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Research Article

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Synthesis and antimicrobial evaluation of some chalconyl semicarbazones

C. S. Sharma[a], K. S. Shekhawat[a], C. S. Chauhan[a] and Neeraj Kumar[b]

[a]Department of Pharmaceutical Chemistry, B N College of Pharmacy, Udaipur, Rajasthan, India
[b]Geetanjali Institute of Pharmacy, Udaipur, Rajasthan, India

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ABSTRACT

In this article, we have fused chalcone and semicarbazone nucleus and design a scheme for synthesizing a series of chalconesemicarbazones was evaluated for antimicrobial activity. Most of the compounds were found to be more or comparable potent than the reference standard drug.

Keywords: chalcones**,** Claisen Schmidt reaction, semicarbazone, antimicrobial activity.

INTRODUCTION

The chalcones are α-β unsaturated ketones containing the reactive keto ethylenic group – CO – CH = CH –. Presence of α-β- unsaturated carbonyl system in chalcone makes it biologically active. Some substituted chalcones and their derivatives have been reported to possess some interesting biological properties such as antibacterial, insecticidal, anaesthetic, analgesic, ulcerogenic etc[1-4].

Chalcones are well known intermediates for synthesizing various heterocyclic compounds. The compounds with the backbone of chalcones have been reported to possess various biological activities such as anti-inflammatory, antiplatelet, antiulcerative, antimalarial, anticancer, antiviral, antileishmanial, antioxidant, antitubercular, antihyperglycemic, immunomodulatory, inhibition of chemical mediators release, inhibition of leukotriene B4, inhibition of tyrosinase and inhibition of aldose reductase activities[5-21].

Now a days, the overall problem associated with antimicrobials is bacterial resistance. This means that it is necessary to produce new antimicrobial agents that have different mechanisms of action at regular intervals.

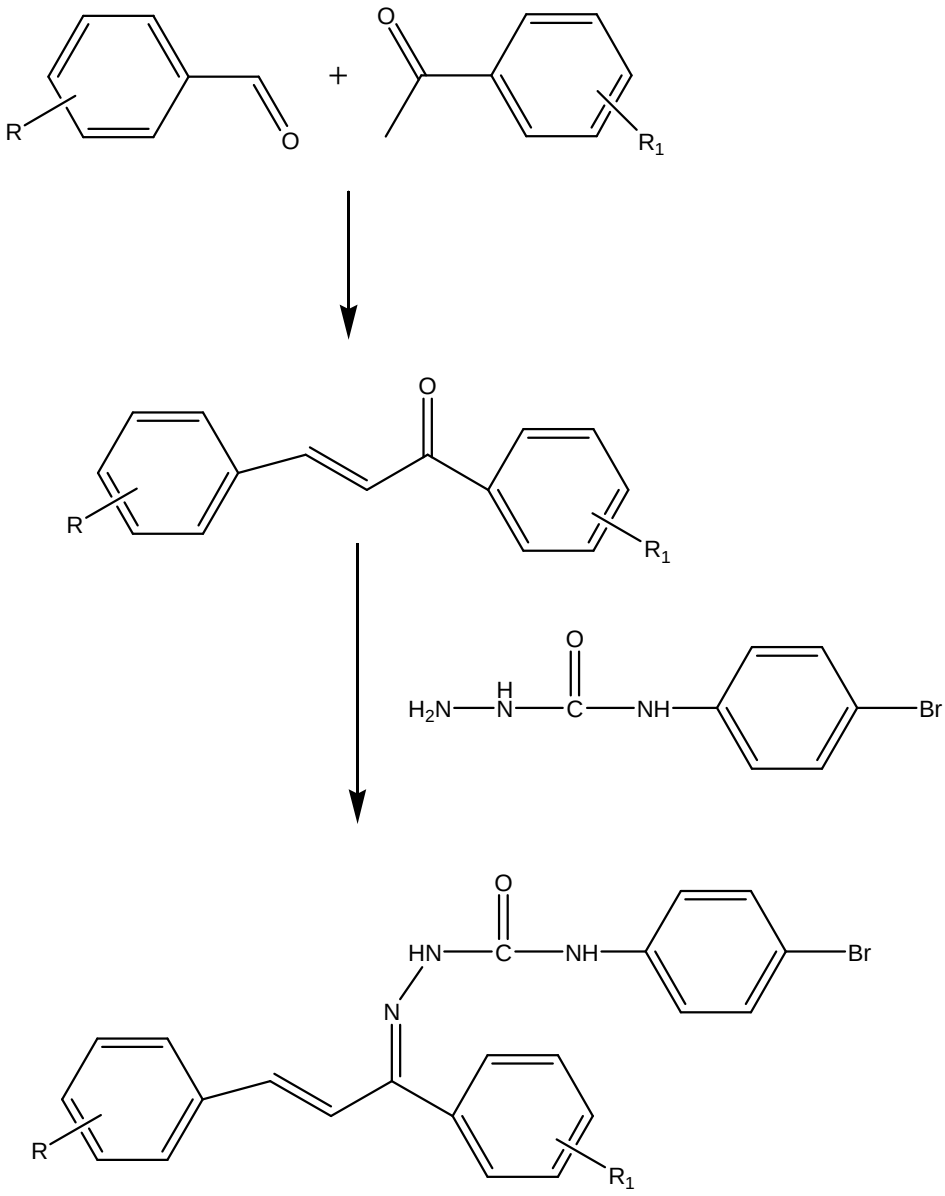
It has been decided to carry out the antibacterial and antifungal studies of the synthesized compounds, because of the previous literature benzyliden hydrazides may show a potent antibacterial and antifungal activity with better efficacy and less side effects.

