IJPSR (2017), Vol. 8, Issue 3 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 August, 2016; received in revised form, 14 October, 2016; accepted, 19 October, 2016; published 01 March, 2017

SYNTHESIS AND *IN VITRO* ANTIBACTERIAL ACTIVITY OF SOME PHENYL URENYL CHALCONES

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Keywords:

Chalcone; Antibacterial activity; phenyl urenyl, aminoacetophenone

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ABSTRACT: Despite significant progress made in the treatment of infectious diseases, caused by bacteria and fungi, it remains a major worldwide health problem due to rapid development of resistance against the existing antimicrobial drugs. In the present investigation, a novel series of chalcones 2a–2h were synthesized by the clasein-schmidt condensation of various aldehydes with methyl ketone in the presence of KOH in ethanol which lead to the formation of new chalcones. The structures of these compounds were elucidated by, IR, 1H-NMR spectral data. The in vitro antibacterial activity of these compounds was evaluated against two Gram positive and two Gram-negative bacteria *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli* and *Pseudomonas aeruginosa* by microdilution method and then the minimum inhibitory concentration (MIC) of these compounds was determined. The results showed that compounds 2d, 2e and 2h showed most promising antibacterial activity as compared to the antibiotics ciprofloxacin in (Tables 1). Compound 2e which carries the nitro substituent appears to exhibit the highest antibacterial activity against all gram positive and gram negative bacteria.

INTRODUCTION: With the continuation of developing new treatment for bacterial disease, it remains a major worldwide health problem due to rapid development of resistance against the existing antimicrobial drugs. Developing novel antimicrobial agents with different mechanism of action is one of the main challenges to overcome the antimicrobial resistance. In view of these facts, the current interest in the development of new antimicrobial agents can be partially ascribed both to the increasing emergence of bacterial resistance to antibiotic therapy and to newly emerging pathogens [1-3].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.8(3).1205-09

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.8 (3).1205-09

Thus, the synthesis and discovery of more efficient antimicrobial agents has been intensively considered during the last decade. Different heterocyclic compounds containing nitrogen, sulphur and oxygen as hetero atoms have been explored for the development of new antimicrobial agents [4].

Medicinal chemists have carried out considerable research on chalcones derivatives due to their diverse therapeutic applications extending from central nervous system applications to antimicrobials. Chalcones and their derivatives are an attractive molecular scaffold for the search of new biologically active molecules [5]. The most predominant biological activity is observed for the class of 'antimicrobial agents'. Chalcones containing several functional groups have been exhibited a wide spectrum of biological activities including antitumor [6, 7], antibacterial [8, 9], anti-inflammatory [10], antileishmanial [11, 12], antimalarial

[13, 14] and antitrypanosomal [15, 16] activity [17]. Keeping this observation we have synthesized new chalcone derivatives which were characterized by IR and NMR spectroscopy. Synthesized compounds were screened for antibacterial activity.

2. MATERIAL AND METHOD:

2.1 Chemistry: A mixture of the aminoacetophenone (1 mmol) and phenyliso cyanates recently distilled (1 mmol) was dissolved in dry acetone (5 mL). The mixture was stirred under nitrogen atmosphere for 3-7 h at room temperature. The resulting solid was filtered, and crystallization with the appropriate solvent afforded the desired urenylacetophenone 1. Chalcones 2(a-h) were synthesized from the Claisen–Schmidt reaction of phenyl urenyl acetophenone with different aldehydes in the presence of KOH (30%) as shown in **Fig. 1**, which were crystallized from CH_3OH or C_2H_5OH to give pure crystalline solid compounds in moderate yields. All the compounds are insoluble in water but soluble in organic solvents. The structures of these compounds were analyzed by the rigorous analysis of their IR and ^{1}H- NMR spectral data.

