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Antileishmanial screening, physicochemical properties and drug likeness of pyrazole carbaldehyde derivatives

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ABSTRACT

Antileishmanial activities of the five pyrazole derivatives were evaluated in vitro on a culture of Leishmania donovani promastigotes (Strain S1). The results for Antileishmanial activity were compared with the standard drug Amphotericin B. Compound three and four were found to possess good activity than the standard drug. All the compounds were characterized by various spectroscopic techniques such as IR, ^{1}H-NMR, ^{13}C-NMR etc. Physicochemical properties and bioactivity score studies were carried out using Lipinski's rule of five, Molinspiration (web based software). The results of computational studies found in accordance with the results obtained experimentally.

Key words: Antileishmanial activity, synthesis and characterization, bioactivity score, physicochemical properties.

Introduction

Leishmanisis, a tropical disease resulting from infection of macrophages by obligate intracellular parasites of the genus Leishmania [1-3]. It is a worldwide 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) occurs 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]. Many parts of Asia and Africa are vulnerable to leishmaniasis [8]. The first line treatment options for the visceral form of leishmaniasis are limited and involve the administration of pentavalent antimonials (sodium stibogluconate (SSG) and meglumine antimoniate) and amphotericin B [9].

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Second line drugs include, pentamidine, paromomycin and miltefosine, but these drugs have not experienced widespread use due to the severe toxicities, parenteral administration and resistance issues [9]. Pentamidine presents several side effects, including renal and hepatic toxicities, pancreatitis, hypotension and cardiac abnormalities [10]. Paromomycin has limited use for the treatment of VL [11]. Miltefosine, an orally effective drug also suffers from nephrotoxicity, hepatotoxicity and teratogenicity [11]. So far, no vaccine has been clinically approved for human use [12]. Pyrazole, a five membered heterocycle have been reported to show a broad spectrum of biological activities [13-28] including antibacterial, antifungal, anti-inflammatory, and anti-depressant activities. Its derivatives, possess a wide range of biological and physiological activities such as anti-implantation, antitumor, antiarthritic, analgesic, immunosuppressive activities and industrial applications and also possess cerebroprotective effect antiviral activity against flavivirus and HIV and antiprotozoal. The compounds possessing the pyrazole nucleus are widely investigated as antileishmanial agent [29-34]. Our research is designed keeping in mind the importance of pyrazole nucleus and its

antileishmanial activity to find out the potential antileishmanial agents.

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 F254, 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. 1H NMR and 13C NMR spectra were recorded on Bruker AVANCE 300 spectrometer using CDCl3 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.

General procedure for the synthesis of compounds (E)-2-[1-(substituted-phenyl)ethylidene]-1-phenylhdrazine (a1-a5)

To a 100 mL round bottom flask was added an appropriate ketone (10 mmol), phenylhydrazine (10 mmol), few drops of glacial acetic acid and 50 mL absolute ethanol. The reaction mixture was refluxed at 80 0C. Completion of reaction was monitored by TLC, solid precipitate was obtained, filtered, dried and recrystallized from ethanol.

General procedure for the synthesis of compound 1-5

Phosphorous oxychloride (25 mmol) was added to DMF (100 mL) at 0 0C and stirred for 30 min. Compound a1-a5 (10 mmol) was added slowly to this mixture and stirred for 5 h. The crude reaction mixture was then quenched into water (1 L) and stirred for an additional 1 h and extracted with ethyl acetate. The organic layer was separated, washed with water, dried and evaporated under reduced pressure. The crude was recrystallized from ethanol.

