. 1
3g	> 646.5 \pm 0	< 23.9 \pm 0	ca. 27
3h	72.82	< 20.9 \pm 0	ca. 3
3i	> 786.52 \pm 0	> 592.3 \pm 0	ca. 1
3j	> 783.48 \pm 0	> 783.5 \pm 0	ca. 1
3k	> 737.09 \pm 0	> 737.1 \pm 0	ca. 1
Pentamidine	ca. 12	< 1.18	ca. 10.25

LC₅₀: lethal concentration 50; EC₅₀: effective concentration 50.

if this activity is conserved. The mechanism of action of this chemical compound needs to be elucidated for the development of novel therapeutic agents to treat cutaneous leishmaniasis or parasitocidal compounds against promastigote forms.

Conclusions

In the present work, we report the preparation in two steps of N-(4-((E)-3-arylacryloyl)phenyl)acetamide derivatives under ultrasonic irradiation. This mild, convenient and improved protocol for the ultrasound-promoted preparation of chalcones indicates that, unlike conventional conditions, ultrasonic irradiation results in higher yields, shorter reaction times and milder conditions. Due to the broad spectrum of biological activities of chalcones, specifically N-(4-((E)-3-arylacryloyl)phenyl)acetamide derivatives were selected to biological evaluation against *Leishmania panamensis* promastigotes (in an initial screening to analyze the antileishmanial potential).

Higher cytotoxic activity against promastigotes was observed with compounds with oxygenated functions on the ring A. Due to its significant antileishmanial activity and high selectivity index, compound **3g** (methylenedioxy derivative) appears to be a potential candidate for more detailed future studies for the development of new drugs against leishmaniasis, specifically, cutaneous forms associated with the infection caused by *Leishmania* (*Viannia*) *panamensis*.

Experimental

General

All the chemicals and solvents were purchased from Merck or Sigma Aldrich and used without purification. Melting points were determined using a Thermo Scientific Fluke 51 II, model IA 9100 melting point apparatus and are reported uncorrected. ¹H and ¹³C NMR (400 and 100 MHz, respectively) spectra were recorded at room temperature on a Bruker Ultra Shield 400 using TMS (tetramethylsilane) as internal standard and deuterated chloroform (CDCl₃) as solvent. High-resolution mass spectrometry ESI-MS analyses were conducted in a high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) mass spectrometer (Waters/Micromass Q-TOF micro, Manchester, UK) with a constant nebulizer temperature of 100 °C. The experiments were carried out in positive ion mode, and the cone and extractor potentials were set at 10 and 3.0 V, respectively, with a scan range of *m/z* 100-600. MS/MS experiments were carried out by mass selection of a specific ion

in Q1, which was then submitted to collision-induced dissociation (CID) with helium in the collision chamber. The product ion MS analysis was accomplished with the high-resolution orthogonal TOF analyzer. The samples were directly infused into the ESI source, via a syringe pump, at flow rates of 5 μL min⁻¹, via the instrument injection valve. EIMS spectra were run on a Shimadzu GC-MS 2010 spectrometer, which was operating at 70 eV. IR spectra were recorded as KBr pellets on a Shimadzu FTIR-8400 instrument. The ultrasonic irradiation was performed by using a Branson ultrasonic cleaner bath, model 1510, 115 V, 1.9 L with mechanical timer (60 min with continuous hold) and heater switch, 47 KHz.

Typical procedure for the synthesis of 4-acetylaminochalcones (**3**)

A mixture of 4-acetamidoacetophenone (5 mmol), appropriate aromatic aldehyde (5 mmol), KOH (1 mmol) and ethanol (2 mL) was sonicated for 5-20 min in the water bath of an ultrasonic cleaner bath. The progress of the reaction was monitored by thin layer chromatography (TLC) using dichloromethane:ethyl acetate (9:1 v/v) as eluent. The reaction mixture was cooled in ice-water bath. The formed precipitate was filtered, washed with cool water and purified by recrystallization from ethanol to give the target compounds in high yields of 71-92%. The spectral data and melting point of compounds **3a-c**, **3e-f** and **3j-k** were consistent with literature values.²⁶ The authenticity of the products (**3d**, **3g**, **3h** and **3i**) was established by their ¹H NMR, IR and MS data.