EXPERIMENTAL SECTION

Melting points of the synthesized compounds were determined in open capillary tubes and are uncorrected. IR absorption spectra were recorded on Bruker Tensor-27/Jasco FT/IR-470 PLUS, KBr diffuse reflectance, ^{1}H-NMR spectra were recorded on the Bruker DPX-400 instrument at 400 and 100 MHz, respectively. The ^{1}H chemical shifts are reported as parts per million (ppm) downfield from TMS (Me_4Si). ^{1}H-NMR, IR and Mass spectra were

consistent with the assigned structures. Purity of the compounds was checked by thin layer chromatography (TLC). The elemental analysis (CHN analysis) was done on a CHN rapid analyzer. All the compounds gave satisfactory analysis within ±0.4% of the theoretical values. The LC mass spectra of the compounds were recorded on Shimadzu 8201PC spectrometer.

Scheme 1



General method for the synthesis of chalcone (1a-1f, 2a-2e)

A solution of appropriate substituted benzaldehyde (0.1 mol) in methanol was mixed with appropriate substituted acetophenone (0.1 mol) and an aqueous solution of potassium hydroxide (60%) was added to it till, further no turbidity occurs. The reaction mixture was stirred and kept overnight at room temperature and then it was poured into crushed ice and acidified with dilute hydrochloric acid. The crude product so obtained was filtered and recrystallized from methanol and dried at room temperature. The completion of reaction was monitored by running TLC.

Synthesis of 4-bromophenylurea(XBr)

4-Bromoaniline (0.1mol) was dissolved in 40 ml of glacial acetic acid. To this, 0.1 mole of sodium cyanate (6.5 gm) in about 100ml of hot water was added with vigorous stirring. Then the reaction mixture was allowed to stand for 1 hour, cooled by means of ice and filtered. The crude product so obtained was thoroughly washed with ice cold water and dried and recrystallized from methanol. The completion of reaction was monitored by running TLC.

