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Synthesis, Antimicrobial and Sedative Hypnotic Activity of Cinnamoyl Ureas

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Abstract: The present investigation is concerned with the synthesis of a series of cinnamoyl ureas with the object of discovering novel and potent sedative hypnotic and antimicrobial agent. Substituted cinnamoyl ureas were synthesized from cinnamoyl chloride derivatives by reaction with urea. The structure of all synthesized compounds was elucidated by IR and ^{1}H NMR analysis. The compounds were screened for sedative hypnotic and antimicrobial activity. 1-((E)-3-p-nitrocinnamoyl) urea showed good sedative hypnotic activity at 80mg/kg dose level. 1-((E)-3-(4- chlorophenyl)acryloyl) urea showed good antibacterial activity.

Keywords: cinnamoyl urea, sedative, hypnotic, antimicrobial.

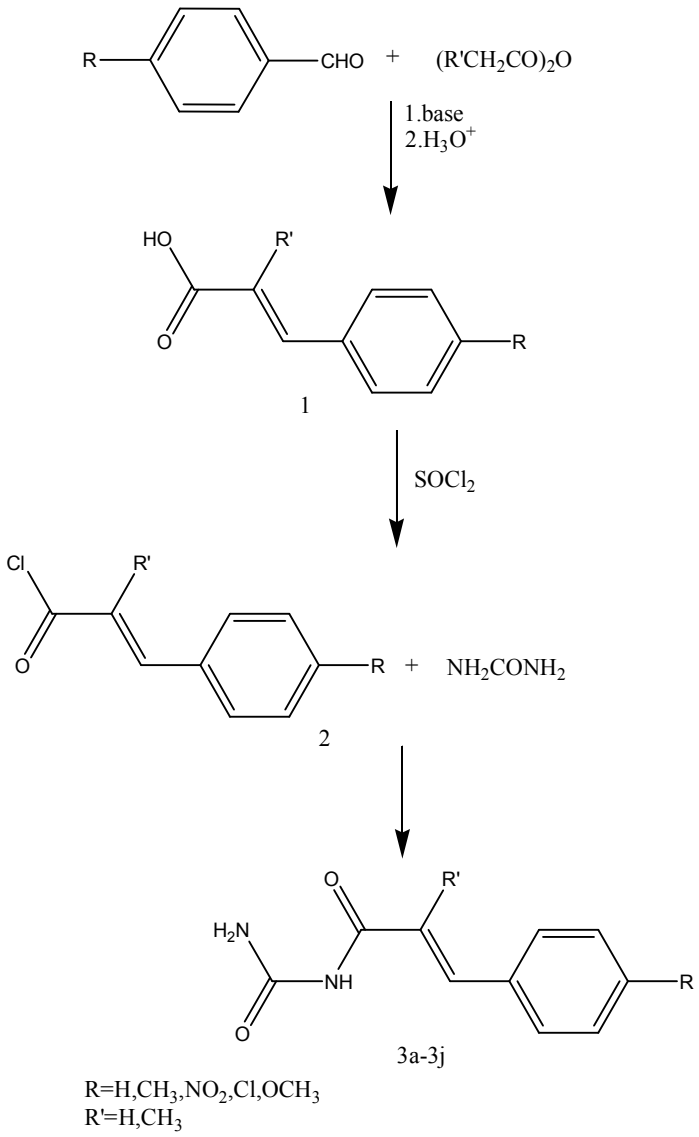
INTRODUCTION:

Cinnamic acid plays an important role in antimicrobial activity[1-3]. Piperine and its derivatives are effective sedative hypnotic and smooth muscle relaxant agents[4, 5]. The Chemical structure of piperine places it in the group of cinnamamides. Antiepilepsirine, one of the derivatives of piperine is used as an antiepileptic drug[6]. Congeners of cinnamamides possess sedative, hypnotic, anticonvulsant, antidepressant and skeletal muscle relaxing activity[7,8]. The amino group of cinromide which is an analogue of cinnamamide with antimicrobial and smooth muscle relaxant action can be replaced by urea giving rise to acyl urea derivatives. On the basis of this, various compounds were synthesized having urea in place of amino group and by substituting benzene ring with different functional groups producing a series of acyl ureas (Scheme 1). These new compounds possess features similar to above mentioned series of compounds and are exhibiting similar pattern of pharmacological activities.