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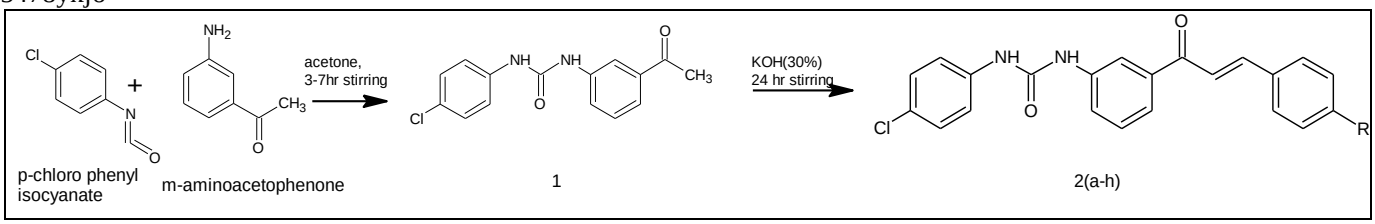

FIG.1: SCHEMATIC DIAGRAM INDICATING THE SYNTHESIS OF COMPOUND NOS. 2a–2h.R = -OH (2a), -OCH_3 (2b), -F (2c), -Cl (2d), -NO_2 (2e), -CH_3 (2f), Br (2g), -$N(CH_3)_2$ (2h)

2.2 Pharmacology:

B.1 *In vitro* antimicrobial activity: Antibacterial activities were evaluated by using agar well diffusion method. The nutrient agar medium (peptone, beef extract, NaCl and agar-agar) were used for antibacterial screening respectively. The inoculums of the different bacteria were spread over agar medium. After the media had cooled, wells of bore size (6 mm) were made in solid medium by using a sterile metallic borer and 25 mL test drug (2.0 mg/ml in DMSO) in 100µg/ml concentration was poured in each cavity of different plates. Standard drug, Ciprofloxacin (100µg/ml) was used against bacteria *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli* and *Pseudomonas aeruginosa* were placed aseptically in a separate petri dish. The plates were kept at room temperature for one hour to diffuse the drug in surrounding medium and then incubated at 37ºC for 24 h. The diameter of the zone of inhibition formed around the cavities and disc of standard drug after incubation was accurately measured in mm.

B.2 MIC of all active compounds: MIC measurements of all active compounds were carried out using the two fold serial dilution technique. Twofold serial dilutions of the selected compounds were prepared using proper nutrient broth. Compounds were prepared in the concentration range of 100, 50, 25, 12.5, 6.25, 3.125, 1.56 and 0.78 mg/mL. The microorganism suspensions (10^6 CFU/mL) were used to inoculate the test compounds in their suitable broth. The plates were incubated at 37ºC for 24 h for bacteria, respectively. At the end of experiment the growth of microorganisms was observed by turbidity measurements. The lowest concentrations showing no growth was taken as the minimum inhibitory concentration (MIC) which is presented in **Table 1.**

TABLE 1: RESULTS OF ANTIBACTERIAL SCREENING OF COMPOUNDS (2a-h).

Entry	R	Minimum Inhibitory concentration for bacteria (µg/ml) ±SD			
		Gram negative		Gram positive	
		E coli	*P aeroginosa*	*S aureus*	*S pyogenes*
2a	-OH	250 ± 1.60***	500 ±3.78*	500±2.64*	500±2.64**
2b	-OCH_3	500±3.60	500 ±1.16*	500 ±2.50*	250 ±3.60*
2c	-F	250 ±1.20**	50 ±3.60*	100±2.04*	100 ± 1.92*
2d	-Cl	50±1.60**	100±2.04**	100 ±3.05*	25 ± 3.21*

2e	$-NO_2$	50 ±2.44*	25 ± 1.21*	100 ±4.16***	50 ±1.78
2f	$-CH_3$	250 ±3.05	250 ±1.00*	250 ±4.04*	100 ±3.46*
2g	-Br	500 ± 4.40	500 ±3.26	500 ±3.78**	500 ± 4.61*
2h	$-N(CH_3)_2$	50 ±3.61*	100 ± 4.04	250 ±1.16*	50 ±3.21*
	Ciprofloxacin	100 ±2.05	100 ±1.0	250 ±1.52	100 ± 2.06

±SD, standard deviation. All values are presented as mean of 6 experiments (n = 6). All significant differences are considered from control value 0.00.

* P < 0.05 significant.

** P < 0.01 moderately significant.

*** P < 0.001 extremely significant.

RESULTS AND DISCUSSION: The present study describes the synthesis and antimicrobial evaluation of some phenyl urenyl chalcones which were synthesized in satisfactory yields (62–80%) as illustrated in **Fig. 1** and their structures were characterized by spectral data. It may be concluded that this study describes the general method for the synthesis of some Chalcones linked through the phenyl urenyl ring under the normal conditions. All the eight synthesized compounds 2a-2h were screened for their potential to inhibit emerging pathogens Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli and Pseudomonas aeruginosa responsible for gastrointestinal diseases.