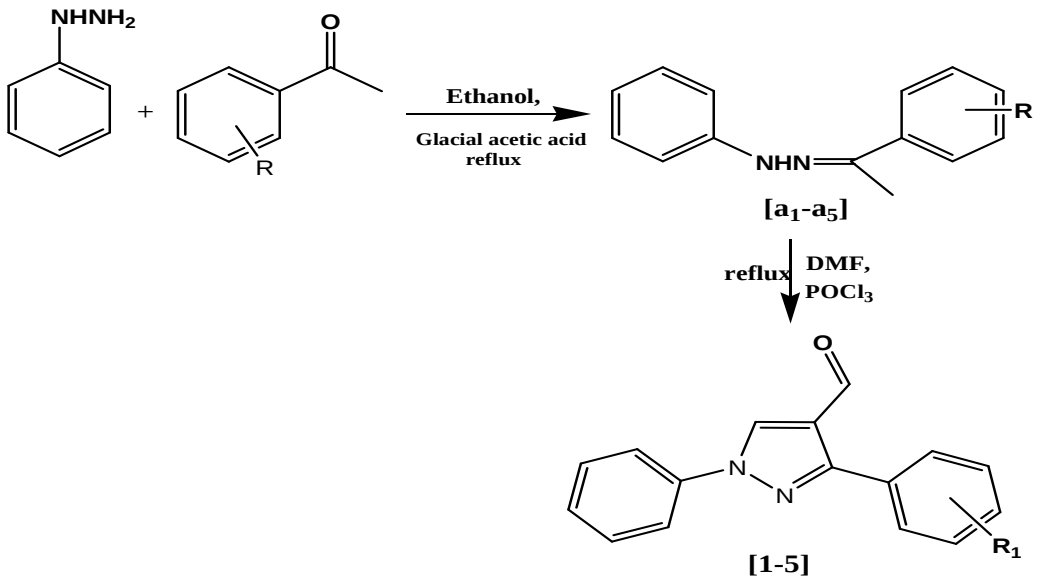

Figure 1: Representing the diagrammatic route adopted for the synthesis of substituted pyrazole carbaldehyde derivatives (1-5)

1,3-diphenyl-1H-pyrazole-4-carbaldehyde

Yield: 95%; mp: 218-220 ^{0}C; yellowish crystals; Anal. calc. for $C_{16}H_{12}N_2O$: C 77.40%, H 4.87%, N 11.28%, found: C 77.92%, H 5.10%, N 11.18%; IR ν_{max}(cm^{-1}): 1603 (C=N), 1719 (C=O), 3022 (CH-Ar); ^{1}H-NMR ($CDCl_3$)δ(ppm): 7.260-7.547 (m, Ar-H), 7.792-7.844 (m, Ar-H), 8.532 (s, 1H, CH, pyrazole ring), 10.062 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$)δppm: 107.19 (1C-pyrazole ring), 120.57, 127.03, 127.68, 229.31, 129.92, 135.93 (1C-pyrazole ring), 139.75, 151.03 (1C pyrazole ring), 189.20 (HC=O); ESI-MS(m/z): [M$^+$+1] 248.11.

1-phenyl-3-p-tolyl-1H-pyrazole-4-carbaldehyde

Yield: 95%; mp:198-200 ^{0}C; white crystals; Anal. calc. for $C_{17}H_{14}N_2O$: C 77.84%, H 5.38%, N 10.68%; found: C 77.79%, H 5.42%, N 10.65%; IR ν_{max}(cm^{-1}): 1619 (C=N), 1723 (C=O), 3022 (CH-Ar); ^{1}H-NMR ($CDCl_3$)δ(ppm): 2.388 (s, 3H, CH_3), 7.259-7.413 (m, Ar-H), 7.485-7.537 (m, Ar-H), 7.702 (d, 1H, Ar-H), 7.781(d, 1H, Ar-H), 8.532 (s, 1H, CH, pyrazole ring), 10.051 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$)δppm: 21.39 (CH_3), 107.44 (1C-pyrazole ring), 120.35, 127.64, 127.81, 229.74, 129.76, 135.89 (1C-pyrazole ring), 139.70, 151.23 (1C-pyrazole ring), 188.91 (HC=O); ESI-MS(m/z): [M$^+$+1] 262.13.

3-(4-methoxyphenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde

Yield: 95%; mp: 210-212 ^{0}C; creamy white crystals; Anal. calc. for $C_{187}H_{14}N_2O_2$: C 73.37%, H 5.07%, N 10.07%; found: C 73.39%, H 5.11%, N 10.04%; IR ν_{max}(cm^{-1}): 1611 (C=N), 1729 (C=O), 3032 (CH-Ar); ^{1}H-NMR ($CDCl_3$)δ(ppm): 3.875 (s, 3H, OCH_3)7.014-7.532 (m, Ar-H), 7.777-7.807 (m, Ar-H), 8.518 (s, 1H, CH, pyrazole ring), 10.032 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$)δppm: 56.71 (OCH_3), 107.58 (1C-pyrazole ring), 120.75, 127.22, 127.91, 229.53, 129.76, 135.85 (1C-pyrazole ring), 139.25, 151.19 (1C-pyrazole ring), 190.20 (HC=O); ESI-MS(m/z): [M$^+$+1] 278.35.

3-(4-chlorophenyl)-1-phenyl-1H-pyrazole-4-carbaldehyde

Yield: 95%; mp: 220-222 ^{0}C; white crystals; Anal. calc. for $C_{16}H_{11}ClN_2O$: C 67.97%, H 3.92%, N 9.91%; found: C 68.02%, H 3.88%, N 9.88%; IR ν_{max}(cm^{-1}): 1609 (C=N), 1719 (C=O), 3025 (CH-Ar); ^{1}H-NMR ($CDCl_3$)δ(ppm): 7.261-7.549 (m, Ar-H), 7.773-7.848 (m, Ar-H), 8.537 (s, 1H, CH, pyrazole ring), 10.063 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$)δppm: 106.59 (1C-pyrazole ring), 120.87, 127.59, 127.69, 229.78, 129.38, 135.56 (1C-pyrazole ring), 139.68, 151.11 (1C-pyrazole ring), 190.11 (HC=O); ESI-MS(m/z): [M$^+$+1]282.70.