EXPERIMENTAL

All protocols of animal experiments have been approved by the Institutional Animal Ethics Committee (IAEC). Melting points were determined by open capillary method and were uncorrected. The reaction was monitored by TLC using solvent Hexane: Ethyl acetate (2:1). FT-IR spectra was recorded on Shimadzu FT 8300 and ^{1}H NMR were recorded at JEOL GSX400 spectrometer. The chemicals used were obtained from Merck, SD fine and Sigma Aldrich Laboratories and were of the laboratory grade. The physical data of synthesized compounds are given in Table 1.

SCHEME



R=H,CH_3,NO_2,Cl,OCH_3
R'=H,CH_3

Table 1: Physical Properties of synthesized compounds 3a-3j

COMPOUND	MOL.FORMULA	R	R'	R_f VALUE	M.P(°C)	% YIELD
3a	$C_{10}H_{10}N_2O_2$	H	H	0.34	115	40
3b	$C_{10}H_9N_2O_2Cl$	P-Cl	H	0.64	118	44
3c	$C_{11}H_{12}N_2O_2$	P-CH_3	H	0.42	120	49
3d	$C_{11}H_{12}N_2O_3$	P-OCH_3	H	0.36	121	58
3e	$C_{10}H_9N_3O_4$	P-NO_2	H	0.37	122	60
3f	$C_{11}H_{11}N_3O_4$	P-NO_2	CH_3	0.45	133	52
3g	$C_{11}H_{12}N_2O_2$	H	CH_3	0.49	134	60
3h	$C_{11}H_{11}N_2O_2Cl$	P-Cl	CH_3	0.48	136	54
3i	$C_{12}H_{14}N_2O_2$	P-CH_3	CH_3	0.50	140	47
3j	$C_{12}H_{14}N_2O_3$	P-OCH_3	CH_3	0.52	138	59

Synthesis of cinnamic acid derivatives (1):
Substituted aldehyde (0.2 mol), acetic/propionic anhydride (0.29mol) and freshly powdered potassium acetate (0.122mol) were heated in an oil bath at 180ºC for 3hrs. The reaction mixture was then poured into 100 ml of water. Unreacted aldehyde was removed by steam distillation. Residual solution was cooled and filtered at pump from resinous byproducts. Filtrate was acidified to get substituted cinnamic acid.

Synthesis of cinnamoyl chloride derivatives (2):
Substituted cinnamic acid (0.2 mol) and of thionyl chloride (0.84 mol) was stirred for about 4 hrs. Excess of thionyl chloride was removed in vacuum and yellow residue of cinnamoyl chloride derivative was obtained.

Synthesis of cinnamoyl urea derivatives (3):
A mixture of urea (0.1 mol) in 5% alkali was added to cinnamoyl chloride with constant shaking and cooling in water (if necessary).Then mixture was shaken vigorously for 5 -10 minutes until odour of cinnamoyl chloride had disappeared. The solid obtained was collected by filtration and washed with cold water. The product was recrystallised from dilute ethanol and purity of the compound was checked by TLC.

SPECTRAL DATA

1-((E)-3-PHENYLACRYLOYL)UREA (3a): IR (KBr) Vmax cm^{-1} :3406 (N-H Streching), 2975(C-H Aromatic), 1685 (C=O Diketone), 1627 (C=C Aromatic), 1684 (C=O), 1220 (C-N Amines); ^{1}H NMR (DMSO): 10 (s, 1H), 6 (s, 2H), 7.47 (s, 5H), 7.49 (s, 1H), 6.48 (s, 1H)

1-((E)-3-(4- CHLOROPHENYL)ACRYLOYL) UREA (3b): IR (KBr) Vmax cm^{-1}: 3424 (N-H Streching), 2963 (C-H Aromatic), 1694 (C=O Diketone), 1625 (C=C Aromatic), 1694 (C=O), 1225 (C-N Amines); ^{1}H-NMR (DMSO) 10 (s, 1H), 6(s, 2H), 7.47 (m, 4H), 6,57 (d, 1H), 7,67 (m, 1H)

