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EXPEDIENT PROTOCOL FOR THE SYNTHESIS OF ISOXAZOLE, PYRAZOLE, PYRIMIDINE DERIVATIVES AND THEIR MEDICINAL IMPORTANCE

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Abstract: Exceedingly facile expedient protocol based on the versatility and reactivity of intermediate chalcone **(5)** derived from (E)-2-(4-acetylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one **(4)**, have been developed to provide isoxazole, pyrazole, pyrimidine derivatives by utilizing the synthetic strategy depicted in schemes-**1** and **2**. Condensed derivatives **(6-9)** were screened for their in-vitro antimicrobial potential against various bacterial and fungal species. Besides this pyrazole derivative (**7**) was also evaluated for its CNS depressant potential in mice using photoactometer.

Keywords: Isatoic anhydride, Chalcone, Isoxazole, Pyrazole, pyrimidine derivatives, antimicrobial activity and CNS depressant activity.

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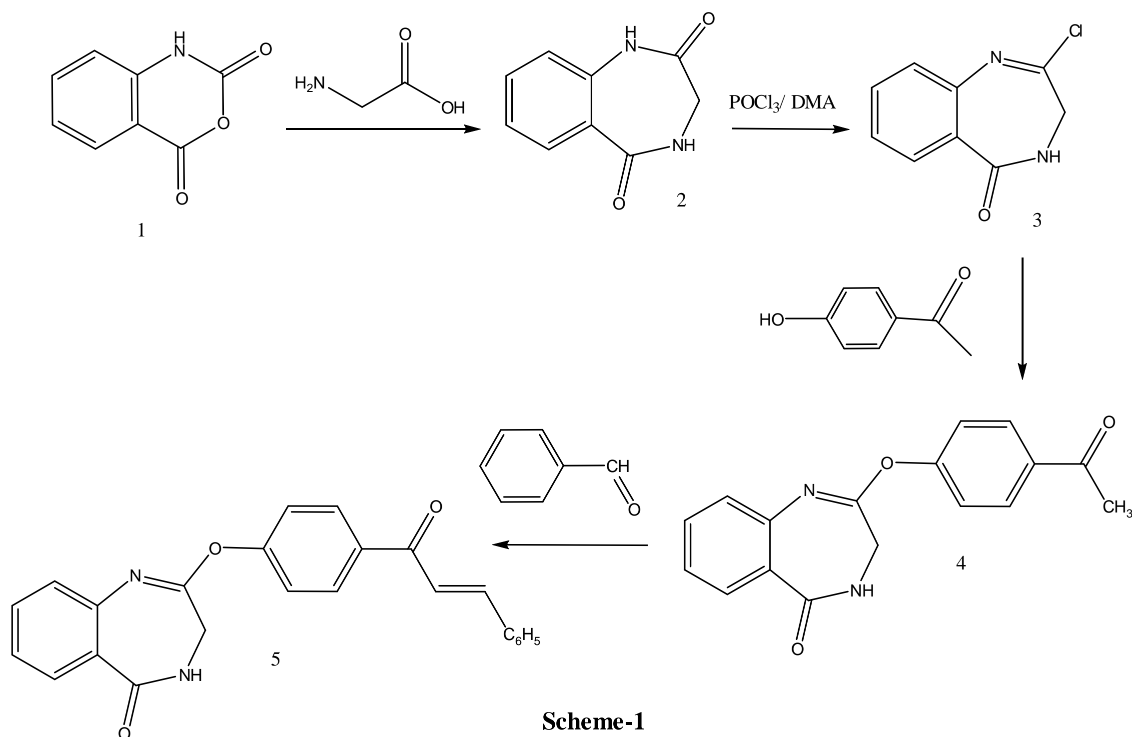
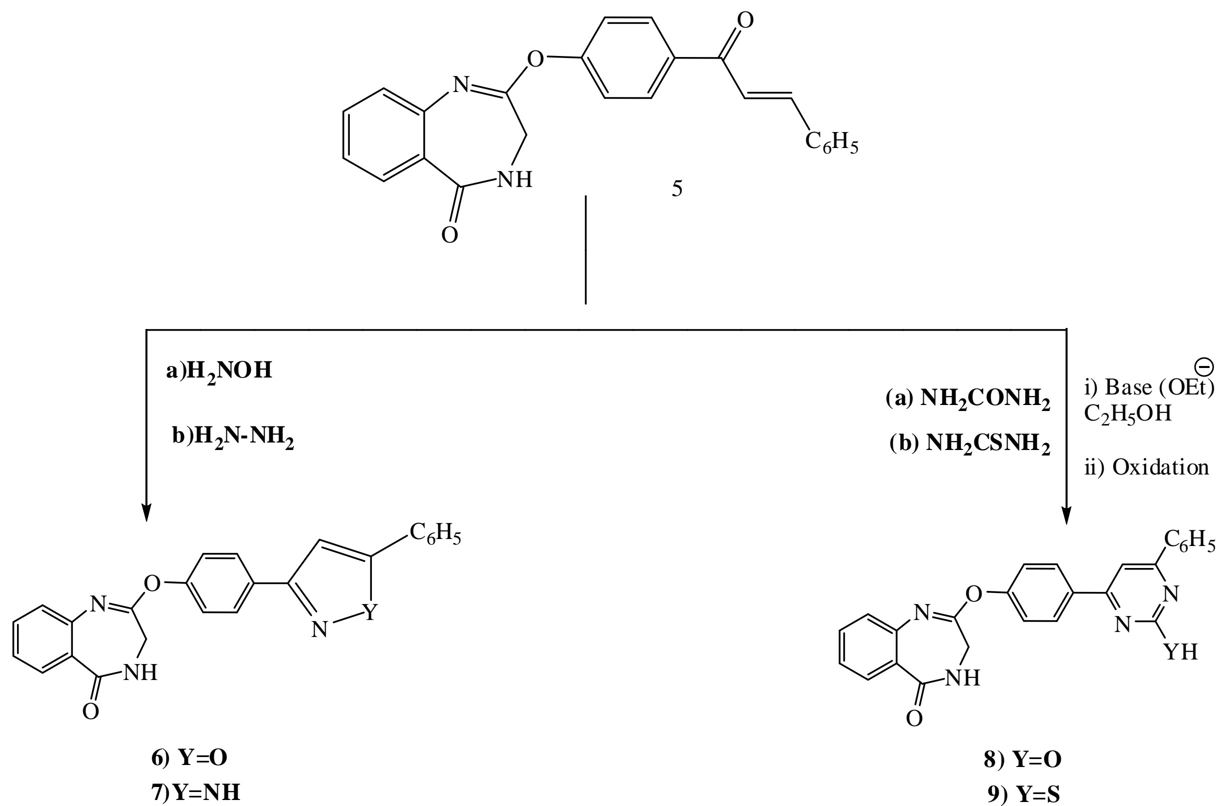
INTRODUCTION

