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SYNTHESIS AND CHARACTERIZATION OF SOME CURCUMIN ANALOGUE AS NOVEL ANTILEISHMANIAL AGENT

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ABSTRACT

Some novel benzilidine cyclohexanone derivatives have been synthesised from cyclohexanones and cycloheptanones. The structures of the compound have been conformed by ^{1}H NMR, IR spectra, Mass .The Synthesised compound were screened for in-vitro antilesihmanial activity. The synthesized compounds showed significant antilesihmanial activity activity.

Keywords: Dienones; Antileishmanial; curcumin derivative.

INTRODUCTION

Leishmaniasis is an infection caused by protozoa of the genus *Leishmania* presenting several forms of the disease such as cutaneous (CL), mucocutaneous (MCL) and visceral leishmaniasis (VL)[1-5]. The current treatment for the leishmaniasis is based on the pentavalent antimonials, such as sodium stibogluconate (pentostam) and meglumine antimoniate (glucantine). Pentamidine is a second line of drugs for the treatment of VL in patient who failed to respond to antimony therapy. Antibiotic amphoterecin-B in the second line of drugs for the treatment of VL. It shows better response ever in cases resistant to the antimonials and diamidines. In view of the high toxicity associated with the existing antileishmanial drugs. Efforts are being made to search for the new molecule from natural sources[6-10]. This can act as a new lead in the chemotherapy of Leishmaniasis

In the present study condensation of cyclohexanone or cycloheptanone with Substituted benzaldehyde in the presence of conc. HCl acid at room temperature (48 hrs) furnished dienone **(2a-c) or (3a-c)** derivatives, respectively **(Scheme 1)**. The synthesized compounds were purified by pre coated TLC Plates using solvent Methanol:Hexane (1:1 ratio). Thus synthesized derivatives were characterized in **Table 1**. The antileishmania activity of all the synthesized compounds was investigated by using the MTT assay method. In these all the synthesized compounds showed significant activity.

EXPERIMENTAL

Melting points were determined using an open-ended capillary method and are uncorrected. The infrared spectra were recorded in KBr on a Perkin Elmer model 881. NMR spectra were obtained in DMSO-D^6 (with Me4Si internal standard, Aldrich) and are reported in ppm downfield from Me4Si. Proton, Carbon NMR spectra were recorded on Bruker Advance DRX 2000 instrument. Electron impact (EI) mass spectra were recorded on a Jeol JMS-D-300 spectrometer with the ionization potential of 70 eV.

General procedure: Cyclohexanone (5mL) or Cyclohepatone(5ml) and Substitued benzaldehyde (6.1gm) were taken in a 250 mL RB flask and gently heated on water bath (60-70^{0}C) till we get clear solution. Conc. HCl (1mL, 36N) was added in one lot and stirred for 20 minutes. The resulting mixture

was left at room temperature for two days. Solid reaction mixture was broken into pieces and treated with cold AcOH/H_2O (1:1) 15 ml and stirred for 1 hr. Solid was filtered and washed with cold ethanol (15mL×3) followed by hot water (5mL×3). The crude product was recrystallised from hot methanol to get (**2a-c & 3a-c)** as a yellow crystalline solid.

2,6-bis(4-hydroxybenzylidene)cyclohexanone (compd 2a)

M.P:280-285^{0}C. IR (KBr, cm^{-1}) :3250, 2945, 1650,1594,1573,1436. ^{1}H NMR (300MHz, D^6-DMSO): δ 1.70(m,2H), 2.85(m,4H),6.80(d,4H), 7.40(d,4H), 7.50(s,2H), 10.00(s,2H). MASS M/e : 307 (M^++1).

2,6 bis(4-hydroxy-3-methoxybenzylidene)cyclohexanone (compd 2b)

M.P:172-175^{o}C. IR (KBr, cm^{-1}): 3376, 2929, 1639, 1578, 1514, 1420, 1257, 1166, 1127. ^{1}H NMR (300MHz, D^6-DMSO) δ:- 1.73(bs,2H), 2.859(bs,4H),6.85(d,2H), 7.03(d,2H), 7.11(s,2H), 7.56(s,2H). MASS M/e : 367 (M^++1).

