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Study on synthesis of 6-phenyl-4-(4-(4-(p-tolyloxy) phenoxy) phenyl)-5, 6-dihydropyrimidin-2(1H)-one and their antimicrobial activity

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ABSTRACT

1-chloro-4-(p-tolyolxy)benzene react with 1-(4-hydrogy phenyl)-ethanone in presence of copper metal as a catalyst gives 1-(4-(4(p-tolyolxy) phenoxy)phenyl)ethanone,this derivatives react with various substituted aldehyde to give corresponding substituted chalcone derivatives (N-1).Now these derivatives(N-1).on condensation with used gives 6-phenyl-4(4-(4-(p-tolyolxy)phenoxy)phenyl)-5,6-dinydropyridinmin-2(H)-one.(N-2) Structure elucidation of synthesized. Compound has been made on the basis of element analysis, 1H NMR Spectra studies. The microbial activity of the synthesized compounds has been studied against the species bacillus subtillis, staphylococcus aureus, Escherichia coli, and salmonella typhi.

Keywords: Synthesis, heterocyclic substituted chalcone derivatives, Pyrimidine derivatives, Chalcones

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INTRODUCTION

Chalcone (1) are the compounds were aromatic substitutes are introduced in to the terminal position of system C═C-C═, So chalcone are characterized by their position of a Ar(A)-CO-CH ═ CH-Ar(B) Structure in which two aromatic ring are linked by an aliphatic three carbon chain, thus chalcones are phenyl-styryl ketones containing reactive ketoethylenic group –C-CO═CH- .

Chalcones are also known as benzalacetophomes or benzylidene actophenones. chalcones are colored compounds because of presence of chromophore auxochromes. Chalcones are the precursors in the biosynthesis of anthocuanins and flavones.

Chalcones and substituted chalcones can be synthesized in laboratory by calisen-schmidt condensation of acetophenone or substituted acetophenone with aldehyde.

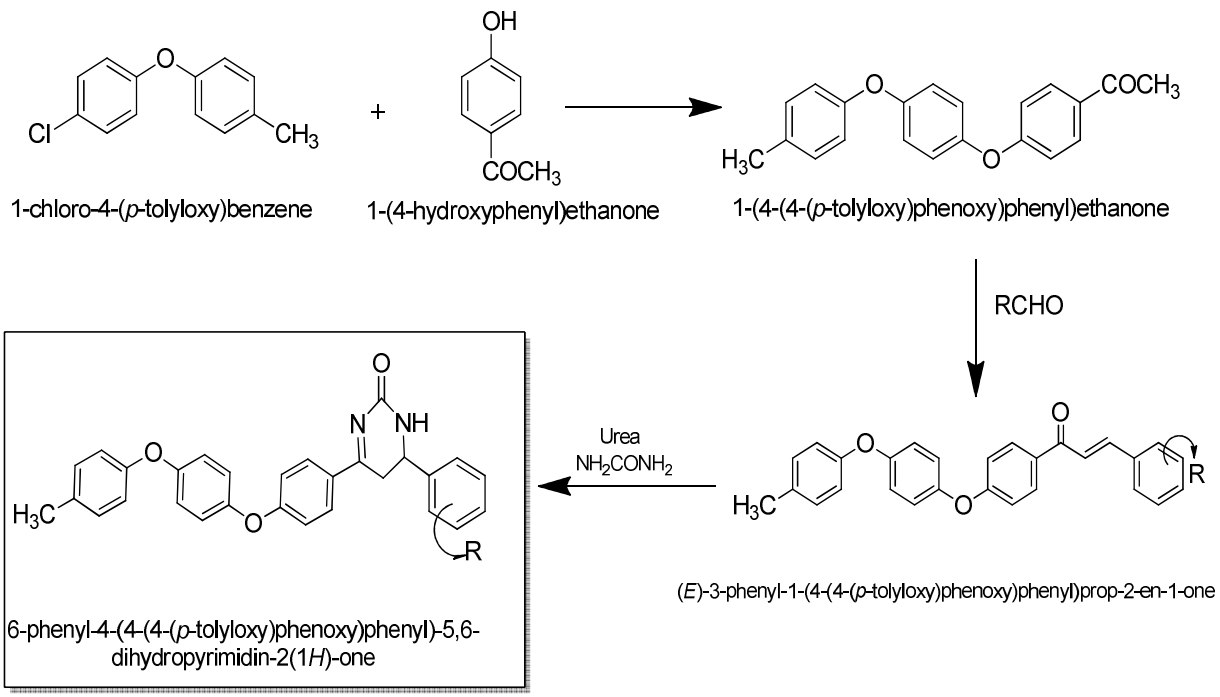
The first condensation was reported by kestanecki (2, 3) and he gave the name “Chalcones”. some substituted chalcones and their derivatives have been reported to process some interesting biological properties such as antibacterial, antifungal, insecticidal, anesthetic, analgesic, Ulcerogenic etc

