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RESEARCH ARTICLE

Synthesis, Characterization and Antimicrobial Activity of Substituted Pyrimidines

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Abstract: A series of novel pyrimidine derivatives were synthesized from chalcones and evaluated for their antimicrobial activities. Chalcones were prepared by treatment of substituted acetophenones with benzaldehyde by Claisen-Schimidt condensation. Various pyrimidine derivatives (CA01-CA04) were prepared by reaction of chalcone with substituted phenylurea in ethanolic sodium hydroxide solution. The structures of the newly synthesized pyrimidine derivatives have been established on the based on IR, ^{1}H & ^{13}C NMR and elemental analysis. The synthesized compounds (CA01-CA04) were evaluated for their antibacterial and antifungal activity.

Keywords: Pyrimidine, Chalcones, Antimicrobial activity

Introduction

Pyrimidine is a heterocyclic aromatic compound containing two nitrogen atoms at position 1 and 3 of the six member ring system. The substituted pyrimidines are prepared by corresponding chalcones with phenyl urea in ethanolic sodium hydroxide solution. Chalcones and their derivatives, whether synthetic or naturally occurring are an interesting and significant group of molecules as they possess a wide range of pharmacological activities such as anti-inflammatory, antimicrobial, antifungal, antibacterial, antioxidant, cytotoxic, antitumor, anticancer, antimitotic, antileishmanial, anti-malarial, antitubercular, antiviral and so on[1-14]. Pyrimidine derivative suggest that Nitrogen containing heterocyclic compounds posses wide variety of activities. Pyrimidine derivatives have played an important role in the medicinal chemistry. They are reported to possess a broad spectrum of biological activities such as antimicrobial, anti-inflammatory, anthelmentic[15-17].

Some of the other activities which are associated with these compounds are analgesic, anticancer, antiviral, antimalarial, anti-tubercular. Let by these considerations, it appeared of interest to synthesis of pyrimidine derivatives and to investigate for their antimicrobial activities. All the synthesized compounds were characterized on the basis of their physical properties such as melting point, IR, ^{1}H & ^{13}C NMR spectral data and elemental analysis. The physical data of titled compounds are summarized in Table 1.

Table 1. Physical and analytical data of the synthesized compounds

Compd.	R	R'	Mol. Formula	Yield %	M.P ^{0}C	Analysis found (Calculated) %		
						C	H	N
C01	3-NO_2	H	$C_{15}H_{11}NO_3$	62	253.25	71.06 (71.03)	4.34 (4.30)	5.52 (5.50)
C02	4-NO_2	H	$C_{15}H_{11}NO_3$	60	253.25	71.06 (71.01)	4.34 (4.32)	5.52 (5.48)
A03	H	2-NO_2, 4-Cl	$C_7H_6ClN_3O_3$	74	215.59	38.96 (38.92)	2.78 (2.76)	19.48 (19.46)
A07	H	3-$COCH_3$	$C_9H_{10}N_2O_2$	73	178.18	60.61 (60.59)	5.61 (5.58)	15.71 (15.65)
CA01	4-NO_2	2-NO_2, 4-Cl	$C_{22}H_{15}ClN_4O_5$	58	450.83	58.55 (58.53)	3.32 (3.30)	12.42 (12.40)
CA02	4-NO_2	3-$COCH_3$	$C_{24}H_{19}N_3O_4$	62	413.18	69.66 (69.63)	4.59 (4.57)	10.15 (10.13)
CA03	3-NO_2	2-NO_2, 4-Cl	$C_{22}H_{15}ClN_4O_5$	57	450.83	58.55 (58.56)	3.32 (3.30)	12.42 (12.38)
CA04	3-NO_2	3-$COCH_3$	$C_{24}H_{19}N_3O_4$	56	399.44	69.66 (69.72)	4.59 (4.63)	10.15 (10.10)

Experimental

The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^1H & ^{13}C NMR spectra were recorded in DMSO-D_6 on BRUKER 400 MHz spectrometer using TMS as an internal standard (chemical shifts in δ, ppm) (Table 2). The elemental analysis for C, H, & N were in an agreement with the calculated values. The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1.

General procedure

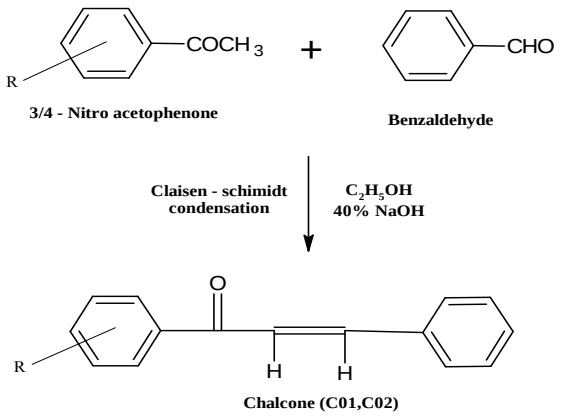
Step - I (a): Synthesis of Chalcone[18] (C01& C02)

A equimolar (0.01 mole) quantity of substituted acetophenone and benzaldehyde was dissolved in 20 mL of ethanolic sodium hydroxide and then stirred about 2-3 h with a magnetic stirrer and kept in refrigerator for 24 h. The content was poured into crushed ice and acidified with dil. HCl. The solid separated was filtered and crystallized from ethanol.