(2E)-1-(4-Acetylamino-phenyl)-3-(4-fluorophenyl)prop-2-enone (**3d**): 80% yield; mp 119-121 °C; FTIR v/cm⁻¹ 3473 (H-NCO, *st*), 1657 (NC=O, *st*), 1596 (-C=O, *st*), 1508 (-C=C, *st*); ¹H NMR δ 8.04 (d, 2H, *J* 8.5 Hz, 1-Aryl), 7.84 (t, 2H, 3-Aryl), 7.76 (d, 1H, *J* 15.6 Hz, Hβ), 7.69 (d, 2H, *J* 8.5 Hz, 1-Aryl), 7.63 (d, 1H, *J* 15.6 Hz, Hα), 7.21 (t, 2H, *J* 8.5 Hz, 3-Aryl), 2.06 (s, 3H, CH₃); MS (ESI, positive scan) *m/z* 306.1270 [M + Na]⁺.

(2E)-1-(4-Acetylamino-phenyl)-3-(3,4-metileendioxy-phenyl)prop-2-enone (**3g**): 92% yield; mp 175 °C (dec); FTIR v/cm⁻¹ 3455 (H-NCO, *st*), 1657 (NC=O, *st*), 1599 (-C=O, *st*), 1532 (-C=C, *st*); ¹H NMR δ 8.00 (d, 2H, *J* 8.7 Hz, Hm, 1-Aryl), 7.72 (d, 1H, *J* 15.6 Hz, Hβ), 7.63 (d, 2H, *J* 8.6 Hz, 1-Aryl), 7.35 (d, 1H, *J* 15.5 Hz, Hα), 7.15 (d, 1H, *J* 1.5 Hz, Ho, 3-Aryl), 7.12 (dd, 1H, *J* 8.03, 1.5 Hz, Ho, 3-Aryl), 6.84 (d, 1H, *J* 8.03 Hz, Hm, 3-Aryl), 6.01 (d, 1H, *J* 8.0 Hz, CH₂), 2.21 (s, 3H, CH₃); ¹³C NMR δ 188.8, 149.9, 148.5, 129.8, 101.6; MS *m/z* 309 (100, M⁺).

(2*E*)-1-(4-Acetylamino-phenyl)-3-(3,4,5-trimethoxyphenyl)prop-2-enone (**3h**): 83% yield; mp 150 °C (dec); FTIR ν/cm^{-1} 3456 (H-NCO, *st*), 1671 (NC=O, *st*), 1599 (C=O, *st*), 1532 (C=C, *st*); $^1\text{H NMR}$ δ 7.99 (d, 2H, *J* 8.5 Hz, H_m, 1-Aryl), 7.93 (s, 1H, N-H), 7.68 (m, 3H, H_o, 1-Aryl y H α), 7.39 (d, 1H, *J* 15.6 Hz, H β), 6.83 (s, 2H, H_o, 3-Aryl), 3.90 (s, 6H, m (OCH₃)₂), 3.88 (s, 3H, *p*-OCH₃), 2.20 (s, 3H, CH₃); $^{13}\text{C NMR}$ δ 189.0, 153.5, 144.7, 142.1, 130.4, 129.8, 121.2, 105.9, 60.9, 56.2, 56.0; MS *m/z* 355 (100, M⁺).

(2*E*)-1-(4-Acetylamino-phenyl)-3-(2-pirryl)prop-2-enone (**3i**): 90% yield; mp 216-218 °C; FTIR ν/cm^{-1} 3301 (H-NCO, *st*), 1669 (NC=O, *st*), 1647 (C=O, *st*), 1527 (C=C, *st*); $^1\text{H NMR}$ δ 11.65 (s, 1H, NH), 9.91 (s, 1H, NH), 7.98 (d, 2H, *J* 8.3 Hz, 1-Aryl), 7.73 (d, 2H, *J* 8.3 Hz, 1-Aryl), 7.54 (broad signal, 2H, H α and H β), 7.10 (broad signal, 1H, 2-pirryl), 6.69 (broad signal, 1H, 2-pirryl), 6.20 (broad signal, 1H, 2-pirryl), 2.08 (s, 3H, CH₃); MS (ESI, positive scan) *m/z* 277.1696 [M + Na]⁺.