The replacement of two –CH units in benzene by nitrogen atoms gives pyrimidines.Some substituted pyrimidines and their derivatives have been reported to possess antimicrobial, antitumour and antifungal (4-8) activities.

All these observation and the essential role of heterocyclic chalcones derivatives, pyrazolline depravities, and pyrimidines derivatives in the certain biological reaction encourage us to synthesis all these heterocyclic derivatives.

All effort are done in the research is to synthesized a novel compound that can be used for formulation of anticancer drugs.

REACTION SCHEME



Where R = (a) Benzaldehyde ,(b) -4- Anisaldehyde, (c)2- anisaldehyde,(d)salicyaledhyde, (e) 2- chlorobenzaldehyde, (f)Bromobenzaledyhde, (g) 3-4 dimethoxybenzaldehyde, (h) -4, 5 trimethoxybenzaldehyde.

MATERIALS AND METHODS

(1) Preparation of 1-(4-(4-(p-tolyloxy) phenoxy) phenyl) ethanone.
In 250 round bottom flask 1-(4-hydroxy phenyl)ethanone (13.5g,0.1 mole) was dissolved in pyridine (75 ml) and 1-chloro-4- (p-tolyloxy)benzene (23.6 g,0.01 mole) was added to it with constant stirring by maintaining temperature 25 deg. After completion of addition, the mixture was refluxed for 2 hrs. The solid was separated by filtration and crystallized from ethanol.

(2) Preparation of (E) -3-Phenyl-1-(4-(4-(p-tolyloxy) phenoxy) phenyl) prop-2-en-1-one
To well stirred solution of 1-(4-(4-(p-tolyloxy)phenoxy)phenyl)ethanone (3.3 gm,0.01 mole) in methanol (40 ml) and 40 %sodium hydroxide solution (4ml) ,Benzildehyde (1.06 gm,0.01 mole) was added drop wise at 0 deg.After addition of the mixture was stirred for further ice water and acidified with diluted hydrochloric acid. The solid separated out was filtered and crystallized from ethanol.

(3) Preparation of 6-phenyl-4-(4-(4-(p-tolyloxy)phenyl)-5-6-dihyhropyrimidin-2(1H)-One
A mixture of [E] -3-phenyl-1-(4-(4(p-tolyloxy)phenoxy)phenyl prop-2-en-one (4.5 g 0.01 mole) urea (0.60 g , 0.01 mole) and sodium ethoxide (17 g ,0.25 mole) in ethanol, (30 ml) was refluxed for 4 hours. The content was them

poured over crushed ice and acidified, washed with diluted distilled water. The solid was isolated and crystallized from ethanol.

RESULTS AND DISCUSSION

Melting points

All melting points were determined in open capillaries in a liquid paraffin bath and are uncorrected. The IR spectra were recorded with KBr pellets on Perkin - Elmer - 783 spectrophotometer and 1H NMR spectra were recorded on a Varian Geminy 200 MHz spectrophotometer with CDCl3 / DMSOd6 as a solvent using tetramethylsilane (T.M.S.) as an internal standard; the chemical shift values are in d ppm. The purity of the compounds was checked by thin layer chromatography (T.L.C.) on silica gel coated glass plates. The elemental analysis (i.e. C, H and N analysis) has been done on Carlo - Erba - 1108 analyzer and the values are within the permissible limits (i.e. + 0.5) of their calculated values.

