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SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF SUBSTITUTED 1,5-BENZODIAZEPINE DERIVATIVES FOR ITS ANTIDEPRESSANT ACTIVITY IN EXPERIMENTAL ANIMALS

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ABSTRACT

The reaction of OPD with acetoacetic acid in presence of heat gives substituted benzimidazoles, which on treatment with substituted aromatic aldehydes undergoes claisen-schmidt condensation to offer chalcones, which on further treatment with OPD gives substituted benzodiazepines (A_1-A_5) as a result of Michael addition reaction. The purity of the synthesized compounds was checked by TLC and the structure of the synthesized compounds was established using IR, 1H-NMR and elemental analysis. The purified compounds were then screened for their anti-depressant activity using forced swim test model on mice.

KEYWORDS: Anti-depressant, forced swim test, 1,5-BZD, synthesis, chalcones, Michael addition.

1.0 INTRODUCTION

Benzodiazepines and their derivatives are an important class of medicinally active compounds having profound biological activities and reported in variety of literature. The specific type of benzodiazepines that is 1,5-benzodiazepines have gain much more attention because of their potential structural diversity as a privileged scaffolds in arrays of compounds bioactive towards several major drug target families which include

cholecystokinin receptors[1], interlukin converting enzymes[2] and ion channels.[3] Benzodiazepine derivatives have attracted the attention of researchers owing to their interesting pharmacological activities and their low toxicitiy. They are widely used as anti-anxiety[4], analgesic[5], anti-inflammatory[6], DNA binding activity[7], anti-cancer[8], anti-tumor[9], adenosine binding activity[10], antisialogogic[11], cutaneous anaphylaxis[12], antimicrobial[13], anthelmintic[14], anti-neuroinflammatory[15], antiparkinson[16], antileishmanial[17], muscle relexant[18], anticonvulsant[19], anti-HIV[20] and sedative and hypnotic.[21] However, 1, 5-benzodiazepines are important scaffold used for the synthesis of various fused ring compounds such as triazolo-, oxadiazolo-, oxazino-, or furano-benzodiazepines.[22]

2.0 MATERIALS AND METHODS

Melting points of all the synthesized compounds were determined by open capillary tubes using paraffin bath and are uncorrected. ^{1}H NMR spectra were recorded on a Varian-NMR-mercury 300 MHz spectrophotometer in $CDCl_3$ using TMS as an internal standard.

3.0 EXPERIMENTAL

Synthesis of Benzimidazole

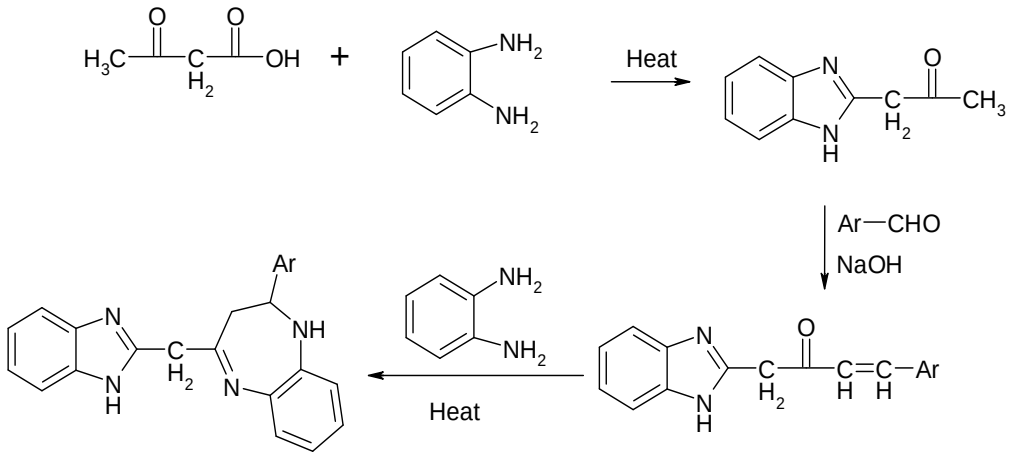
0.01 mole of acetoacetic acid and 0.01 mole of OPD were refluxed for 60 minutes in presence of ethanol cool to room temperature and precipitate formed is filtered to offer benzimidazoles.

Synthesis of Chalcone (I-V)[23]

0.01 mole of Benzimidazoles was stirred on magnetic stirrer with 0.01 mole of substituted aldehydes in presence of 10% potassium hydroxide for 30 minutes and the precipitate will be filtered and purified from hot ethanol by recrystallization.