The individual minimum inhibitory concentration (MIC, µg/mL) obtained for compounds 2a-h are presented in (**Table 1**). It was observed that compounds 2d (4-Cl), 2e (4-NO_2) and 2h (4-$N(CH_3)_2$) were most active compounds.

On the basis of antibacterial screening, compounds 2d (4-Cl), 2e (4-NO_2) and 2h (4-$N(CH_3)_2$) were found to show very good activity against *E. coli* at MIC = 50 µg/mL. Compounds 2c (4-F) displayed very good activity at MIC = 50 µg/mL, whereas compounds 2e (4-NO_2) displayed excellent inhibitory activity against *P. aeruginosa* at MIC = 25µg/mL as compared to ampicillin (MIC = 100µg/mL). Compounds 2c (4-F) and 2d (4-Cl) were found to exhibit activity at MIC = 100 µg/mL against *S. aureus* as compared to standard ampicillin (MIC = 250 µg/mL). Compounds 2e (4-NO_2) and 2h (4-$N(CH_3)_2$) showed very good activity (MIC = 50 µg/mL), while compounds 2d (4-Cl) have shown excellent activity against *S. pyogenes* as compared to ampicillin (MIC = 100 µg/mL).

EXPERIMENTAL:

4′-*N*-(*N*′-*p*-chlorophenylurenyl)acetophenone (1). The solid was recrystallized in EtOH: yield 65%; mp 224-225 °C; IR 3376 (NH), 1715 (COMe) cm^{-1}, 1648 (CO); ^{1}H NMR (DMSOd_6) δ 2.51 (s, 3H, COMe), 7.33 (d, 2H,*J* = 8.67 Hz, ArH), 7.49 (d, 2H, *J* = 8.67 Hz, ArH), 7.57 (d, 2H, *J* = 8.64 Hz, ArH), 7.90 (d, 2H,*J* = 8.64 Hz, ArH), 8.94 (br s, NH), 9.13 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3- (p-hydroxyphenyl)-2-propen-1-one (2a). IR 3340 (NH), 1657 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) δ 7.32 (d, 2H, *J*= 8.91 Hz, ArH), 7.46-7.52 (m, 2H, ArH), 7.67 (d, 2H, *J* = 8.40 Hz, ArH), 7.73 (d, 2H, *J* = 15.82 Hz, ArH),7.59-8.14 (d, 2H, *J* = 8.40 Hz, CH),7.56(d,2H, ArH), 6.65(d, 2H, ArH), 5.35(s, 1H, -OH), 9.63 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3- (p-methoxyphenyl)-2-propen-1-one (2b). IR 3344 (NH), 1654 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) δ 7.47 (d, 2H, *J*= 8.88 Hz, ArH), 7.52-7.56 (m, 2H, ArH), 7.75 (d, 2H, *J* = 8.38 Hz, ArH), 8.13 (d, 2H, *J* = 15.82 Hz, ArH), 7.62-8.01 (d, 2H, *J* = 8.26 Hz, CH), 7.60 (d,2H, ArH), 6.94(d, 2H, ArH), 3.84 (s, 3H, $-CH_3$), 9.61 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3-(p-fluorophenyl)-2-propen-1-one (2c). IR 3339 (NH), 1648 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) δ 7.37 (d, 2H, *J*= 8.76 Hz, ArH), 7.53-7.61 (m, 2H, ArH), 7.65 (d, 2H, *J* = 8.41 Hz, ArH), 7.78 (d, 2H, *J* = 15.69 Hz, ArH), 7.59-8.06 (d, 2H, *J* = 8.38 Hz, CH), 7.72 (d,2H, ArH), 7.19(d, 2H, ArH), 9.57 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl) phenyl]-3-(p-chlorophenyl)-2-propen-1-one (2d). IR 3340 (NH), 1652 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) δ 7.42 (d, 2H, *J*= 8.94 Hz, ArH), 7.47-7.53 (m, 2H,

