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ANTILEISHMANIAL ACTIVITY AND COMPUTATIONAL STUDIES OF SOME HYDRAZONE DERIVATIVES POSSESSING QUINOLINE NUCLEUS

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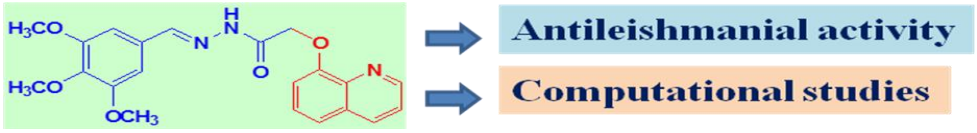
ABSTRACT

Antileishmanial activity of the previously synthesized hydrazone derivatives 1-3 was evaluated in vitro on a culture of Leishmania donovani promastigotes (Strain S1). The results were compared with the standard drug Amphotericin B. out of all, compound three was found to possess good activity when compared to the standard drug. Physicochemical properties and bioactivity score studies were carried out using Lipinski's rule of five, Molinspiration (web based software). The results of computational studies were found in accordance with the results obtained experimentally. All compounds were found to follow Lipinski's rule of five with the bioactivity score better than standard.



KEYWORDS: Antileishmanial activity, hydrazone derivatives and computational studies.

1. INTRODUCTION

Leishmaniasis is a diseases caused by parasitic protozoans classified as Leishmania species.[1,2] The transmission of the disease may occur naturally by zoonotic or anthroponotic mode, and it is generally by the bite of a phlebotomine sandfly species.[2,3] Leishmaniasis is reported as the worldwide public health problem in at least 88 countries with an estimation of 350 million people at risk, global prevalence of all forms 12 million, 1.5 to 2 million new cases, 70,000 deaths per year due to cutaneous leishmaniasis (CL) and 500,000 new cases and 59,000 deaths per year from visceral leishmaniasis (VL).[4] Clinically the spectrum of leishmaniasis is changed and encompasses subclinical (inapparent), localized (skin lesions) and disseminated infection (cutaneous, mucosal or visceral) while the visceral manifestation are more severe form of leishmaniasis due to fatality and no treatment. The pentavalent antimonials such as sodium stibogluconate (pentostam) and meglumine antimoniate (glucantime) play vital role in the chemotherapy of all leishmaniasis manifestations since 1940 but these have some toxic effects.[5,9] Variety of heterocyclic nucleus has been evaluated as antileishmanial agents.[10,13] Quinolines and their derivatives have been found to exhibit variety of pharmacological activities such as antibacterial, antifungal, antimycobacterial, antidepressant, antimalarial, anticonvulsant, antiviral, anticancer, hypotensive and anti-inflammatory activities.[14,20] On the other hand hydrazones owing to their physiological activity and co-ordination capability are widely investigated as potential antileishmanial, antiplatelet, antiulcer, antitumor, antiprotozoal, antibacterial and antifungal agents.[21,28] In a recent study the quinoline hydrazone hybrids are evaluated for leishmanicidal trypanocidal and cytotoxic activity.[29] Some other studies also represented the importance of hydrazone and the quinoline nucleus as antileishmanial agent.[30,35] Keeping in mind the versatile biological application of quinoline nucleus and hydrazone functionality we designed our work in such a way that the combination of these two moieties will be responsible to enhance the activity.

2. EXPERIMENTAL

2.1. Materials and method

Solvents and organic reagents were purchased from Sigma Aldrich, Merck (Germany) and were used without further purification. Melting points (mp) were performed using a Mel-temp instrument, and the results are uncorrected. Precoated aluminium sheets (silica gel 60 F_{254}, Merck Germany) were used for thin-layer chromatography (TLC) and spots were visualized under UV light. Elemental analyses were performed on Heraeus Vario EL III analyzer. IR spectra were recorded on Perkin-Elmer model 1600 FT-IR RX1 spectrophotometer as KBr discs. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 300 spectrometer using $CDCl_3$ and DMSO as solvents with TMS as internal standard. Splitting patterns are designated as follows; s, singlet; d, doublet; dd, double

doublet; t, triplet; m, multiplet. Chemical shift values are given in ppm. ESI-MS was recorded on a MICROMASS QUATTRO II triple quadrupole mass spectrometer.

2.2. General procedure for the synthesis of substituted quinoline hydrazone derivatives (1-3)

The compound 1, 2 & 3 were synthesized and subjected for their structure elucidation by various spectroscopic techniques as reported[28], Figure-1.

