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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME CURCUMIN ANALOGS AND THEIR DERIVATIVES

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ABSTRACT
Some diarylidene piperidone derivatives have been synthesized form 4-piperidone. The diarylidene piperidone were coupled with sulfonyl chlorides and carbonyl chloride.The synthesized compounds were characterized with LCMS, ^{1}H NMR, ^{13}C NMR and melting point analysis. The synthesized compounds were screened against bacteria's (Gram +ve, Gram –ve).
Keywords: Diarylidene piperidone, sulfonyl chloride, antimicrobial activity.

INTRODUCTION

An antibiotic could be identified via genomic, HTS (High Throughput Screening), improving existing antibiotic, most importantly improving the antimicrobial activity of natural product by structural modification using SAR analysis.

Curcumin a secondary metabolite and the main yellow compound of *cucuma longa* rhizome which is the main component of curry powder widely used as a traditional medicine in widespread in several parts of Asia[1], has found to have various biological properties including, antimicrobial, anti-tumoral activity, anti-inflammatory, antioxidant, cytotoxicity[2-4]. Thus Curcumin is undoubtedly a model compound.

The five carbon mono carbonyl piperidine analogues of curcumin possess various kinds of biological activities including antioxidant, anti-inflammatory and Anticancer Drug delivery system[5-7]. In our present work three diarylidene-4-piperidone were synthesized, then coupled with different sulfonyl chlorides, carbonyl chloride and screened for antimicrobial activity.

EXPERIMENTAL

Melting Point (º C uncorrected) were recorded in Buchi B 545. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 400 spectrophotometer using DMSO-D^{6}, TMS as the internal reference. TLC using silica gel G60 (Merck, Germany).

Isolation of Curcumin[8]

The rhizome of *curcuma longa* was dried in sun shade and finely powdered. The fine powder was extracted with Methanol. The crude extract was purified by column chromatography using Methanol : DCM system to get crude curcuminoid mixture i.e., curcumin, demethoxy curcumin (DMC) and bisdemethoxy curcumin (BDMC). Then Curcumin (1,7-Bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) was purified using preparative TLC plate using 3% Methanol:dichlormethane system followed by prep HPLC purification in acetonitrile: Water system..

General procedure for the synthesis of 3,5-diarylidene-4-piperidone[9]

To a solution of 4-piperidone (10 mmol) and aromatic aldehyde (20 mmol) in ethanol (4 ml), added con. HCl (2 ml) at 0º C. The reaction mixture was refluxed for 4.5 h. The reaction was monitored by TLC and allowed to settle at room temperature. The solid portion was filtered and dried. It was further purified by recrystallisation from suitable solvents.

General procedure for the synthesis of 1-arylsulfonyl-3,5-diaryliden-4-piperidone
To a solution of 3,5-diarylidene-4-piperidone(10 mmol) and triethylamine (12 mmol) in DCM, added sulfonyl chloride (10 mmol). The reaction mixture was stirred for 30 mins. The reaction was monitored by TLC. The reaction mixture was diluted with water, extracted with DCM. The crude product was purified by gravity column using silica gel as stationary phase and DCM : Methanaol as eluent system.
General procedure for the synthesis of 1-(4-dimethylamino-benzoyl)-3, 5-diaryliden-4-piperidone
To a solution of 3,5-diarylidene-4-piperidone(10 mmol) and triethylamine(12 mmol) in DCM, added freshly prepared 4-dimethylaminobenzoyl chloride(10 mmol). The reaction mixture was stirred for 30 mins. The reaction was monitored by TLC. The reaction mixture was diluted with water, extracted with DCM. The crude product was purified on gravity column using silica gel as stationery phase and DCM : Methanaol as eluent system.

Curcumin
^{1}H NMR (400 MHz, D^{6}-DMSO) 6.06(s,1H),6.73(d,2H), 6.82(d,2H), 7.14(m,2H), 7.32(d,2H), 7.53(d,2H), 9.65(s,2H);
^{13}C NMR (100 MHz) 56.17,101.26,111.85,116.18,121.55,123.57,126.79,141.15,148.47,148.85,183.66;
LCMS (m/z):369.2 [M^{+}]; m.p. 182.6 º C [lit^{10} 182-183 º C]

3,5-bis(4-fluorobenzylidene)piperidin-4-one (1)
^{1}H NMR (400 MHz, D^{6}-DMSO) δ 4.40(s,4H), 7.35(m,4H), 7.59(m,4H), 7.84(s,2H), 9.64(s,2H);
^{13}C NMR (100 MHz) 44.49,116.36,116.58,128.90,130.89,133.53,138.00,161.99,164.46,183.27;
LCMS (m/z): 312.2 [M^{+}]; m.p. 236.8 º C