ANALYSIS DATA

No.	Code No.	R	Molecular Formula	Molecular Weight (g/m)	Yield (%)	M.P. °C	C %	H %	N %
							Found (Required)		
1	a	-H	$C_{29}H_{24}N_2O_3$	448.51	69	160	50.30 (52.34)	4.20 (4.21)	9.38 (9.35)
2	b	4-OCH_3	$C_{30}H_{26}N_2O_4$	478.54	70	207	50.62 (50.62)	4.29 (4.30)	9.66 (9.70)
3	c	2-OCH_3	$C_{30}H_{26}N_2O_4$	478.54	72	210	55.30 (55.35)	4.20 (4.20)	9.66 (9.73)
4	d	2-OH	$C_{29}H_{24}N_2O_4$	464.51	64	150	54.46 (54.45)	4.00 (4.05)	9.55 (9.49)
5	e	2-Cl	$C_{29}H_{23}ClN_2O_3$	482.14	78	154	50.82 (50.21)	4.10 (4.07)	9.32 (9.33)
6	f	4-Cl	$C_{29}H_{23}ClN_2O_3$	482.14	80	160	55.42 (55.35)	4.22 (4.29)	9.78 (9.80)
7	g	2-NO_2	$C_{29}H_{23}N_3O_5$	493.16	73	184	50.84 (53.20)	4.42 (4.35)	9.77 (9.70)
8	h	3-Br	$C_{29}H_{23}BrN_2O_3$	526.09	66	198	53.26 (53.24)	4.30 (4.29)	9.08 (9.11)
9	i	3,4-$(OCH_3)_2$	$C_{31}H_{28}N_2O_5$	508.56	88	204	55.27 (55.32)	4.62 (4.60)	9.31 (9.31)
10	j	3,4,5-$(OCH_3)_2$	$C_{32}H_{30}N_2O_6$	538.59	85	200	60.80 (60.77)	4.20 (4.30)	9.85 (9.90)

Antimicrobial activity

Antimicrobial activity of newly synthesized compounds was studied against gram-positive bacteria *Staphylococcus aureus* and gram-negative bacteria *Escherichia coli* (for antibacterial activity) and against the culture "Candela albicans" (for antifungal activity). The antimicrobial screening was carried out by cup - plate method10 at a concentration of 50 mg. mL^{-1} in solvent D.M.F. The zone of inhibition was measured in mm. The antimicrobial activity of the synthesized compounds was compared with standard drugs Ampicillin, Penicillin and Tetracycline at the same concentration.