1-((E)-3-p-TOLYACROYL) UREA (3c): IR (KBr) Vmax cm^{-1} : 3424 (N-H Streching), 2963 (C-H Aromatic), 1694 (C=O Diketone), 1625 (C=C Aromatic), 1694 (C=O), 1225 (C-N Amines); ^{1}H NMR (DMSO) 10 (s, 1H), 6 (m, 2H), 7.20 (m, 4H), 6,50 (d, 1H), 7,55 (s, 1H), 2.08 (m, 3H)

1-((E)-3-(METHOXY PHENYLACRYLOYL) UREA (3d): IR (KBr) Vmax cm^{-1}: 3428 (N-H Streching), 2973 (C-H Aromatic), 1681(C=O), 1898 (C=C Aromatic), 1681 (C=O), 1216 (C-N Amines); ^{1}H NMR (DMSO) 10 (s, 1H), 6 (m, 2H), 6.99 (m, 4H), 7,61 (s, 1H), 7.61 (s,1H), 6.97 (m, 3H)

1-((E)-3-(4-NITROPHENYL)ACRYLOYL)UREA (3e); IR (KBr) Vmax cm^{-1}: 3406 (N-H Streching), 2975 (C-H Aromatic), 1604 (C=O), 1694 (C=O Aromatic group), 1220 (C-N Amines); ^{1}H-NMR (DMSO) 10 (m, 1H), 6 (m, 2H), 7.47 (m, 4H), 6.57 (s, 1H), 7.67 (s, 1H)

1-((E)-(P-NITRO CINNAMOYL UREA) (3f): IR (KBr) Vmax cm^{-1}: 3405 (N-H Streching), 2998 (C-H Aromatic), 1664 (C=O), 1600 (C=C Aromatic), 1665 (C=O Urea), 1222 (C=N Aminec group), 932 (C-C Methyl group), 2928 (C-H Methyl group); ^{1}H NMR (DMSO): 10 (s, 1H), 6 (d, 2H), 7.43 (m, 5H), 7.41 (d, 1H), 1.93 (s, 1H)

1-((E)-2-METHYL-3-PHENYLACROYL)UREA (3g): IR (KBr) Vmax cm^{-1}: 3600 (N-H Streching), 2976 (C-H Aromatic), 1684 (C=O Diketone), 1617 (C=C Aromatic), 1665 (C=O Urea group), 1217 (C-N Amines), 931 (C-C Methyl); ^{1}H-NMR (DMSO): 10 (d, 1H), 6 (d, 2H), 7.45 (m, 5H), 7.41 (s, 1H), 2.06 (m, 3H)

1-((E)-3-(4-CHLOROPHENYL)-2-METHYLACROYL) UREA (3h): IR (KBr) Vmax cm^{-1}: 3478 (N-H Streching), 3072 (C-H Aromatic), 1668 (C=O Diketone), 1665 (C=O Urea group), 1360 (C-N Amines), 931 (C-C Methyl); ^{1}H-NMR (DMSO) 10 (m, 1H), 6 (s, 2H), 7.45 (m, 5H), 7.65 (m, 1H), 2.05 (m, 3H)

1-((E)-2-METHYL-3-*P*-TOLYACROYL) UREA (3i): IR (KBr) Vmax cm^{-1}: 3405 (N-H Streching), 2998 (C-H Aromatic), 1664 (C=O Diketone),1665 (C=O Urea group), 1665 (C-N Amines), 932 (C-C Methyl), 2928 (C-H Methyl); ^{1}H NMR (DMSO) 10 (s, 1H), 6 (d, 2H), 7.37 (m, 4H), 7.87 (s, 1H), 2.05 (d, 3H), 2.09 (m,3H)

1-((E)-3-(4-METHOXYPHENYL)-2-METHYLACROYL) UREA (3j): IR (KBr) Vmax cm^{-1}: 1361 (N-H Streching), 2950 (C-H Aromatic), 1677 (C=O Diketone), 1681 (C=O Urea group), 1681 (C=C Aromatic), 1681 (C-N Amines), 915 (C-C Methyl), 2928 (C-H Methyl); ^{1}H NMR (DMSO) 10 (s, 1H), 6 (d, 2H), 7.45 (m, 4H), 7.68 (s, 1H), 2.03 (d, 3H), 2.09 (d, 3H), 3.83 (d, 3H)

BIOLOGICAL EVALUATION

Anti microbial activity

The synthesized compounds 3a- 3j were screened *in vitro* for their antibacterial activity against pathogenic organisms *S. aureus* (209p) and *E. coli* (ESS 2231) using cup- plate method at a concentration of 100µg/ml with DMF as the solvent. After 24h of incubation at 37°C the zones of inhibition formed were

measured in mm with standard drug Fluconazole and are shown in Table 2.