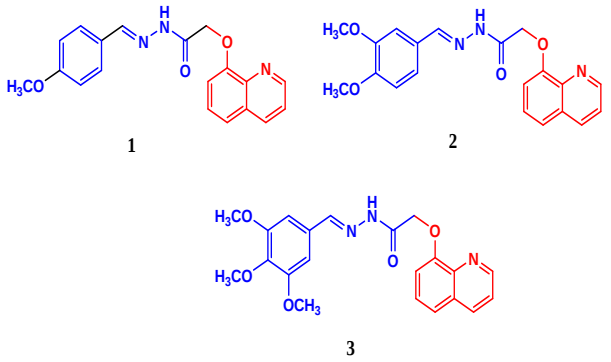


Figure-1- Representing the structures of compounds 1-3

2.3. In vitro antileishmanial assay (36-37)

Antileishmanial activity of the compounds was tested in vitro on a culture of Leishmania donovanipromastigotes (Strain S1). In a 96 well microplate assay the compounds with Regional Issue "Organic Chemistry in Argentina" ARKIVOC 2011 (vii) 297-311 Page 309 ©ARKAT-USA, Inc. appropriate dilution were added to the promastigotes culture (2 x 10^6cell/mL) to get the final concentrations of 40, 8 and 1.6 µg/ml. The plates were incubated at 26 C for 72 hours and growth was determined by Alamar blue assay. Amphotericin B was used as the standard antileishmanial agent.

2.4. Physicochemical properties (38-40)

Physico-chemical properties of compounds 1-3 and Amphotericin B were checked with the help of software Molinspiration physicochemical prpperties calculator available online (www. molinspiration.com). The properties which are calculated are partition coefficient (log P), molar refractivity, molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation.

2.5. Bioactivity score (38-40)

The compounds and standard were also checked for the bioactivity score by calculating the activity score for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www. molinspiration.com). Calculated drug likeness score of each compounds and compared with the specific activity of each compound, and the results were compared with standard drug.

3. RESULTS AND DISCUSSION

3.1. Chemistry

The schematic representation of the diagrammatic route for the synthesis of substituted quinoline hydrazone derivatives 1-3, and their spectral details to confirm the formation of compounds is reported.[28]

3.2. Antileishmanial activity

Antileishmanial activity of the compounds (1-3) was tested in vitro on a culture of Leishmania donovani promastigotes (Strain S1) and Amphotericin B was used as the standard antileishmanial agent. The results are reported in **table-3**, the obtained results revealed that compound three was found to possess good activity while the rest all were found to possess moderate activity. The results obtained experimentally also supported by the results of computational studies.

Table-3: Representing the IC_{50} values of all the synthesized substituted pyrazole carbaldehyde derivatives (1-3) against Leishmania donovani promastigotes (Strain S1).

S. No.	Molecular formula	IC_{50} (µg/ml)
1	$C_{19}H_{17}N_3O_3$	35
2	$C_{20}H_{19}N_3O_4$	25
3	$C_{21}H_{21}N_3O_5$	7.0
Amphotericin B	$C_{47}H_{73}NO_{17}$	0.15

3.4. Physicochemical properties

Lipinski's rule of five states that, in general, an orally active drug has not more than 5 hydrogen bond donors (OH and NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P less than 5, number of violation less than 4.[39] All the compounds were found in compliance with Lipinski 'Rule of Five' and the results are reported in **Table-1,** while the standard is not in accordance with the Lipinski 'Rule of Five'.

Table-1: Representing the physicochemical properties of all the synthesized compounds (1-3) and ciprofloxacin.

Physicochemical property score	Compounds			
	1	2	3	Amphotericin B
miLogP	2.682	2.672	2.657	-2.49
TPSA	72.822	82.056	91.29	319.61
Natoms	25.0	27.0	29.0	65
MW	335.363	365.389	395.415	924.09
nON	6	7	8	18
nOHNH	1	1	1	13
Nviolations	0	0	0	3
Nrotb	6	7	8	3
Volume	301.266	326.812	352.357	865.48

3.5. Bioactivity Score

The bioactivity score was calculated for GPCR ligand, Ion channel modulator, Kinase inhibitor, nuclear receptor ligand, Protease inhibitor and enzyme inhibitor. For average organic molecule the probability of bioactivity score is more than 0.00 then it is active, -0.50 to 0.0 then moderately active and if less than -0.50 then inactive. Here in our study all the synthesized compounds 1-3 were subjected for bioactivity score presented in **Table-2**. The results for bioactivity score exhibited that all the compounds have better bioactivity score than the standard used in the study but still they are falling in the category of moderately active compounds range.

Table-2: Representing the bioactivity score of all the synthesized compounds (1-3) and ciprofloxacin.

Bioactivity score	Compounds			
	1	2	3	Amphotericin B
GPCR ligand	-0.34	-0.33	-0.32	-3.06
Ion channel modulator	-0.69	-0.65	-0.62	-3.53
Kinase inhibitor	-0.39	-0.37	-0.34	-3.59
Nuclear receptor ligand	-0.66	-0.64	-0.65	-3.45
Protease inhibitor	-0.50	-0.50	-0.48	-2.45
Enzyme inhibitor	-0.32	-0.30	-0.28	-2.95

4. CONCLUSION

The substituted quinoline hydrazone derivatives 1-3 were synthesiszed and evaluated for antileishmanial activity against the culture of Leishmania donovanipromastigotes (Strain S1). Results revealed that compound three exhibited good activity. To support the experimental results the computational studies were carried out, the drug likeness and physicochemical properties was checked. The results revealed that all the compounds follow the Lipinski rule of five and bioactivity score is found better than the standard used in the study.

5. CONFLICT OF INTEREST

The authors have no conflict of interests.

6. ACKNOWLEDGEMENT

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