The development of efficient methodologies to facilitate the preparation of compound libraries from molecules having proven record of bio-efficacy is an intense area of research in medicinal chemistry. The development of '**privileged heterocyclic scaffolds**'[1] is a rapidly emerging subject in medicinal chemistry.[2] Benzodiazepines and their analogues have been identified as the heterocyclic scaffolds which belong to this class.[1,3(a-d)] Recently, isoxazole[4], pyrazoles[5] and pyrimidine derivatives have been widely studied as this nucleus, has also been recognized to belong to the class of privileged ligands for a number of functionally and structurally discrete biological receptors.[6(a-d)] A diarylpyrimidine-based NNRTIs the **etravirine** (TMC-125)[7] has emerged as one of the highly active second generation drug, which has found FDA approval for the treatment of HIV infected patients with NNRTI-resistant viruses. Federal Drug administration has allowed its application in the highly active antiretroviral therapy [HAART][8] along with other antiretroviral agents, to adult patients showing multidrug-resistant HIV infections.[9]

Literature has been replete with examples showing that heterocycles which incorporate chalcone, isoxazoles[4], pyrazoles[5] and pyrimidine[10] derivatives etc. in their molecules exhibit wide range of bio-efficacies such as anti-cancer[11], anti-leukemic[12], antiproliferative[13], anticonvulsant[14], antiviral[15] and antimicrobial[16] etc. In view of exploring, their impressive biological activities further, we reasoned that it could be worthwhile to develop libraries of materials which contained chalcone moiety and bioactive pharmacophores such as the isoxazole, pyrazole and pyrimidine, on the premise, that their presence in tandem in the same molecular framework could contribute significantly to produce interesting series of compounds with enhanced biological potency. To examine the validity of this hypothesis, we required to develop versatile synthetic protocols which allowed an easy access of **6, 7, 8 and 9 from 5 (Scheme 2).**