ArH), 7.72 (d, 2H, *J* = 8.54 Hz, ArH), 7.89 (d, 2H, *J* = 14.97 Hz, ArH), 7.79-8.13 (d, 2H, *J* = 8.63 Hz, CH), 7.68 (d,2H, ArH), 7.44(d, 2H, ArH), 9.60 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3- (p-nitrophenyl)-2-propen-1-one (2e). IR 3346 (NH), 1668 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) *δ* 7.47 (d, 2H, *J*= 8.88 Hz, ArH), 7.49-7.58 (m, 2H, ArH), 7.59 (d, 2H, *J* = 8.63 Hz, ArH), 7.81 (d, 2H, *J* = 15.12 Hz, ArH), 7.88-8.23 (d, 2H, *J* = 8.51Hz, CH), 8.03 (d,2H, ArH), 8.21 (d, 2H, ArH), 9.50 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3 -(p-methylphenyl)-2-propen-1-one (2f). IR 3340 (NH), 1653(CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) *δ* 7.45 (d, 2H, *J*= 8.88 Hz, ArH), 7.32-7.38 (m, 2H, ArH), 7.56 (d, 2H, *J* = 8.13 Hz, ArH), 7.18 (d, 2H, *J* = 12.5Hz, ArH), 7.79-8.13 (d, 2H, *J* = 8.63 Hz, CH), 7.58 (d,2H, ArH), 7.18(d, 2H, ArH), 2.34(s, 3H, CH_3), 9.47 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]-3-(p-bromophenyl)-2-propen-1-one (2g). IR 3346 (NH), 1660 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) *δ* 7.39 (d, 2H, *J*= 8.89 Hz, ArH), 7.41-7.46 (m, 2H, ArH), 7.89 (d, 2H, *J* = 8.75Hz, ArH), 7.52 (d, 2H, *J* = 13.55Hz, ArH), 7.61-8.11 (d, 2H, *J* = 6.63 Hz, CH), 7.61 (d,2H, ArH), 7.55 (d, 2H, ArH), 9.43 (br s, NH).

1-[4′-*N*-(*N*′-*p*-Chlorophenylurenyl)phenyl]- 3-(p-dimethylaminophenyl)-2-propen-1-one (2h). IR 3337 (NH), 1648 (CO) cm^{-1}, ^{1}H NMR (DMSO-*d*6) *δ* 7.41 (d, 2H, *J*= 8.90 Hz,ArH), 7.46-7.52 (m, 2H, ArH), 7.62 (d, 2H, *J* = 8.34 Hz, ArH), 8.01 (d, 2H, *J* = 15.02 Hz, ArH), 7.53-8.04 (d, 2H, *J* = 8.98 Hz, CH), 7.72 (d,2H, ArH), 6.71(d, 2H, ArH), 3.06(s, 6H, $N(CH_3)_2$), 9.63 (br s, NH).

CONCLUSIONS: The novel chalcones derivatives were synthesized by the reaction of urenyl acetophenone with different aldehydes and were studied for their antibacterial activity. This research involves the synthesis of chalcone derivatives 2a-2h and antibacterial activity of these chalcone compounds were examined using culture *S. aureus*, *S. pyogenes*, *E. coli* and *P. aeruginosa*. The results of antibacterial screening reveal that among all the compounds screened, compound 2c showed moderate antibacterial activity while compounds 2d and 2h displayed good antibacterial activity when compared with Ciprofloxacin used as the standard drugs. Particularly, compound 2e which carries the nitro substituent appears to exhibit the highest antibacterial activity against all bacteria.

ACKNOWLEDGEMENT: The authors are thankful to Microbial Type Culture Collection and Gene Bank, Chandigarh, Punjab to provide the bacterial culture to conduct the above research.

CONFLICT OF INTEREST: The authors report no conflict of interest.

The entire chemicals were purchased from Aldrich Chemical Company (USA) and were used without further purification. The reactions were monitored by percolated aluminium silica gel 60F 254 thin layer plates procured from Merck (Germany). All melting points were measured with a capillary apparatus.

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How to cite this article:
Himangini and Pathak DP: Synthesis and *in vitro* antibacterial activity of some phenyl urenyl chalcones. Int J Pharm Sci Res 2017; 8(3): 1205-09.doi: 10.13040/IJPSR.0975-8232.8(3).1205-09.