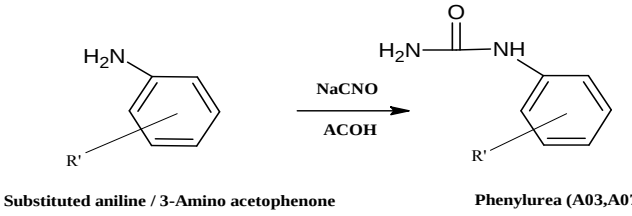
Step - I (b): Synthesis of substituted phenylurea[19] (A03 & A07)

A substituted aniline (0.05 mole) was dissolved in glacial acetic acid (20 mL) and diluted with water (100 mL). To this, an equimolar quantity (0.05 mole) of sodium cyanate in warm water (50 mL) was added with constant stirring. The reaction mixture was allowed to stand for 1 h and the solid precipitate was formed and dried after recrystallization from boiling water.

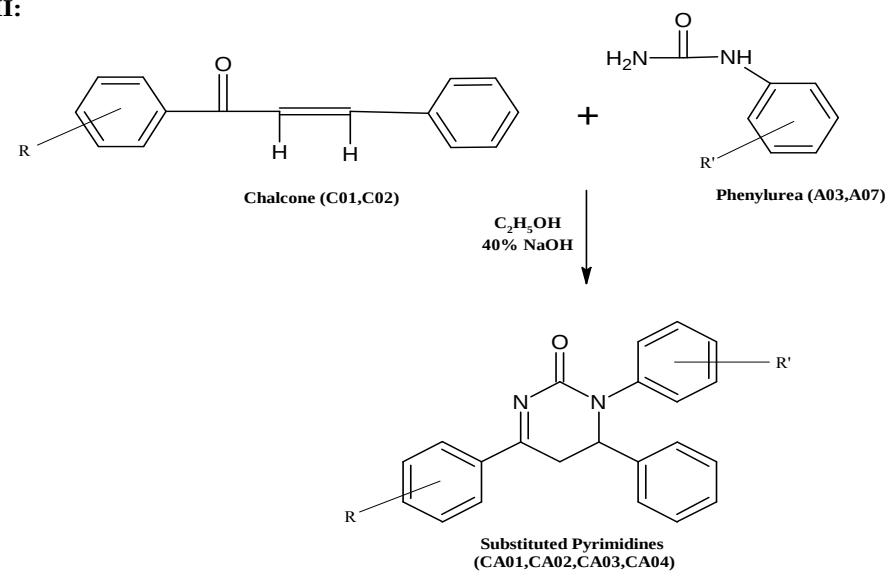
Step-I (a):



Step-I(b):



Step-II:



CA01: R = 4-NO_2, R'=2-NO_2, 4-CI; CA02: R =4-NO_2, R' = 3-$COCH_3$; CA03: R=3-NO_2, R'2-NO_2, 4-Cl; CA04 : R = 3-NO_2; R' = 3-$COCH_3$