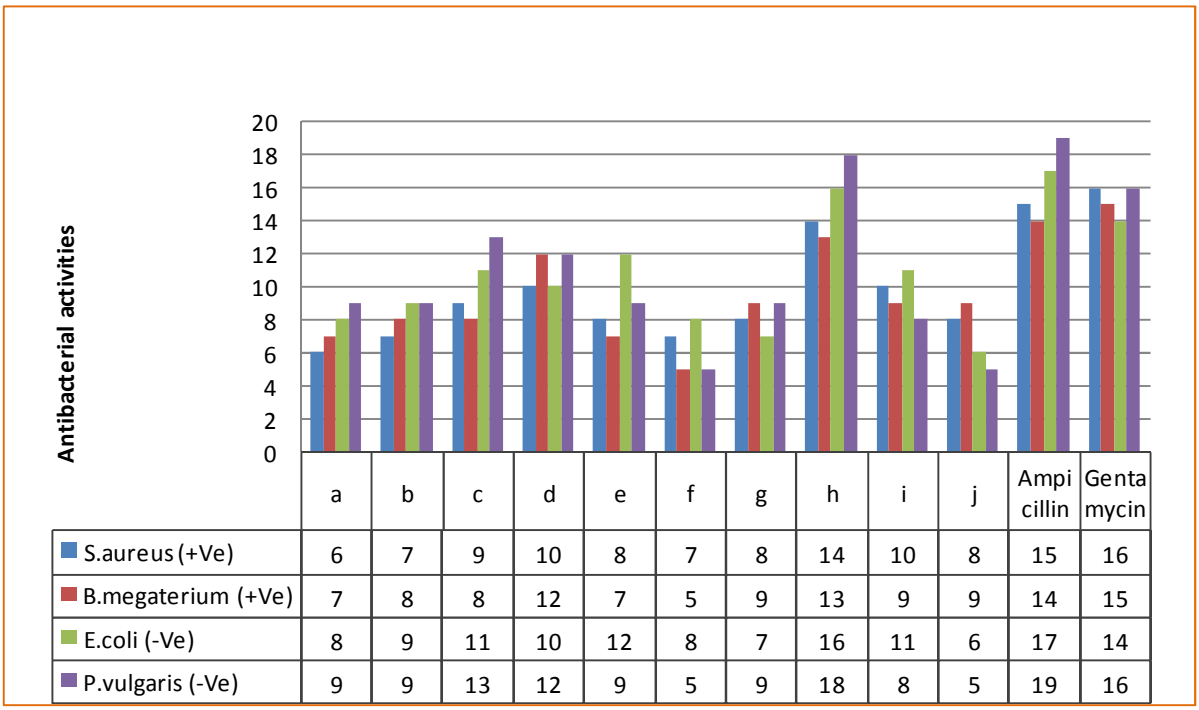
RESULTS

Organisms	Compounds	Ampicillin	Gentamycin
S.aureus	3-Br	-	-
B. megaterium	3-Br	-	-
E.coli	3-Br	✓	✓
P. vulgaris	3-Br	-	✓

I.R. (cm-1) (KBr) spectral data of compound :-

A) 1662 n (C=O stretching, chalcone moiety); 1604 n (C=N stretching, dihydropyrimidin moiety);1585 n (C=Cstretching, chalcone moiety); 1526 n (N=O stretching, Ar-NO_2 at phenyl ring of chalcone moiety); (C-Cl stretching, Ar-Cl at phenyl ring).

B) 3400 n (N-H stretching, dihydropyrimidin moiety); 1658 n (C=O stretching, dihydropyrimidin moiety);1465 n (C-H bending, -CH2- of pyrimidine ring);745 n (C-Cl stretching,Ar-Cl at phenyl ring).
C) 3367 n (N-H stretching, dihydropyrimidin moiety); 2833 n (C-H stretching, Ar-OCH3 at phenyl ring); 736 n (C-Cl stretching, Ar-Cl at phenyl ring).



	a	b	c	d	e	f	g	h	i	j	Ampicillin	Gentamycin
S.aureus (+Ve)	6	7	9	10	8	7	8	14	10	8	15	16
B.megaterium (+Ve)	7	8	8	12	7	5	9	13	9	9	14	15
E.coli (-Ve)	8	9	11	10	12	8	7	16	11	6	17	14
P.vulgaris (-Ve)	9	9	13	12	9	5	9	18	8	5	19	16

^{1}H N.M.R. (CDCl3) spectral data of compound
A) 3.30 d ppm (s, 2H, -CH_2- of dihydropyrimidin ring); 3.38 d ppm (s, 1H, Ar-CH); 7.03 to 7.75 d ppm (m,14H, Ar-H); 7.79 d ppm (d, 1H, -CH=CH-Ar); 8.14 d ppm (d, 1H, -CO-CH=CH-).
B) 3.35 d ppm (s, 2H, -CH_2- of dihydropyrimidin ring); 3.41 d ppm (s, 1H, Ar-CH); 3.78 d ppm (s, 3H,Ar-OCH_3 at phenyl ring); 7.01 to 7.71 d ppm (m, 14H,Ar-H); 7.84 d ppm (s, 1H, -NH- of dihydropyrimidin ring).
C) 3.33 d ppm (s, 2H, -CH_2- of dihydropyrimidin ring); 3.40 dppm (s, 1H, Ar-CH); 3.80 d ppm (s, 3H,Ar-OCH_3 at phenyl ring); 6.99 to 7.68 d ppm (m, 14H, Ar-H); 7.83 d ppm (s, 1H, -NH- of dihydropyrimidin ring).

CONCLUSION

The screening results revealed that the compounds (h) showed significant antimicrobial activity. In particular compounds (d) and (j) showed moderate to considerable antibacterial and antifungal activities against all the organisms employed at a conc. of 1000 _g/mL (0.1ml dose level) Comparable to that of standard drugs Ampicillin and Gentamycin.

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