3-(4-bromophenyl)-1-phenyl-1-H-pyrazole-4-carbaldehyde

Yield: 95%; mp: 202-204 ^{0}C; white crystals; Anal. calc. for $C_{16}H_{11}BrN_2O$: C 58.74%, H 3.39%, N 8.56%; found: C 59.07%, H 3.42%, N 8.80%; IR ν_{max}(cm^{-1}): 1611 (C=N), 3025 (CH-Ar); ^{1}H-NMR ($CDCl_3$)δ(ppm): 7.260-7.645 (m, Ar-H), 7.755-7.796 (m, Ar-H), 8.533 (s, 1H, CH, pyrazole ring), 10.036 (s, 1H, HC=O); ^{13}C-NMR ($CDCl_3$)δppm: 109.21 (1C-pyrazole ring), 120.75, 127.54, 127.75, 229.63, 129.68, 135.76 (1C-pyrazole ring), 139.57, 151.53 (1C-pyrazole ring), 186.89 (HC=O); ESI-MS(m/z): [M$^+$+1] 326.03.

In vitro antileishmanial assay (35)

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^{6}cell/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.

Physicochemical properties (36)

Physico-chemical properties of compounds 1-5 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.

Bioactivity score (37)

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.

Results and discussion

Synthesis and characterization

The synthetic route for substituted-1H-pyrazole-4-carbaldehyde (1-5) is shown in the Figure-1, which completes in two steps. In the first step substituted phenyl hydrazine was obtained by simple condensation reaction between carboxy group of ketone and amine group on refluxing in ethanol (39). Thin Layer Chromatographic plates were used to monitor the progress of the reaction and to confirm the conversion and FT-IR, ^{1}H NMR and ^{13}C-NMR helped in establishing the structure. The obtained substituted phenyl hydrazine was further refluxed with mimethylformamide (DMF) and phosphorous oxychloride ($POCl_3$) to yield the corresponding substituted pyrazole carbaldehyde (40). The detailed spectroscopic data obtained for structural elucidation of the synthesized compounds (1-5) is present in the experimental part.

Antileishmanial activity

Antileishmanial activity of the compounds (1-5) was tested in vitro on a culture of Leishmania donovanipromastigotes (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 and four 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.

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 [38]. 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 Drug Likeness/ Bioactivity score of all the synthesized substituted pyrazole carbaldehyde derivatives (1-5)

Bioactivity Score	Compounds					
	1	2	3	4	5	Amphotericin B
GPCR ligand	-0.33	-0.32	-0.28	-0.27	-0.39	-3.06
Ion channel modulator	-0.20	-0.28	-0.27	-0.20	-0.28	-3.53
Kinase inhibitor	-0.28	-0.28	-0.22	-0.24	-0.28	-3.59
Nuclear receptor ligand	-0.30	-0.27	-0.20	-0.26	-0.38	-3.45
Protease inhibitor	-0.76	-0.75	-0.68	-0.73	-0.82	-2.45
Enzyme inhibitor	-0.28	-0.33	-0.30	-0.30	-0.35	-2.95

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 1-5 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 physicochemical properties of all the synthesized substituted pyrazole carbaldehyde derivatives (1-5)

Physicochemical property score	Compounds					
	1	2	3	4	5	Amphotericin B

miLogP	3.05	3.50	3.11	3.73	3.86	-2.49
TPSA	34.90	34.90	44.13	34.90	34.90	319.61
natoms	19	20	21	20	20	65
MW	248.28	262.31	278.31	282.73	327.18	924.09
nON	3	3	4	3	3	18
nOHNH	0	0	0	0	0	13
nviolations	0	0	0	0	0	3
nrotb	3	3	4	3	3	3
Volume	227.06	243.62	252.60	240.59	244.94	865.48

Table-3: Representing the IC_{50} values of all the synthesized substituted pyrazole carbaldehyde derivatives (1-5) against Leishmania donovanipromastigotes (Strain S1)

S. No.	Molecular formula	IC_{50} (µg/ml)
1	$C_{16}H_{12}N_2O$	40
2	$C_{17}H_{14}N_2O$	30
3	$C_{187}H_{14}N_2O_2$	5.5
4	$C_{16}H_{11}ClN_2O$	15
5	$C_{16}H_{11}BrN_2O$	40
Amphotericin B	$C_{47}H_{73}NO_{17}$	0.15

Conclusion

The substituted-pyrazole-4-carbaldehyde (1-5) was synthesized and their structures were elucidated by various spectroscopic techniques. All the compounds were screened for antileishmanial activity against the culture of Leishmania donovanipromastigotes (Strain S1). Results revealed that compound three compound three and four exhibited good activity. To support the experimental results the computational studies were carried out to evaluate the drug likeness and physicochemical properties. And results revealed that all the compounds follow the Lipinski rule of five and bioactivity score.

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