Table 1

Compound No	IR Wave No.(cm^{-1})	^{1}H NMR Chemical Shift (δ, ppm)	Mass (M/Z)	Elemental analysis	
				Calculated	Found
Y1aBr	3343(-NH), 1684(C=O), 1577(CH=CH), 1483(Ar. C=C), 2914, 2803(CH Str.), 1339(C-N), 810(C-Br)	10.26 (s, 1H, NHCO), 8.88 (s, 1H, NHCO), 7.31-7.61 (m, 14H, Ar-H), 7.23 (d, 1H, CH), 6.68 (d, 1H, CH)	419.1 (M), 421.1 (M+2), 420.1 (M+1)	C, 62.87 H, 4.32 N, 10.00	C, 62.56 H, 4.2 N, 9.72
Y1bBr	3339(-NH), 3218 (OH Str.), 1684(C=O), 1523(CH=CH), 1483(Ar. C=C), 2917, 2796(CH Str.), 1396(C-N), 809(C-Br)	10.39 (s, 1H, NHCO), 9.35 (s, 1H, NHCO), 8.58 (s, 1H, OH), 7.02-7.62 (m, 11H, Ar-H), 6.94 (d, 1H, CH), 6.91 (d, 1H, CH), 6.71-6.81 (m, 2H, Ar-H)	435.1 (M), 437.1 (M+2), 436.1 (M+1)	C, 60.56 H, 4.16 N, 9.63	C, 60.13 H, 4.10 N, 9.41
Y1cBr	3337(-NH), 1690(C=O), 1516(CH=CH), 1490(Ar. C=C), 2912, 2734(CH Str.), 1397(C-N), 812(C-Br)	10.22 (s, 1H, NHCO), 9.16 (s, 1H, NHCO), 7.05-7.45 (m, 11H, Ar-H), 6.78 (d, 1H, CH), 6.57 (d, 1H, CH), 6.38 (s, 2H, Ar-H), 2.72 (s, 6H, $N(CH_3)_2$)	462.1 (M), 464.1 (M+2), 463.1 (M+1)	C, 62.21 H, 5.00 N, 12.09	C, 61.88 H, 4.72 N, 11.92
Y1dBr	3319(-NH), 1691(C=O), 1587(CH=CH), 1486(Ar. C=C), 2962, 2817(CH Str.), 1320(C-N), 818(C-Br)	10.40 (s, 1H, NHCO), 9.36 (s, 1H, NHCO), 7.27-7.65 (m, 14H, Ar-H), 7.25 (d, 1H, CH), 6.95 (d, 1H, CH)	453.0 (M), 455.0 (M+2), 454.0 (M+1)	C, 58.11 H, 3.77 Cl, 7.80 N, 9.24	C, 57.61 H, 3.63 Cl, 7.20 N, 9.04
Y1eBr	3344(-NH), 1685(C=O), 1623(CH=CH), 1529(Ar. C=C), 2964, 2798(CH Str.), 1394(C-N), 835(C-Br)	10.24 (s, 1H, NHCO), 8.87 (s, 1H, NHCO), 7.22-7.61 (m, 14H, Ar-H), 6.90 (d, 1H, CH), 6.81 (d, 2H, CH_2), 6.55 (d, 1H, CH)	445.0 (M), 447.0 (M+2), 446.0 (M+1)	C, 64.58 H, 4.52 N, 9.41	C, 64.11 H, 4.23 N, 9.26
Y1fBr	3332(-NH), 3151OH Str.), 1684(C=O), 1577(CH=CH), 1520(Ar. C=C), 2929, 2803(CH Str.), 1399(C-N), 809(C-Br)	10.32 (s, 1H, NHCO), 9.26 (s, 1H, NHCO), 8.29 (s, 1H, OH), 7.17-7.55 (m, 13H, Ar-H), 6.92 (d, 1H, CH), 6.65-6.67 (d, 1H, CH)	435.1 (M), 437.1 (M+2), 436.1 (M+1),	C, 60.56 H, 4.16 N, 9.63	C, 60.12 H, 4.13 N, 9.52
Y2aBr	3332(-NH), 3187(OH Str.), 1687(C=O), 1516(CH=CH), 1481(Ar. C=C), 2923, 2856(CH Str.), 1357(C-N), 808(C-Br)	10.30 (s, 1H, NHCO), 8.96 (s, 1H, NHCO), 8.41 (s, 1H, OH), 7.21-7.62 (m, 13H, Ar-H), 6.89 (d, 1H, CH), 6.75 (d, 1H, CH)	435.1 (M), 437.1 (M+2), 436.1 (M+1)	C, 60.56 H, 4.16 N, 9.63	C, 59.68 H, 3.98 N, 9.42
Y2bBr	3413(-NH), 3285(OH Str.), 1662(C=O), 1527(CH=CH), 1460(Ar. C=C), 2921, 2847(CH Str.), 1365(C-N), 814(C-Br)	10.37 (s, 1H, NHCO), 9.32 (s, 1H, NHCO), 8.35 (s, 1H, OH), 6.82-7.52 (m, 12H, Ar-H), 6.73 (d, 1H, CH), 6.55 (d, 1H, CH), 2.89 (s, 6H, $N(CH_3)_2$)	478.1 (M), 480.1 (M+2), 479.1 (M+1)	C, 60.13 H, 4.84 N, 11.69	C, 60.32 H, 4.62 N, 11.33
Y2cBr	3338(-NH), 3208(OH Str.), 1683(C=O), 1571(CH=CH), 1485(Ar. C=C), 2957, 2811(CH Str.), 1380(C-N), 846(C-Br)	10.48 (s, 1H, NHCO), 9.38 (s, 1H, NHCO), 8.90 (s, 1H, OH), 8.51 (s, 1H, OH), 6.92-7.60 (m, 12H, Ar-H), 6.88 (d, 1H, CH), 6.80 (d, 1H, CH)	451.1 (M), 453.1 (M+2), 452.1 (M+1),	C, 58.42 H, 4.01 N, 9.29	C, 57.93 H, 3.86 N, 9.02
Y2dBr	3415(-NH), 3297(OH Str.), 1688(C=O), 1587(CH=CH), 1447(Ar. C=C), 2913, 2843(CH Str.), 1339(C-N), 815(C-Br)	10.37 (s, 1H, NHCO), 9.30 (s, 1H, NHCO), 8.42 (s, 1H, OH), 7.23-7.52 (m, 12H, Ar-H), 6.93 (d, 1H, CH), 6.84 (d, 1H, CH)	469.0 (M+1), 471.0 (M+2), 470.0 (M+1)	C, 56.13 H, 3.64 N, 8.93	C, 55.76 H, 3.32 N, 8.56
Y2eBr	3424(-NH), 3316(OH Str.), 1694(C=O), 1593(CH=CH), 1485(Ar. C=C), 2920, 2849(CH Str.), 1389(C-N), 809(C-Br)	9.89 (s, 1H, NHCO), 8.93 (s, 1H, NHCO), 8.29 (s, 1H, OH), 6.89-7.53 (m, 13H, Ar-H), 6.79 (d, 1H, CH), 6.36 (d, 1H, CH)	461.0 (M), 463.0 (M+2), 462.0 (M+1)	C, 62.35 H, 4.36 N, 9.09	C, 61.71 H, 4.21 N, 8.63