2,6 bis(3-ethoxy-4-hydroxybenzylidene)cyclohexanone (compd 2c)

M.P:140-145^{o}C. IR (KBr, cm^{-1}) :3381,2979,2936,1655,1595,1510,1432,1283,1259. ^{1}H NMR(300MHz, D^6-DMSO): δ 1.3(t,6H), 1.71(m,2H),2.87(m,4H), 4.05(m,4H), 6.8(m,4H), 6.8(d,2H), 7.0(d,2H), 7.09(m,2H), 7.54(s,2H). MASS M/e : 395 (M^++1).

2,7 bis (4-hydroxybenzylidene) cycloheptanone (compd 3a)

M.P: 282^{o}C. IR (KBr, cm^{-1}): 3150,2928,2852,1654,1574,1507,1374,1278,1235,1171. ^{1}H NMR (300MHz, D^6-DMSO) :δ 1.60(m,4H), 2.60(m,4H),6.80(d,4H), 7.22(s,2H), 7.25(d,4H). MASS M/e: 321 (M^++1).

2,6 bis(4-hydroxy-3-methoxybenzylidene)) cycloheptanone(compd 3b)

M.P:272-275^{o}C. IR (KBr, cm^{-1}): 3376, 2929, 1639, 1578, 1514,1500, 1420, 1257, 1166, 1127. ^{1}H NMR (300MHz, D^6-DMSO) δ:- 1.73(bs,2H), 2.859(bs,4H),6.85(d,2H), 7.03(d,2H), 7.11(s,2H), 7.56(s,2H). MASS M/e : 338 (M^++1).

2,6 bis(3-ethoxy-4-hydroxybenzylidene)cycloheptanone (compd 3c).

M.P:240-245^{o}C. IR (KBr, cm^{-1}) :3381,2979,2936,1655,1595,1510,1432,1451,1283,1259. ^{1}H NMR(300MHz, D^6-DMSO): δ 1.3(t,6H), 1.71(m,2H),2.87(m,4H), 4.05(m,4H), 6.8(m,4H), 6.8(d,2H), 7.0(d,2H), 7.09(m,2H), 7.54(s,2H). MASS M/e : 353(M^++1).

Extracellular (against promastigotes) leishmanicidal activity

The effect of compounds on the viability of *Leishmania* promastigotes was assessed by monitoring the MTT [3-(4,5-dimethylthiazol- 2-yl)-2,5-diphenyl-tetrazolium bromide] metabolism (Sigma Chemical Co.) after a 96 hrs culture period in the presence of the respective compounds. Parasites in stationary culture stage were seeded at 1 × 10^6/100 µl medium 199 per well in 96-well flat bottom microtitre plates (Cellstar). Further 100 µl of medium 199 per well with different concentrations of test compounds or drug standard, dissolved in DMSO were added in triplicate to achieve desired concentrations (12.5–200 µg ml^{-1}). Parallel dilutions of DMSO alone did not affect the parasite growth. The plates were incubated at 25 °C for 92 hrs prior to MTT (20 µl per well of a 5 mg ml^{-1} PBS stock) addition and then for further 4–5 hours. MTT processing was stopped and formazan crystals solubilized by adding 50 µl per well acidified 20% SDS (Qualigens, India) and incubating overnight at 37 °C. The relative amount of formazan per well produced by viable cells was measured photometrically at 570 nm. Two independent experiments were performed for the determination of sensitivity of each compound. As a control, the activity of each compound was determined, and no substantial interaction was found.