Scheme-1



Scheme-2

Experimental Section

Melting points were determined on an open capillary and are uncorrected. The IR sprectra were recorded on Schimadzu FTIR-8400S. ^{1}H-NMR spectra were recorded in $CDCl_3$ on Bruker DRX-400 MHz spectrometer using TMS as internal reference and values are expressesd in δ ppm. Mass spectra were taken on a Joel SX-102 (EI/CI/FAB) mass spectrometer at 70 eV. Purity of all the synthesized compounds were routinely checked by TLC on silica gel G in the solvent system (9:1, benzene:methanol).

Preparation of (E)-2-chloro-3H-benzo[e][1,4]diazepin-5(4H)-one (3)

A solution of **2** (0.05 mol), N, N-dimethylaniline (0.02 mol), $POCl_3$ (0.05 mol) and benzene (100 ml) was refluxed for 7 h. and then allowed to cool overnight. The reaction mixture was washed with ether and then with petroleum ether to remove the soluble impurities. Cold water was then added to the reaction mixture and brought to the neutral point by addition of $NaHCO_3$ solution. It was then extracted three times with dichloromethane to give **3** (yield: 72%); m.p: 130-132 °C; IR (KBr) cm^{-1} : 3015 [C-H str. ArH], 1720 [C=O str.], 1570 [C=C str. ArH], 1520 [C=N str.], 1090 [C-N str.], 670 [C-Cl str.]; ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 3.4 [s, 2H, CH_2], 1.54-1.71 [m, 4H, pyrrolidine]; MS: m/z: 195 (M+,10%) ; Anal. Calcd. /found for $C_9H_7ClN_2O$: C, 55.54/ 55.49; H, 3.63/ 3.59; Cl, 18.22/ 18.17; N, 14.39/ 14.45

Preparation of (E)-2-(4-acetylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (4)

A mixture of **3** (0.001 mol) and p-hydroxyacetophenone (0.0012 mol) in DMF (3 ml) in the presence of anhydrous potassium carbonate (0.002 mol) was irradiated under microwave, at 190°C for 15 min. The mixture was poured into ice-water, and the pH adjusted to 7 by adding 5% HCl and the mixture extracted with three times with EtOAc. On removal of the solvent in vacuo, the obtained crude product **4** was purified by PTLC or a silica column (eluent: petroleum ether/EtOAc) (yield: 61%); m.p: 178-180°C; IR (KBr) cm^{-1} : 3020 [C-H str. ArH], 1680 [C=O str.], 1555 [C=C str. ArH], 1525 [C=N str.], 1090 [C-N str.], 1110 [C-O str.]; ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 7.06- 7.77 [m, 4H, phenoxy], 3.4 [s, 2H, CH_2], 2.60 [s, 3H, CH_3]; MS: m/z: 295 (M+, 26.0%) ; Anal. Calcd./found for $C_{17}H_{14}N_2O_3$: C, 69.38/ 69.29; H, 4.79/ 4.75; N, 9.52/ 9.45

Preparation of (E)-2-(4-cinnamoylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (5)

A mixture of **4** (0.01 mol), benzaldehyde (0.01 mol) and fused sodium acetate (0.015 mol) in glacial acetic acid was refluxed for 5 h. The reaction mixture was cooled and poured into water. The resulting solid was filtered, washed with water and recrystallized from aq. ethanol to furnish **5** (yield: 65%) ; m.p: 212-214 °C; IR (KBr) cm^{-1} : 3040[C-H str.], 2910 [C-H str. ArH], 1740

[C=O str.], 1670 [C=C str.], 1590 [C=C str. ArH], 1500 [C=N str.], 1210 [C-N str.], 1050 [C-O str.]; ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 [s, 1H, NH], 8.05 [d, 1H, CH], 7.63-8.13 [m , 4H, ArH], 7.59 [d, 1H, CH], 7.33-7.60 [m, 5H, ArH], 7.14-8.05 [m, 4H, phenoxy], 3.5 [s, 2H, CH_2]; MS: m/z: 383 (M+, 29.3%) ; Anal. Calcd./found for $C_{24}H_{18}N_2O_3$: C, 75.38/ 75.32; H, 4.74/ 4.70; N, 7.33/ 7.28