Synthesis of 4-bromophenyl semicarbazide (X1Br):

A solution of 4-bromophenylurea (0.1 mol) in methanol was refluxed with 99% hydrazine hydrate (1.6 mol) for 70-72 hours. After the completion of reaction, the reaction mixture was allowed to cool at room temperature and poured into crushed ice. The crude white product was filtered, thoroughly washed with water, dried and recrystallized from methanol. The completion of reaction was monitored by running TLC.

General method for the synthesis of chalconyl semicarbazone(Y1aBr- Y1fBr, Y2aBr- Y2eBr):
A mixture of 4-bromophenyl semicarbazide (0.01 mol) and appropriate substituted chalcone (0.01 mol) in methanol was stirred at 60-70^{o}C in the presence of 2-3 ml of conc. hydrochloric acid. The reaction mixture was poured into a beaker containing crushed ice and allowed to stand for two hours. The precipitate so formed was filtered and washed with ice cold water followed by ice cold methanol. The crude product was dried and recrystallized from chloroform. The completion of reaction was monitored by running TLC.

RESULTS AND DISCUSSION

The synthesis of title compounds was started with when Substituted aryl aldehyde was reacted with various aryl ketones to yield chalcone derivatives via Claisen Schmidt reaction. Then synthesized chalcone derivatives were reacted with (4-bromophenyl urea) semicarbazides to give the title compounds.

The structure of title compounds was confirmed by physico-chemical (T.L.C and m.p.) and spectral data (I.R., N.M.R, Mass and elemental analysis) as shown in table 1. The synthesized title compound were screening for antimicrobial activity as shown in table 2.

Table 2: Antimicrobial activity of synthesized title compounds

Compound (1000 µg/ml)	Zone of Inhibition (mm)					
	S. aureus	***B. antracis***	***B. cereus***	***E. coli***	***C. albicans***	***A. niger***
Streptomycin	42	39	36	32	NT	NT
Fluconazole	NT	NT	NT	NT	24	22
Y1aBr	32	29	35	41	27	23
Y1bBr	30	35	40	32	13	30
Y1cBr	12	10	14	11	16	24
Y1dBr	28	37	31	39	27	21
Y1eBr	14	12	13	10	22	11
Y1fBr	12	15	10	12	10	14
Y2aBr	17	12	14	11	15	24
Y2bBr	11	12	12	14	22	22
Y2cBr	13	10	15	12	21	16
Y2dBr	16	12	18	15	22	17
Y2eBr	13	16	15	22	14	16

All the synthesized compounds (Y1aBr-Y1fBr, Y2aBr-Y2eBr) were subjected for *in-vitro* antimicrobial activity using bacterial strains as *Staphylococcus aureus, Bacillus antracis, Bacillus cereus, Escherichia coli* and fungal strains as *C. albicans, A. niger*. During the *in-vitro* antimicrobial study, zone of inhibition was calculated for all the title compounds at 1000 µg/ml concentration. The standard drugs used for antibacterial activity was Streptomycin and Fluconazole for antifungal activity.

The compound Y1aBr and Y1bBr have shown significant antibacterial activity against *Staphylococcus aureus*, compound Y1bBr and Y1dBr against *Bacillus antracis*, compound Y1aBr and Y1dBr against *Bacillus cereus*. The compound Y1bBr against *Bacillus cereus* and Y1aBr & Y1dBr against *Escherichia coli* have shown even more activity as compared to standard drugs used where as compound Y1bBr shows equal activity against *Escherichia coli* w.r.t. standard drug used.

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