Cell cultures

Murine macrophages of the J774 cell line

Macrophages of the J774 cell line were stored in 25 cm² polystyrene boxes (Techno Plastic Products AG, Switzerland) in RPMI 1640 medium (Gibco BRL-Life Technologies Inc, Grand Island, NY) supplemented with 5% of fetal bovine serum and incubated at 37 °C with 5% CO₂. The culture medium was replaced every other day.³²

Parasites

Promastigotes of *Leishmania panamensis* (MHom/CO/87/UA140) were generously donated by Dr. Sara María Robledo from the Universidad de Antioquia (Colombia) and cultivated in 25 cm² polystyrene boxes (Techno Plastic Products AG, Switzerland) in RPMI 1640 medium (Gibco BRL-life Technologies Inc, Grand Island, NY) supplemented (cRPMI) with 5% fetal bovine serum (FBS, Microgen, Bogota, Colombia) and 1% L-glutamine (Gibco BRL-Life Technologies, Inc, Grand Island, NY) at 26 °C. The parasites were incubated in 5 to 6 mL of medium for 6 days. To change the media, the parasite culture was placed in 15 mL polystyrene tubes (BD Biosciences, Falcon) and centrifuged at 1500 rpm for 5 min. Fresh medium was subsequently added.³²

Evaluation of the cytotoxicity of chalcones against the J774 cell line

An aliquot of cell suspension (100 μL , 1×10^4 cells well⁻¹) was used to seed 96 well flat bottom boxes (Techno Plastic

Products AG, Switzerland) for a 24 h incubation period to allow adhesion. Cells were later exposed to 100 μL of 4 different compounds prepared by a series of 1:4 dilutions in curved bottom plates of 96 wells (Techno Plastic Products AG, Switzerland) at the following concentrations: 200, 50, 12.5 and 3.25 $\mu\text{g mL}^{-1}$. Next, the cells were incubated at 37 °C with 5% CO₂ for 72 h. Cells that were not exposed to these compounds and wells containing only the culture medium served as controls. For positive controls for cytotoxicity, cells were exposed to the following concentrations of pentamidine isethionate (Pentacarinat[®], Sanofi-aventiz, UK): 10, 2.5, 0.625 and 0.156 $\mu\text{g mL}^{-1}$. The cells were later exposed to resazurin at a final concentration of 44 $\mu\text{mol L}^{-1}$ well⁻¹ and incubated again for 4 h under the same conditions. Subsequently, the reduction of resazurin to resorufin was evaluated using a plate reader, Tecan GENios Microplate Reader (Tecan Trading AG, Switzerland).^{32,33}

Evaluation of the efficiency of chalcones on *Leishmania* (Viannia) *panamensis* promastigotes

Leishmania (Viannia) *panamensis* promastigotes (2×10^5 parasite well⁻¹) were placed in a 96 well plate containing different concentrations of compounds (200, 66.6, 22.2 and 7.4 $\mu\text{g mL}^{-1}$) and incubated at 26 °C for 72 h. Subsequently, 44 $\mu\text{mol L}^{-1}$ well⁻¹ of resazurin were added to parasites and incubated for 48 h. Resorufin derived from viable cells was quantified using the Tecan GENios Microplate Reader (Tecan Trading AG, Switzerland). Wells with either only promastigotes or culture medium served as controls. As antileishmanial positive control, the promastigotes were exposed to pentamidine isethionate (leishmanicidal drug) in a series of four 1:3 dilutions to an initial concentration of 10 $\mu\text{g mL}^{-1}$.^{32,33}

Variable incubation time in the exposition to resazurin for murine and parasite cells is based in previous assays in which we evidenced a differential metabolism that depends of the kind of cellular population. Specifically J774 macrophages are faster in metabolizing (activity of mitochondria) the resazurin than the promastigotes and a period of 4 and 48 h, respectively, is necessary to obtain the maximum production of resorufin (derived from wells with viable cells without treatment).