Preparation of (E)-2-(4-(5-phenylisoxazol-3-yl)phenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (6)

To hydroxylamine hydrochloride (0.04mole) was added sodium methoxide (0.06mole) in absolute methanol (30ml) and stirred for 10 minutes. To this solution, (E)-2-(4-cinnamoylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one **(5)** (0.004mole) was added and the mixture was refluxed for 5 hours. Most of the methanol was evaporated under reduced pressure and the remaining mixture was poured into ice cold water. The solid separated was filtered, washed with diethylether, dried and recrystallized from ethanol to give the analytically pure product **6** (yield 63%), m.p. 80-82°C IR (KBr) cm^{-1} : 3040[C-H str.], 2930 [C-H str. ArH], 1700 [C=O str.], 1630 [C=C str.], 1620 [C=C str. ArH], 1550 [C=N str.], 1240 [C-N str.], 1070 [C-O str.]; ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 [s, 1H, NH], 8.05 [d, 1H, CH], 7.63-8.13 [m , 4H, ArH], 7.59 [d, 1H, CH], 7.33-7.60 [m, 5H, ArH], 7.14-8.05 [m, 4H, phenoxy], 6.3 [s, 1H, CH], 3.5 [s, 2H, CH_2]; MS: m/z: 398(M+, 23%) ; Anal. Calcd./found for $C_{24}H_{17}N_3O_3$; C, 72.53/ 72.48; H, 4.82/ 4.76; N, 10.57/ 10.52

Preparation of (E)-2-(4-(5-phenyl-1H-pyrazol-3-yl)phenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (7)

(E)-2-(4-cinnamoylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one **(5)** (0.01mole) and hydrazine hydrate (0.3mole) was heated under reflux for 8-12 hrs, in 25ml absolute ethanol then cooled and the residual material was filtered off and recrystallized from DMF/water to give **7** (yield 68%), m.p. 70-72°C. IR (KBr) cm^{-1} : 3030[C-H str.], 2900 [C-H str. ArH], 1710 [C=O str.], 1680 [C=C str.], 1640 [C=C str. ArH], 1520 [C=N str.], 1240 [C-N str.], 1070 [C-O str.]; ^{1}H-NMR (400MHz, CDCl3) δ ppm: 13.7 [s, 1H, NH], 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 7.59 [d, 1H, CH], 7.33-7.60 [m, 5H, ArH], 6.81-7.48 [m, 4H, phenoxy], 3.2 [s, 2H, CH_2]; MS: m/z: 397(M+, 18%); Anal. Calcd./found for $C_{24}H_{18}N_4O_2$; C, 72.71/ 72.70; H, 5.08/ 5.14; N, 14.13/ 14.19

Preparation of (E)-2-(4-(2-hydroxy-6-phenylpyrimidin-4-yl)phenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (8)

To a mixture of urea (0.02mol), sodium ethoxide (0.002 mol) and ethanol (25-30 ml) was added **5** (0.002 mol) and the reaction mixture was refluxed for 14 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (4-5 ml) just enough to dissolved sodium salt of the pyrimidine and refluxed for 15 min. The reaction mixture was poured on crushed ice

and the residue obtained was purified by crystallization with chloroform to give **8** (yield: 88%); m.p: 188-190°C; IR (KBr)cm^{-1} : 3560 [OH str.], 2970 [C-H str. ArH], 1680 [C=O str.], 1570 [C=C str. ArH], 1520 [C=N str.], 1155 [C-O str.] ,1260 [C-N str.]; ^{1}H-NMR (400MHz, CDCl3) δ ppm: 11.88 [s, 1H, OH], 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 7.43 [s, 1H, pyrimidine], 7.41-7.79 [m , 5H, ArH], 6.81-7.49 [m, 4H, phenoxy], 3.2 [s, 2H, CH_2]; MS: m/z: 425 (M+, 21%) ; Anal. Calcd./found for $C_{25}H_{18}N_4O_3$:C, 70.74/ 70.70; H, 4.75/ 4.68; N, 13.20/ 13.15

Preparation of (E)-2-(4-(2-mercapto-6-phenylpyrimidin-4-yl) phenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one (9)