RESULTS AND DISCUSSION

The leishmanicidal activity of dienones 2(a-c) and (3a-c) was studied *in-vitro* on *L. donovani* promastigotes. The compounds having methoxy substitution on the aromatic ring are showing better activity. Compd **2b** (Table 2) having methoxy substitution on the aromatic ring showed IC50 and IC90 values as 25 ± 1.7 and 50 ± 3.5 µg ml^{-1}, respectively. However, none of the compound tested found better than pentamidine. Further synthesis of new substituted dienones and *in-vitro* screening against L. donovani promastigotes would be necessary to find improved drug candidates for *in-vivo* testing.

Table-1: Characterization data for the synthesized compounds

S.No	Compd.	R_1	R_2	Yield%	R_f VALUE	Colour
1	2a	H	0H	47	0. 68	Yellow Crystalline
2	2b	$0CH_3$	0H	56	0. 88	Yellow Crystalline
3	2c	OC_2H_5	0H	74	0 .71	Yellow Crystalline
4	3a	H	0H	48	0. 76	Yellow Crystalline
5	3b	$0CH_3$	0H	59	0.63	Yellow Crystalline
6	3c	OC_2H_5	0H	66	0. 57	Yellow Crystalline

Table-2: leishmanicidal activity data for the synthesized compounds

Mean IC values (µg ml^{-1}) ± S.E. (N)		
Compounds	**IC50**	**IC90**
2a	50± 2.0	90 ± 1.5
2b	25 ± 1.7	50 ± 3.5
2c	Inactive	Inactive
3a	60 ± 3.0	200 ± 3.5
3b	90 ± 4.0	150 ± 5.0
3c	93 ± 4.0	140 ± 5.0
Pentamidine	2.5 ± 0.12	5.0 ± 0.35

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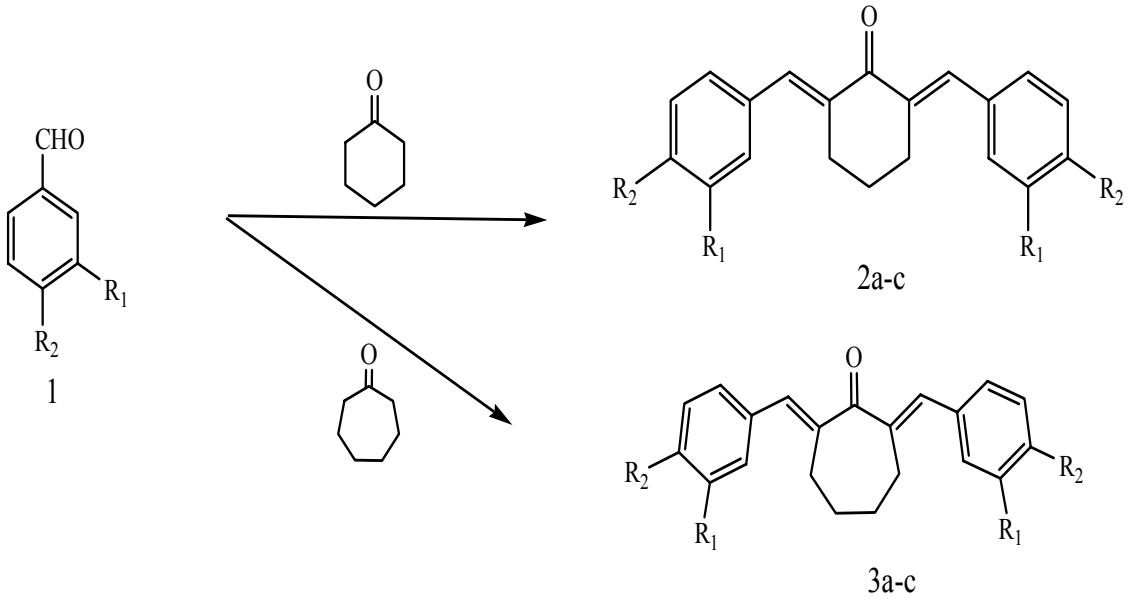

Scheme-1

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