Analysis of results

The results were analyzed using Graph Pad Prism version 5.00 statistical software (Graph Pad Software, USA) to calculate the lethal concentration 50 (LC₅₀) of compounds **3a-k**. This value corresponds to the concentration at which 50% inhibition of the viable cell

population is observed after being exposed to compounds **3a-k** in cytotoxicity assays against J774. The effective concentration 50 (EC₅₀) corresponds to the concentration at which there is a 50% inhibition of promastigote viability with respect to that of the control. These data were obtained in efficiency assays in which compounds (**3a-k**) were incubated with promastigotes.

Supplementary Information

Supplementary information (Figures S1-S12) is available free of charge at <http://jbcs.sbq.org.br> as PDF file.

Acknowledgments

The authors thank the members of their respective research groups from the Universidad Nacional de Colombia and Universidad del Atlántico. Part of this project was financed by Bogotá Research Division (DIB) at the Universidad Nacional de Colombia (project No. 16015).

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Submitted: April 19, 2013

Published online: August 23, 2013

Supplementary Information

N-(4-((E)-3-Arylacryloyl)phenyl)acetamide Derivatives and their Antileishmanial Activity

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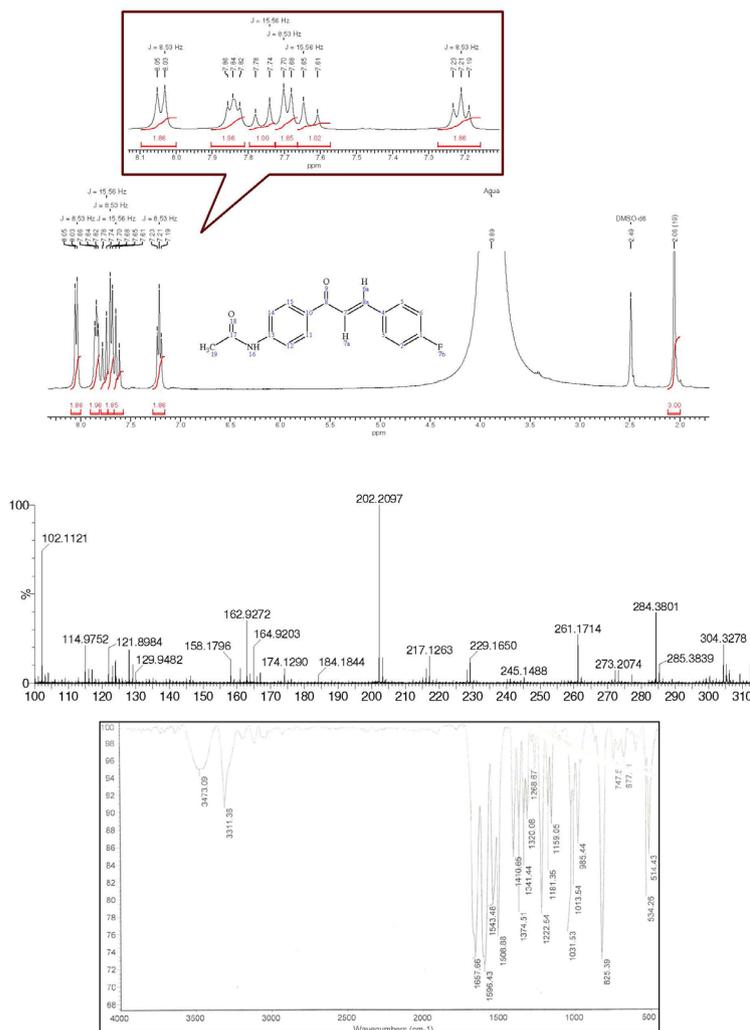


Figure S1. ¹H NMR, MS and IR spectra for compound 3d.