Scheme 1

Table 2. Spectral data of synthesized compounds

Compd.	IR (KBr) ν_{max} in cm^{-1}	^{1}H NMR (DMSO-d_6), δ, ppm	^{13}C NMR (DMSO-d_6), δ, ppm
C01	3086 (aromatic C-H str), 1658 (C=O str),1527 (aromatic C=C), 1342 (NO_2 str)	4.33 (s, 1H ,CH), 4.58 (s, 1H, CH), 7.48 – 8.82 (m, 9H, Ar-H)	187 (C=O), 121-148 (Ar-C)
C02	3055 (aromatic CH str), 1612 (C=O str), 1597 (aromatic C=C), 1327 (NO_2 str)	4.16 (s, 1H, CH), 4.38 (s, 1H, CH), 7.49 – 8.38 (m, 9H, Ar-H)	188 (C=O), 121-149 (Ar-C)
A03	3471 (NH str), 3093 (aromatic CH str), 1635 (C=O str), 1566 (aromatic C=C), 1365 (NO_2 str),763 (O-substitution)	8.98 (s, 1H, NH), 6.53 (s, 2H, NH_2), 6.76 – 8.65 (m, 3H, Ar-H)	168 (CONH), 117-145 (Ar-C)
A07	3363 (NH str), 3078 (aromatic CH str), 1666 (C=O str), 1597 (aromatic C=C), 1350 (C-N str)	8.78 (s, 1H, NH), 5.94 (s, 2H, NH_2), 7.35 – 7.99 (m, 4H, Ar-H), 2.19 (s, 3H, CH_3)	197 (C=O), 155 (CONH), 116 – 140 (Ar-C), 26 (CH_3)
CA01	3471 (NH str), 3093 (aromatic CH str), 1635 (C=O str), 1597 (aromatic C=C), 1342 (NO_2 str), 763 (O-substitution)	4.87 (s, 1H, CH), 3.82 (s, 2H, CH_2), 6.62 – 8.36 (m, 12H, Ar-H).	185 (CONH), 154 (C=O), 112-145, (Ar-C), 60 (CH_2), 44 (CH)
CA02	3464 (NH str), 3060 (aromatic CH str), 1666 (C=O str), 1589 (aromatic C=C), 1342 (NO_2 str)	4.9 (s, 1H, CH str), 3.81 (s, 2H, CH_2 str), 6.89 – 7.59 (m, 13H, Ar-H str), 2.08 (s, 3H, CH_3)	198 (C=O), 155 (CONH), 112-153 (Ar-C), 60 (CH_2), 43 (CH), 26 (CH_3)
CA03	3471 (NH str), 3009 (aromatic CH str), 1635 (C=O str), 1566 (aromatic C=C), 1342 (NO_2 str), 763 (O-substitution)	4.32 (s, 1H, CH), 3.74 (s, 2H, CH_2), 7.04 – 8.26 (m, 12H, Ar-H)	185 (CONH) , 148 (C=N), 113-145 (Ar-C), 60 (CH_2), 43 (CH)
CA04	3363 (NH str), 3062 (aromatic CH str), 1666 (C=O str), 1550 (aromatic C=C), 1327 (NO_2 str)	4.99 (s, 1H, CH), 3.88 (s, 2H, CH_2), 7.07 – 8.94 (m, 13H, Ar-H), 2.72 (s, 3H, CH_3)	197 (C=O), 153 (CONH), 111-151 (Ar-C), 60.19 (CH_2), 43 (CH), 26 (CH_3)

Step – II: Synthesis of substituted pyrimidines[20] (CA01 – CA04)

A equimolar (0.005 mole) mixture of chalcones and substituted phenylurea were dissolved in ethanolic sodium hydroxide (35 mL) and was heated under reflux condition about 5-6 h. Then this was poured into (400 mL) cold water and then kept in room temperature for one day. The precipitate obtained was filtered, washed and recrystallized from ethanol.

Antimicrobial activity

In vitro antibacterial activity was determined by Kirby-Bauer disc diffusion method against bacteria such as *Staphylococcus aureus* and *Bacillus* (Gram +ve), *Salmonella typhi* and

Pseudomonas aeruginosa (Gram -ve) using *Ampicilin* as standard a standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 24 h incubation at 35-37 ^{o}C.

Similarly antifungal activity was performed against Candida. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 48 h at 25 ^{o}C. The results of antimicrobial activity are presented in Table 3.

Table 3. Antimicrobial activity of the synthesized compounds, Zone of inhibition (mm) of synthesized compounds

Sample code	Anti-bacterial activity																Anti-fungal activity			
	Gram positive								Gram negative											
	Staphylococcus .spp				*Bacillus.spp*				*Salmonella.spp*				*Pseudomonas. spp*				*Candida*			
	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std
CA01	7	6	4	10	8	5	2	10	6	5	4	9	6	4	3	9	8	6	4	14
CA02	6	4	-	5	8	6	5	9	8	5	5	8	8	7	5	10	9	6	4	12
CA03	7	6	4	7	7	4	2	8	9	5	3	10	9	8	6	10	11	5	3	21
CA04	11	6	3	11	9	7	5	11	6	5	3	10	9	8	5	10	9	5	4	15

Results and Discussion

Synthesis of substituted pyrimidines was obtained as mentioned in the Scheme 1. The required starting materials of chalcones (C01 & C02) were synthesized according to the procedure reported in the literature[18]. Substituted phenylurea (A03 & A07) is prepared according to the known method[19] from the condensation of substituted aniline with sodium cyanate. Mixture of chalcone and phenylurea were further on heating to give substituted pyrimidines (CA01-CA04). The spectral analysis of all the compounds was done by IR, ^{1}H & ^{13}C NMR and the spectral data were consistent with the assigned structures.

In vitro antibacterial activity of synthesized compounds was carried out by Kirby-Bauer disc diffusion method against bacteria such as Staphylococcus *aureus, Bacillus, Salmonella typhi, Pseudomonas aeruginosa*. The compounds of CA01-CA04 showed significant activity against all the bacteria. Antifungal activity was performed on *candida*. The compounds CA01, CA02 and CA04 showed moderate activity against the fungus. The compound CA03 was more active among screened compounds.

Conclusion

The reaction profile explained in the present work is very efficient to synthesized substituted pyrimidines. The prepared compounds showed significant and moderate activity of antimicrobial activities and these are promising compounds for further pharmacological studies.

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