To a mixture of thiourea (0.02 mol), sodium ethoxide (0.002 mol) and ethanol (25-30ml), **5** (0.002 mol) was added and the reaction mixture was refluxed for 12-13 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (4-5 ml) (just enough to dissolved sodium salt of the pyrimidine) and refluxed for 15 minutes. The reaction mixture was poured on crushed ice and the residue obtained was purified by crystallization with chloroform to give **9** (yield: 88%); m.p : 190-192°C; IR (KBr) cm^{-1} : 3020 [C-H str. ArH], 2180 [SH str.], 1725 [C=O str.], 1645 [C=C str. ArH], 1585 [C=N str.], 1160 [C-N str.], 1135 [C-O str.], 670 [C-S str.] ; ^{1}H-NMR (400MHz, CDCl3) δ ppm: 12.18 [s, 1H, SH], 8.0 [s, 1H, NH], 7.63-8.13 [m , 4H, ArH], 7.75 [s, 1H, pyrimidine], 7.41-7.79 [m , 5H, ArH], 6.85-7.69 [m, 4H, phenoxy], 3.2 [s, 2H, CH_2]; MS: m/z: 441 (M+, 22%) ; Anal. Calcd./found for $C_{25}H_{18}N_4O_2S$: C, 68.16/68.20; H, 4.58/ 4.52; N, 12.72/ 12.79;S, 7.28/ 7.20

Antimicrobial activity

Novel isoxazolo, pyrazolo and pyrimidine derivatives **(6-9)** were screened for their in-vitro antimicrobial activities against bacterial species (E.coli, B.substilis and P. aeruginosa) and fungal species (M. Phaseolina, F. oxysporum and A. flavus) by disc-diffusion method against the standard drugs (ciprofloxacin for bacteria and fluconazol for fungi). In antimicrobial study, the stock solutions of standard and test compounds were prepared in $CHCl_3$ and subsequent dilutions were made with the same solvent. The antibacterial activity of **6-9** was evaluated against three pathogenic strains (E.coli. B.subtilis and P. aeruginosa). The zone of inhibition and activity index were determined by comparison with the standard drug ciprofloxacin. The outcome of this study is presented in **Table 1**. The antibacterial screening against E.coli showed that amongst the compounds **6-9**, the compound **7** displayed highest activity. The compound **9** showed minimum activity amongst all the compound. The remaining compounds 6 and 8 showed only moderate activity. Contrary to this observation, compound **6** showed highest activity and compound **8** showed minimum activity amongst all the compounds screened for this activity, against B.subtilis. As well as compound **6** showed highest activity and

compound **7** showed minimum activity amongst all the compounds screened for this activity, against P. aeruginosa. The antifungal activity was evaluated against three pathogenic strains (M.phaseolina, F.oxysporum and A. flavus). The zone of inhibition and activity index were determined by comparison with the standard drug fluconazol. The outcome of this study is presented in **Table 1**. The antifungal screening against M.phaseolina showed that amongst the compounds 6-9, the compound **9** exhibited highest activity. The compound **8** showed minimum activity amongst all the compounds. The remaining compounds **6** and **7** showed only moderate activity. Contrary to this observation, compound **8** showed highest activity and compound **7** showed minimum activity amongst all the compounds screened for this activity, against F.oxysporum. . As well as, compound **6** showed highest activity and compound **9** showed minimum activity amongst all the compounds screened for this activity, against A. flavus.