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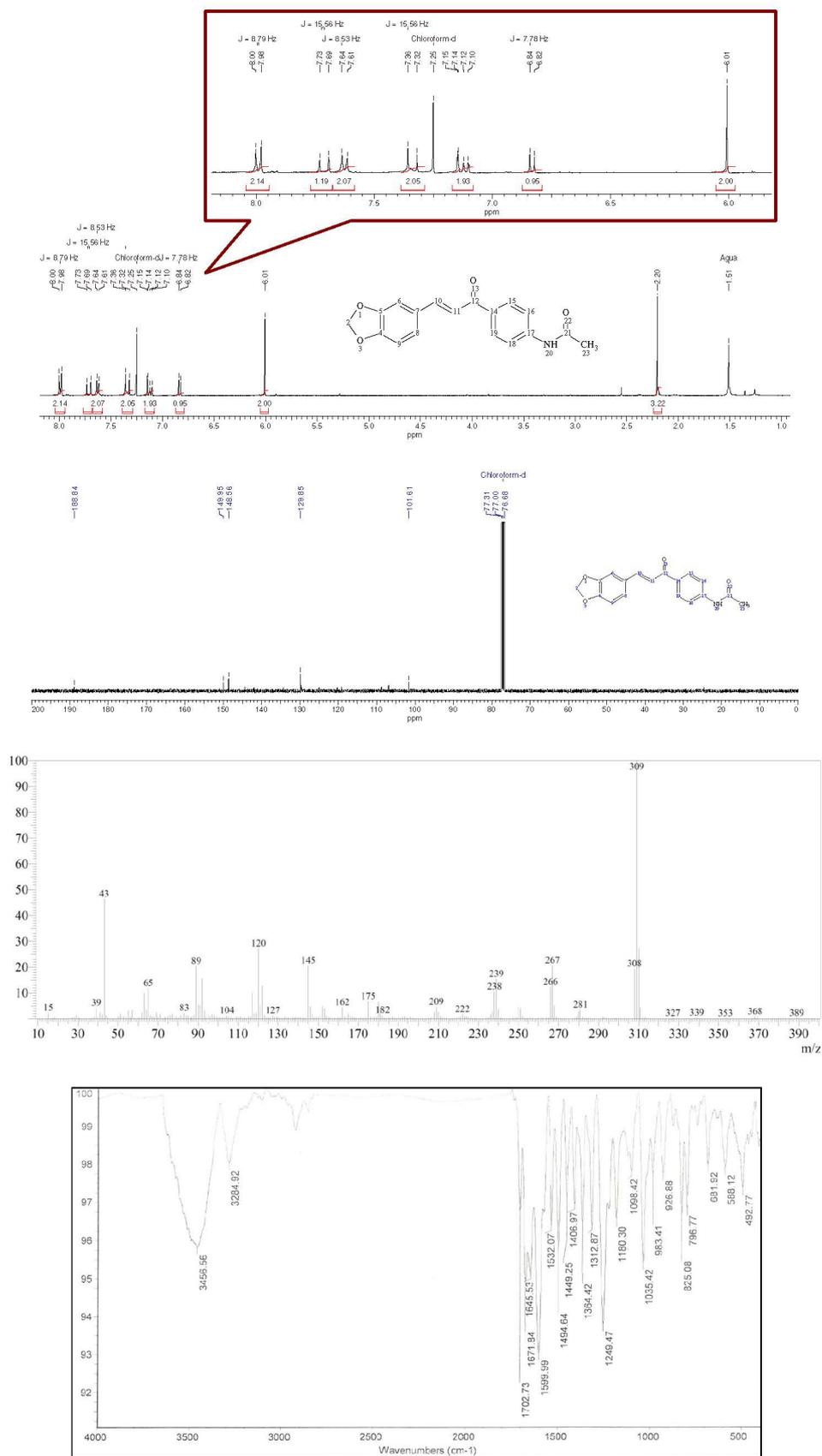


Figure S2. ¹H, ¹³C NMR, MS and IR spectra for compound 3g.