3,5-bis(4-fluorobenzylidene)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)piperidin-4-one (1a)
^{1}H NMR (400 MHz, D^{6}-DMSO) δ 4.73(s,4H), 7.28 (d, 1H), 7.34 (t, 4H), 7.52 (m, 4H), 7.57 (s, 2H), 7.82 (d, 1H), 11(s, 1H);
^{13}C NMR (100 MHz) 46.8,116.2,124.7,128.5,128.8,131.5,133.2,134.3,135.6,161.7,164.2,185.4; LCMS (m/z):534 [M^{-}]; m.p. 221.3 º C

3,5-bis(4-fluorobenzylidene)-1-(3-methoxyphenylsulfonyl)piperidin-4-one (1b)
^{1}H NMR (400 MHz, D^{6}-DMSO) δ 3.73(s,3H), 4.67(s, 4H), 6.95 (d,1H),7.06(d,1H), 7.22 (q,4H), 7.33(t,1H), 7.54(m, 6H);
^{13}C NMR (100 MHz):
47.01,55.98,112.04,116.3,116.5,119.7,120.2,130.7,131.0,131.1,133.3,133.4,136.4,139.2,159.8,161.8,164.3,184.4; LCMS(m/z): 482 [M^{+}]; m.p. 178.1 º C

3,5-bis(4-fluorobenzylidene)-1-(3-fluorophenylsulfonyl)piperidin-4-one (1c)
^{1}H NMR (400 MHz, D^{6}-DMSO) δ 4.67 (s,4H), 7.30 (m, 6H), 7.5(m, 8H);
^{13}C NMR (100 MHz,D^{6}DMSO):
δ46.97,114.52,114,.77,116.39,116.6,121.3,123.8,130.6,130.94,132.29,132.37,133.68,133.45,136.6,140.11,161.89,164.37,184.51;LCMS(m/z): 470 [M^{+}]; m.p. 150.7 º C

3,5-bis(4-fluorobenzylidene)-1-(4-(dimethylamino)benzoyl)piperidin-4-one (1d)
^{1}H NMR(400 MHz,D^{6}-DMSO)
δ 2.84(s,6H),4.82(s,4H),6.31(d,2H),7.0(d,2H),7.29(t,4H),7.56(s,4H),7.75(s,2H);
^{13}C NMR (100 MHz,D^{6}-DMSO):
δ 110.88,116.1,116.3,120.67,129.0,131.3,133.1,133.65,151.69,161.76,164.23,170.12,186.6
LCMS(m/z): 459.2 [M^{+}]; m.p. 197.1 º C
3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (2)
^{1}H NMR (400 MHz, D^{6}-DMSO) δ 4.47 (d,4H), 7.31(m,2H), 7.69(d,2H), 8.02(t,4H), 10.1(s,2H);
^{13}C NMR (100 MHz,D^{6}-DMSO) 37.78,42.54,43.97,124.72,129.30,131.30,133.38,135.98,137.43,181.81;

LCMS(m/z): 288.2 [M^+]; m.p. 356.7 º C

1-(3,5-dichloro-2-hydroxyphenylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (2a)
^{1}H NMR (400 MHz, D^6-DMSO) δ 4.77 (s, 4H), 7.28(m,2H), 7.49(d,1H),7.49(d,2H),7.77(s,2H),7.82(d,1H), 7.98(d,2H),11.16(s,1H);
^{13}C NMR (100 MHz,D^6-DMSO):
δ46.79,48.26,51.23,79.27,123.45,124.57,127.53,128.27,128.81,129.02,129.15,133.06,133.95,134.25.134.56,135.07,135.32,137.86,138.27,150.98,184.31;
LCMS(m/z): 509.82 [M^-]; m.p. 219.7 º C

1-(3-methoxyphenylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (2b)
^{1}H NMR (400 MHz, D^6-DMSO) δ 3.69 (s,3H),4.66(s,4H),7.1(s,1H),7.11(d,2H),7.26(m,2H),7.46(m,1H),7.78(s,2H),8.01(d,2H),8.32(s,2H);
^{13}C NMR (100 MHz D^6-DMSO):
79.71,112.00,112.49,119.84,120.14,120.63,127.43,127.66,129.27,129.64,131.12,131.38,133.31,134.23,135.65,137.77,138.15,138.58,139.01,160.07,183.37;
LCMS(m/z): 457.0 [M^-]; m.p. 182.8 º C

1-(3-fluorophenylsulfonyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (2c)
^{1}H NMR (400 MHz, D^6-DMSO) δ 4.69 (s,4H), 7.31(m,2H), 7.44(d,1H), 7.53(m,5H),7.59(s,2H), 7.65(d,2H);
^{13}C NMR (100 MHz D^{6}DMSO):
46.95,114.63,121.14,127.28,129.31,129.77,133.65,134.99,137.7,161.08,183.4
LCMS(m/z): 445.0 [M^-]; m.p. 190.3 º C