The synthesized compounds were screened for their antifungal activity against *Candida albicans* and *Aspergillus niger* at a concentration of 100µg/ml with incubation for 72 h at 37°C. Standard drug used was Griseofulvin. Similar procedure as for antibacterial activity was followed. The activity data are given in Table 2

Sedative Hypnotic Activity

The synthesized compounds were tested for sedative hypnotic activity by actophotometer apparatus. Healthy male albino mice of approximately same age, weighing about 25-30 gm were used and weer divided in to 3 groups. They were maintained under standard conditions (12 hr light/ 12 hr dark cycle, 25 ± 3^0C, 36-60 % humidity). One group served as positive control (received chlorpromazine 3mg/kg; i.p), one group as negative control (received 5% gum acacia 5 ml/kg) and rest of the groups received test compounds (80 mg/kg orally. The sedative hypnotic activity of mice was observed by recording actophotometer readings after every 30 mins for 120 mins and are shown in Table 3.

Table 2: Antimicrobial activity data of synthesized compounds

Compound	Zone of inhibition (mm)			
	S. aureus	***E. coli***	***A. niger***	***C. albicans***
3a	10	12	7	6
3b	13	14	10	12
3c	6	9	12	11
3d	8	10	9	8
3e	9	8	7	6
3f	10	9	8	7
3g	7	8	13	9
3h	10	8	15	12
3i	11	8	14	11
3j	7	7	9	8
Control	-	-	-	-
Standard	14	16	25	22

Table 3: Effect of Cinnamoyl Ureas on Sedative Hypnotic Activity

Treatment	Dose	30 Mins	60 Mins	90 Mins	120 Mins
Control	5 ml/kg	56.58 ±2.6	55.54 ±2.3	98 ±4.5	59 ±2.98
Chlorpromazine	3 mg/kg	93.83±4.39	93.83±4.39	93.83±1.75	156.6±2.92
3a	80 mg/kg	66.3±2.67*	93.67±4.145*	133±3.9**	78.83±2.62**
3b	80 mg/kg	83.16±6.44**	41.16±2.96*	92±5.56**	146.67±1.94*
3c	80 mg/kg	65.83±2.07**	39.3±1.41*	88.6±2.33*	137.3±1.81**
3d	80 mg/kg	53.5±2.29**	56.67±1.43*	77.67±2.27**	126±2.25**
3e	80 mg/kg	68.3±2.57	69.3±3.67	86.3±2.67	96.3±2.67
3f	80 mg/kg	71± 3.48**	52.3±1.71*	87.67±1.6*	147.5±1.84**
3g	80 mg/kg	69.5±2.68	72.3±2.66	87.3±2.68	98.6±1.68
3h	80 mg/kg	62.3± 2.24**	60.5±0.76*	94.3±1.92*	168±2.61**
3i	80 mg/kg	67.6±1.67	69.2±2.27	89.3±2.53	95.8±2.97
3j	80 mg/kg	64.3±2.34	66.4±2.17	85.3±2.28	98.3±3.82

P<0.001 by Dunnet's't' test (multiple comparison test) compared with control. Values are expressed in mean ± SEM (n = 8)

RESULTS AND CONCLUSION

All the targeted compounds were synthesized in good yield. All synthesized compounds were characterized on the basis of M.P range, R_f value, IR spectra and ^1H NMR spectral analysis. Synthesized compounds have been tested for sedative hypnotic and antimicrobial activities. Amongst all the tested compounds (80 mg/kg) cinnamoyl urea compounds with propionic anhydride as starting material showed better activity than cinnamoyl urea compounds having acetic anhydride as starting material. Compounds 3b and 3f showed greater sedative hypnotic effect and 3b showed greater antibacterial effect. The synthesized compounds exhibited mild to moderate antifungal activity against *A. niger* and *C. albicans* at a concentration of 100µg/ml.

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