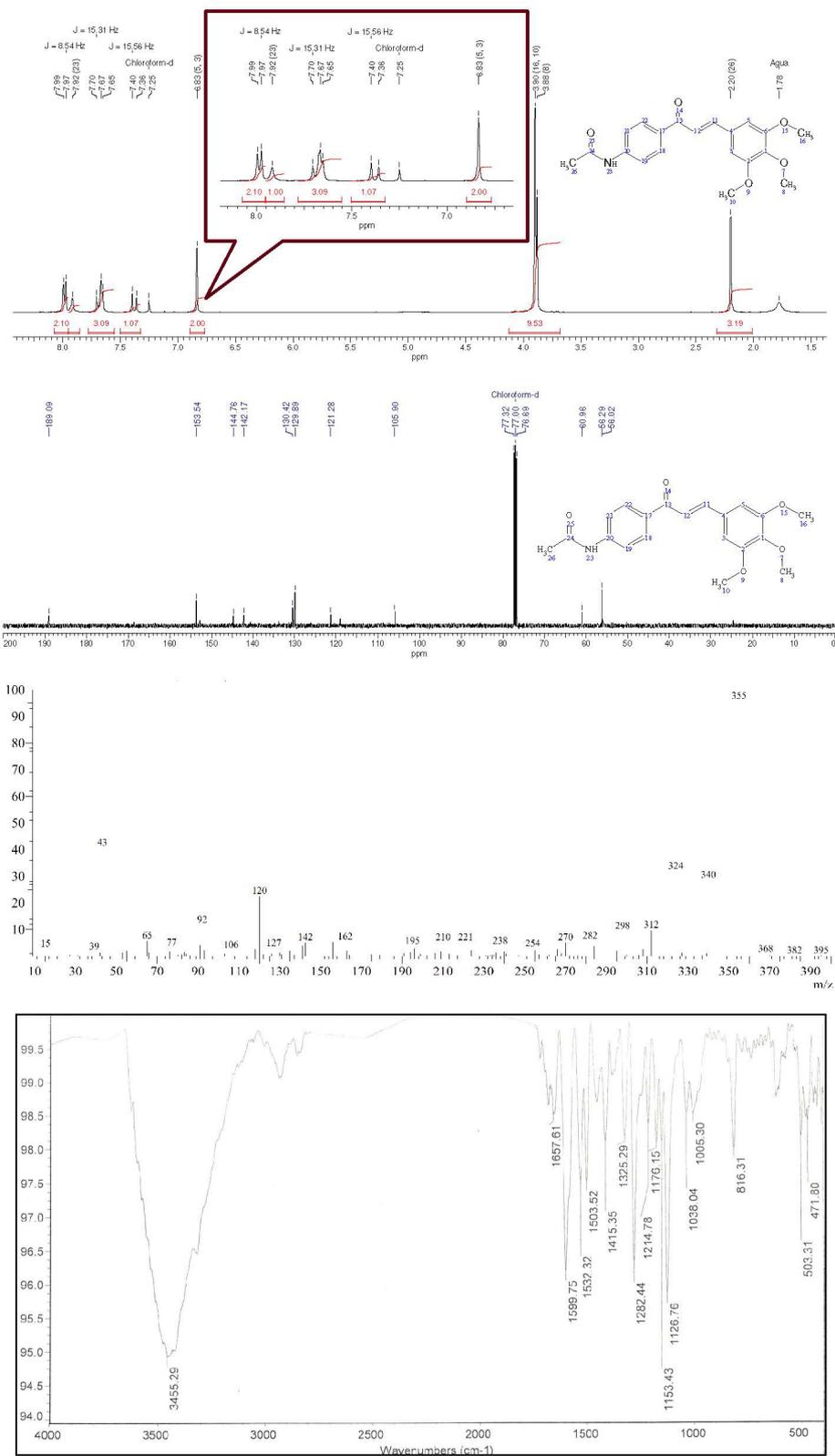


Figure S3. ¹H, ¹³C NMR, MS and IR spectra for compound 3h.