1-(4-(dimethylamino)benzoyl)-3,5-bis(thiophen-2-ylmethylene)piperidin-4-one (2d)
^{1}H NMR (400 MHz, D^6-DMSO) δ 2.9 (s, 6H), 4.93(s, 4H), 6.56(d,2H), 7.24(m, 4H), 7.62(d, 2H), 7.92(m,2H);
^{13}C NMR (100 MHz D^6-DMSO);
111.32,120.90,128.95,129,50,,129.71,132.94,135.18,137.92,151.94,170.32,185.26;
LCMS(m/z): 435.2 [M^+]; m.p. 215.8 º C

3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)piperidin-4-one (3)
^{1}H NMR (400 MHz, D^6-DMSO) δ 3.95(d,4H), 5.75(s, 1H), 6.09(s,4H), 7.01(d,4H), 7.05(s, 2H), 7.49(s,2H);
^{13}C NMR (100 MHz D^6-DMSO):
δ 48.07,55.36,101.98,109.03,110.48,126.21, 129.60,134.05,134.91,148.07,148.49,187.76
LCMS(m/z): 364.2 [M^+]; m.p. 256.1 º C

3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)-1-(3,5-dichloro-2-hydroxyphenylsulfonyl)piperidin-4-one (3a)
^{1}H NMR (400 MHz, D^6-DMSO) δ 4.70 (s,4H), 6.1 (s, 4H), 6.99 (m, 6H), 7.34(d,1H), 7.57(s,2H),7.82(s, 1H);
^{13}C NMR (100 MHz,D^6-DMSO):
δ46.98,102.18,109.2,110.46,126.5,128.54,128.69,130.07,134.4,136.75,148.24,149.05,185.09;
LCMS(m/z): 586.0 [M^{2-}]; m.p. 242.5 º C

3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)-1-(3-methoxyphenylsulfonyl)piperidin-4-one (3b)
^{1}H NMR (400 MHz, D^6-DMSO) δ 3.73 (s, 3H),4.65 (s, 4H), 6.15 (s, 4H), 6.96(d,1H), 6.97(t, 2H),7.07 (d, 5H)7.25 (d, 1H),7.43(m,3H);
^{13}C NMR (100 MHz, D^6-DMSO);

δ47.21,5594,102.2,109.24,110.48,119.68,120.29,126.51,128.63,129.33,131.06,137.43,139.29,148.3,149.55,159.8,184.2
LCMS(m/z): 534.2 [M^+]; m.p. 137.8 º C

3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)-1-(3-fluorophenylsulfonyl)piperidin-4-one (3c)
^{1}H NMR (400 MHz, D^6-DMSO) δ 4.69 (s,4H), 6.15(s,4H), 7.0 (d,2H), 7.01 (d,4H),7.1(d,1H), 7.33 (d,1H), 7.46 (s, 2H),7.55(m, 2H);
^{13}C NMR (100 MHz D^6-DMSO);
δ47.14,102.23,109.27,110.56,121.00,126.54,127.53,128.56,129.16,137.63,148.33,149.21
LCMS(m/z): 522.2 [M^+]; m.p. 188.9 º C

3,5-bis(benzo[d][1,3]dioxol-5-ylmethylene)-1-(4-(dimethylamino)benzoyl)piperidin-4-one (3d)
^{1}H NMR (400 MHz, D^6-DMSO) δ 2.86(s, 6H), 4.82 (s,4H), 6.10(s,4H), 6.37(d,2H),7.03 (m,8H),7.66(s,2H);
^{13}C NMR (100 MHz,D^6-DMSO);
102.09,109.11,110.39,110.96,120.89,126.34,128.98,129.17,131.81,136.59,148.15,148.93,151.74,170.04,186.35;
LCMS(m/z): 511.2 [M^+]; m.p. 246.9 º C

Antimicrobial Activity
The antimicrobial activity of new compounds was investigated on V.Cholera, S.typhi, E.Coli, and S.aureus by using agar diffusion method[11]. The zone of inhibition was measured in mm. Under similar conditions controlled experiment was carried out using pencillin as a standard drug for comparision (Table-1)