Table-1 Antimicrobial activity of compounds 6-9

Comp. no.	Conc. (µg/ml)	E.coli		B.subtilis		P. aeruginosa		M. phaseolina		F. oxysporum		A. flavus	
		A	B	A	B	A	B	A	B	A	B	A	B
6	400	20±0.5	71.42	27±0.4	90.00	20±0.3	76.92	19±0.7	73.07	18±0.7	62.06	24±0.3	88.88
	200	14±0.7	63.64	18±0.7	78.26	13.5±0.6	67.5	13±0.3	65.00	13±0.5	56.52	18±0.6	75
	100	9±0.3	56.25	11.5±0.6	67.64	9±0.2	60	8.5±0.8	56.67	9±0.3	50.00	12±0.7	63.15
7	400	25±0.4	89.28	25±0.4	83.33	16±0.6	61.53	16.5±0.8	63.46	16±0.5	55.17	19±0.4	70.37
	200	17±0.8	77.27	17±0.7	73.91	11±0.8	55	11.5±0.7	57.50	11±0.6	47.82	13.5±0.6	56.25
	100	11.5±0.6	71.80	11±0.2	64.70	7±0.4	46.67	7.5±0.3	50.00	8±0.2	44.44	9±0.3	47.36
8	400	21±0.2	75.00	20±0.9	66.67	19±0.3	73.07	13.5±0.5	51.92	23±0.4	79.31	21±0.5	77.77
	200	15±0.9	68.18	13±0.3	56.52	13.5±0.7	67.5	9.5±0.7	47.50	16±0.8	69.56	16±0.6	66.66
	100	9±0.5	56.25	9±0.5	52.94	10±0.6	66.66	6.5±0.8	43.33	11±0.3	61.11	9±0.8	47.36
9	400	16±0.3	57.14	22±0.9	73.33	17±0.6	65.38	21±0.6	80.76	20±0.3	68.96	18±0.8	66.66
	200	12±0.5	54.55	15±0.6	62.21	12±0.3	60	14±0.7	70.00	13±0.4	56.52	13.5±0.2	56.25
	100	8±0.8	50.00	9±0.5	52.94	10±0.8	66.66	9.5±0.3	63.33	9.5±0.8	52.78	13±0.5	68.42
Ciprof	400	28±0.2	100	30±0.1	100	26±0.3	100						
loxacin	200	22±0.3	100	23±0.2	100	20±0.1	100	--	--	--	--		
	100	16±0.2	100	17±0.1	100	15±0.3	100						
Flucon	400							26±0.1	100	29±0.2	100	27±0.3	100
azole	200	--	--	--	--			20±0.2	100	23±0.1	100	24±0.2	100
	100							15±0.2	100	18±0.3	100	19±0.3	100

A= Zone of inhibition (mm)

B= % activity compared to the standard

Values are mean inhibition zone (mm) ± S.D of three replicates

Minimum inhibitory concentration (MIC)

The estimation of MIC of the crude extracts was carried out using the method of Akinpelu and Kolawole (2004). Twofold dilutions of the crude extract was prepared and 2 ml aliquots of different

concentrations of the solution were added to 18 ml of pre-sterilized molten nutrient agar and SDA for bacteria and fungi respectively at 40°C to give final concentration regimes of 0.050 and 10 mg/ml. The medium was then poured into sterile Petri dishes and allowed to set. The surface of the medium was allowed to dry under laminar flow before streaking with 18 h old bacterial and fungal cultures. The plates were later incubated at 37°C for 24 h and at 25°C for up to 72 h for bacteria and fungi respectively, after which they were examined for the presence or absence of growth. The MIC was taken as the lowest concentration that prevented the growth of the test microorganism Evaluation.

Table 2. Comparative MIC µg/mL values of synthesized compound against bacterial and fungal species using in vitro studies

Compound	6	7	8	9	Ciprofloxacin	Flucanazole
E.coli	0.6	0.2	0.4	0.7	0.05	-
B.subtilis	1.0	1.2	1.4	1.3	0.02	-
P. aeruginosa	0.4	0.6	0.5	0.4	0.06	-
M. phaseolina	0.6	0.8	1.0	0.8	-	0.07
F. oxysporum	1.2	1.4	1.0	1.1	-	0.03
A. flavus	0.6	0.9	0.8	1.2	-	0.04

Evaluation of CNS depressant activity in mice

1. Acute toxicity studies for lethal dose determination (LD_{50}):

Wistar rats weighing 200–250 g (3 nos) were use in the procedure. Acute oral toxicity was performed as OECD-423 guidelines[17]. The animals were fasted overnight, provided only water, after which synthesized compounds was administered to the animals orally at the dose of 5 mg/kg body weight by gastric intubation and the animals were observed for 24 h. If mortality was observed in two or three animals, then the dose administered was assigned as a toxic dose. If mortality was observed in one animal, then the same dose was repeated again to confirm the toxic dose. If mortality was not observed, the procedure was repeated for further higher doses such as 50, 300 and 2,000 mg/kg body weight. The animals were observed for toxic symptoms such as behavioral changes, locomotion, convulsions and mortality for further 72 h.