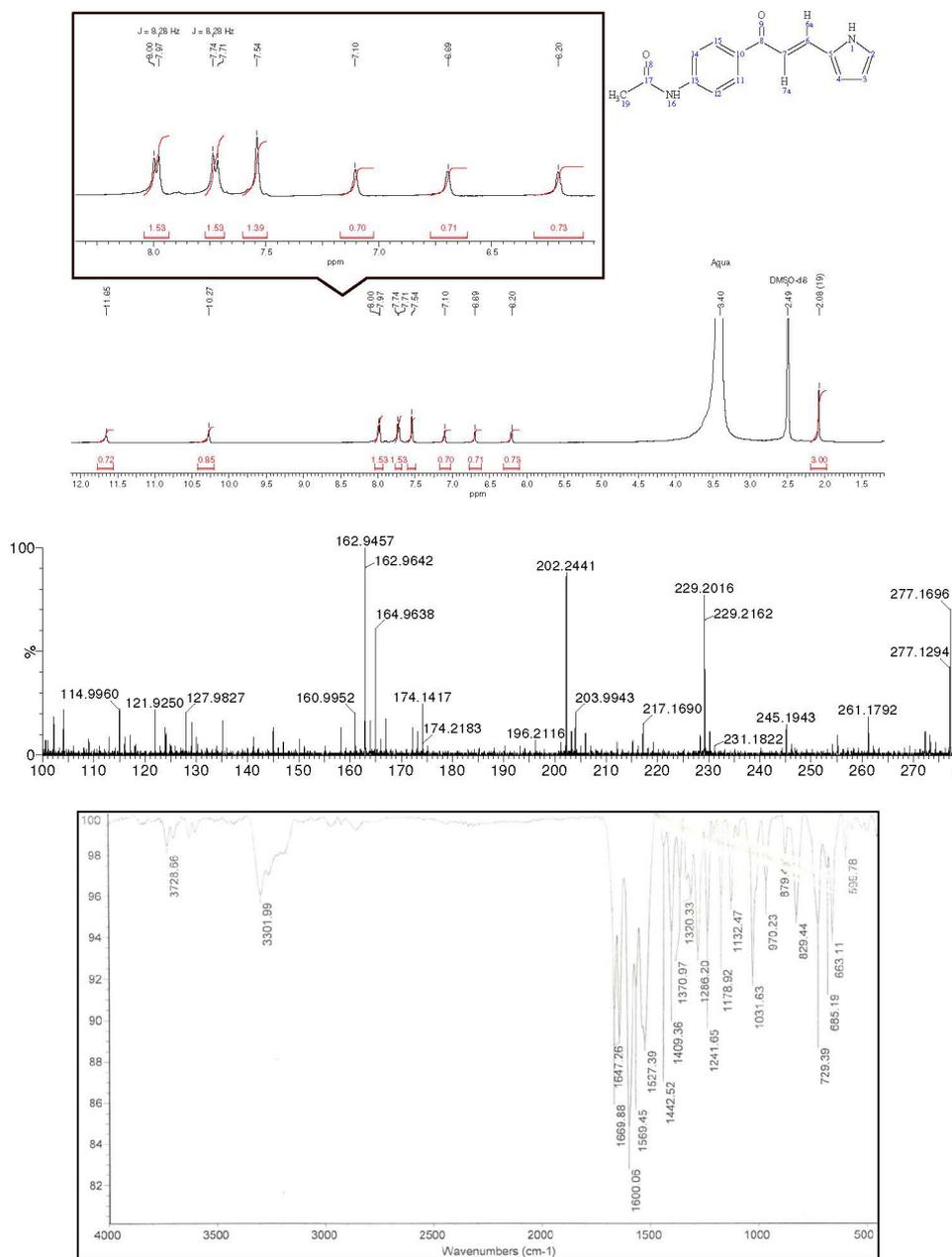


Figure S4. ^1H NMR, MS and IR spectra for compound **3i**.