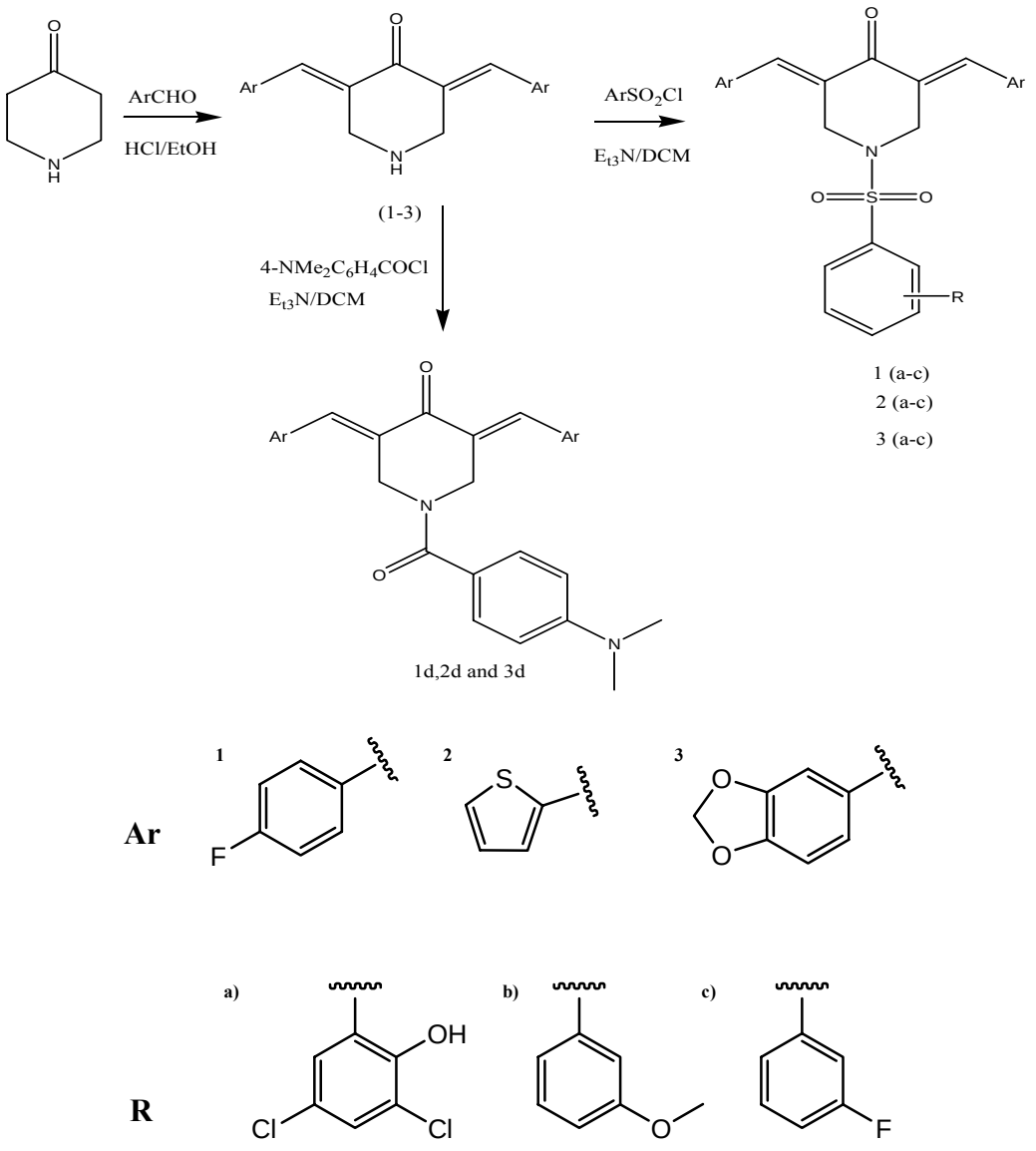
Table-1:Antibacterial activity data of compounds 1-18

Sl. No	Compound	Zone of Inhibition (in mm)			
		S.typhi	V.cholera	E.Coli	S.aureus
1	1	13	14	-	12
2	1a	16	15	7	11
3	1b	14	8	8	8
4	1c	12	10	8	8
5	1d	14	12	8	10
6	2	14	-	9	8
7	2a	20	18	9	10
8	2b	12	14	8	9
9	2c	12	14	8	8
10	2d	-	8	-	10
11	3	10	8	-	7
12	3a	16	10	7	8
13	3b	-	8	8	-
14	3c	-	-	-	-
15	3d	-	8	-	-
16	Curcumin	9	14	9	12
17	Curcuminoids	14	16	10	10
18	Pencillin(positive control)	10	14	16	14

RESULTS AND DISCUSSION

The antimicrobial screening of the compounds reveals that compound 2a exhibited a significant activity against *S.typhi* and *V.cholera* compared to Curcumin. All derivatives of 2-hydroxy-3, 5-dichloro-

phenylsulfonamides (1a, 2a and 3a) showed promising activity against *S.typhi* and *V.cholera*. Most of the synthesized compounds were shown moderate activity against *S.typhi* and *V.cholera* and were poorly active against the other bacteria's. The carboxamide derivatives (1d, 2d, and 3d) were not active compared to sulfonamide derivatives. Further optimization of compound 2a using SAR analysis is required to reach a good antibiotic.



Scheme-1

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