2. Locomotor Activity

Adult Albino Mice of either sex were randomly divided into five groups of five mice each. First group served as a control received normal saline, i.p., second group served as positive control received chlorpromazine 5 mg/kg, i.p. while the third group received a compound **7** at a dose of 50 mg/kg. Group fourth and fifth was given 100 mg/kg and 200 mg/kg of compound 8 respectively. The locomotor activity was studied after 30 min, 60 min and 120 min of administration of the test and standard compound with digital actophotometer. It operated on photoelectric cells connected with a counter. A count was recorded when the beam of light falling on the photocell of the actophotometer was cut off by animal. The percentage inhibition of locomotor activity was calculated by using the following formula.

$$\text{Percentage Inhibition (\%)} = \frac{Vc - Vt \times 100}{Vc}$$

Where, Vc= control reading

Vt= test reading

The effect of compound **7** on spontaneous locomotor activity is summarized in **Table 3**. It indicated that the locomotor activity count in compound **7** treated group was significantly reduced when compared to normal saline control group. The reduction in locomotor activity was found to be dose dependent. The normal reading of group I at 30 min, 60 min and 120 min was 394.5±16.69, 381.24±11.4 and 389.56±6.23. In group V (treated with compound 8, at a dose of 200 mg/kg), resulted in a remarkable reduction in the locomotor activity of mice to 03.33±20.52, 72.52± 9.95 and 53.66±8.08. After 120 min, the reduction in locomotor activity in group III, IV, V was found to be 61.60, 72.18 and 86.40% compared to normal. The 200 mg/kg dose of test compound **7** was found to be more potent than 5 mg/kg chlorpromazine, as it showed more reduction in locomotor activity as compared to standard. Compound **7** showed more marked inhibition in locomotor activity in mice (86.4%) than standard (83.4%).

Table-3 Evaluation of CNS depressant activity of compound 7

Group	Treatment	Photo cell count			Percentage Inhibition
		30 min	60 min	120min	
I	Cntrl-Normal Saline	392.5±16.69	387.24±11.43	394.56±6.23	Nil
II	Chlorpromazine (5mg/kg i.p.)	80.66±15.36 [a]	60.8±9.21 [a]	64.33±4.29 [a]	83.48
III	Comp. 7 (50mg/kg i.p.)	149.16±12.66 [a, b]	130.16±3.89 [a, b]	151.5±6.42 [a, b]	61.60
IV	Comp. 7 (100mg/kg i.p.)	127.14±18.84 [a, b]	114.15±7.53 [a, b]	109.76±6.88 [a, b]	72.18
V	Comp. 7 (200mg/kg i.p.)	103.33±20.52 [a, c, d]	72.52±9.95 [a, c, d]	53.66±8.08 [a, c, d]	86.40

a –Significant variation observed as compared to group I ($P < 0.05$)

b- Significant variation observed as compared to Chlorpromazine treated group ($P < 0.05$)

c- Significant variation observed as compared to 50 mg/kg treated group ($P < 0.05$)

d- Significant variation observed as compared to 100 mg/kg treated group ($P < 0.05$)

Results and Discussion

Ubiquity of isoxazole, pyrazole and pyrimidine derivatives in chemical literature is undoubtedly a consequence of multifarious biological response which they elicit in combating a variety of body ailments. Recent demonstrations that some of their derivatives can serve as potential agents in the treatment of cancer[11], leukemia[12] and microbial-infection[16] has stimulated further interest in these molecules from yet another perspective. As a part of an ongoing endeavour to create novel heterocyclic scaffolds of anticipated biological activity from easily accessible starting materials, we report herein, the

preliminary results of our studies on the synthesis of isoxazole, pyrazole and pyrimidine derivatives **6-9** from (E)-2-(4-cinnamoylphenoxy)-3H-benzo[e][1,4]diazepin-5(4H)-one **(5)**. A perusal of literature on the potential of α, β-unsaturated ketones (chalcones) in synthesis demonstrated that it was readily formed from the base catalyzed condensation of carbonyl species containing an active methylene group with C_6H_5CHO. All the synthesized compounds gave satisfactory results for elemental analysis. IR and ^{1}H-NMR spectral data were found to be consistent to the assigned structures.

Conclusion

In summary, elegant protocol has been developed to provide an easy access of the biologically active novel isoxazol, pyrazol and pyrimidine derivatives **(6-9)** from the α, β-unsaturated ketones **5** in high yield and purity.

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