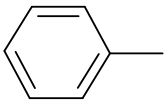
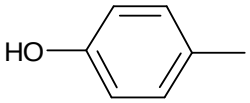
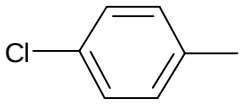
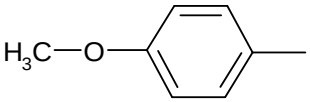
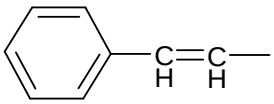
Synthesis of Benzodiazepine (A_1-A_5)

0.01 mole of chalcones are refluxed in presence of 0.01 mole of OPD then cooled to room temperature and precipitate was filtered and purified by recrystallization from hot ethanol to offer title compounds (A_1-A_5).[24]



Scheme.

Table no. 01: Physicochemical data of synthesized compounds (A_1-A_5).

C.C	Ar	Molecular formula	Molecular weight	Melting point (^{0}C)	Yield (%)	Elemental analysis Found (cald.)		
						C	H	N
A_1		$C_{23}H_{20}N_4$	352.44	128-120	70.25	78.38	5.72	15.90
A_2		$C_{23}H_{20}N_4O$	368.44	120-122	74.33	74.98	5.47	15.21
A_3		$C_{23}H_{19}ClN_4$	386.89	228-230	82.85	71.40	4.95	14.48
A_4		$C_{24}H_{22}N_4O$	382.47	180-182	78.71	75.37	5.80	14.65
A_5		$C_{25}H_{22}N_4$	378.48	158-160	90.23	79.34	5.86	14.80

4.0 SPECTRAL DATA

A_1: IR (KBr): 3420.34 (-NH str.); 3008.79 (Ar-CH str.); 2810.45 (-CH_2 str.). **^{1}H NMR: δ:** 6.67-7.10 13H of phenyl, 5.0 2H of -NH;3.25-3.40 3H of benzodiazepine, 1.4-1.6 2H of –CH_2.

A_2: IR (KBr): 3420.34 (-NH str.); 3220.43 (-OH str.); 3008.79 (Ar-CH str.); 2810.45 (-CH_2 str.). **^{1}H NMR: δ:** 6.67-7.10 12H of phenyl, 5.0 2H of -NH; 4.0 1H of –OH;3.25-3.40 3H of benzodiazepine, 1.4-1.6 2H of –CH_2.

A_3: IR (KBr): 3420.34 (-NH str.); 3008.79 (Ar-CH str.); 2810.45 (-CH_2 str.); 687.92 (-C-Cl str.). **^{1}H NMR: δ:** 6.67-7.10 12H of phenyl, 5.0 2H of -NH; 3.25-3.40 3H of benzodiazepine, 1.4-1.6 2H of –CH_2.

A_4: IR (KBr): 3420.34 (-NH str.); 3008.79 (Ar-CH str.); 2810.45 (-CH_2 str.) 1005.45 (-C-O-C str.). **^{1}H NMR: δ:** 6.67-7.10 12H of phenyl, 5.0 2H of -NH; 3.25-3.40 3H of benzodiazepine, 1.4-1.6 2H of –CH_2; 0.8-1.2 3H of –CH_3.

A_5: IR (KBr): 3420.34 (-NH str.); 3310.39 (-CH=CH str.); 3008.79 (Ar-CH str.); 2810.45 (-CH_2 str.). **^{1}H NMR: δ:** 6.67-7.10 12H of phenyl, 6.0-6.2 2H of –CH=CH; 5.0 2H of -NH; 3.25-3.40 3H of benzodiazepine, 1.4-1.6 2H of –CH_2.

5.0 EVALUATION OF ANTIDEPRESSANT ACTIVITY

The synthesized compounds A_1-A_5 were evaluated for antidepressant activity by forced swim test (FST) in mice at dose of 100 mg/kg and compared with the standard drugs Desipramine (20mg/kg). There were no mortality and noticeable behavioral changes in acute oral toxicity for all the groups tested. The synthesized compounds were found to be safe up to 1500 mg/kg body weight. Initially, dose-dependent study of compound A1 at different doses (25, 50, 100, and 200mg/kg, i.p.) were performed to ensure the maximum effective dose for new synthesized compounds as antidepressant in FST. From this study, we found that 100 mg/kg is the maximum effective dose and therefore was selected for further pilot study of antidepressant-like effects of compounds A_2-A_5 in FST. Antidepressant activity was assessed as mean immobility time in seconds, and data has been presented as mean ± S.E.M as shown in (Table 2).[25,27]

Table no. 2: Anti-depressant activity of synthesized compounds.

Sr.no.	Compound code	Duration of immobility Sec. (mean ± SEM)	% decrease in immobility	Locomotor activity scores for 10 minutes (sec.) (mean ± SEM)
1	A1	33.6 ± 4.1***	68.3	423 ± 14.0^{ns}
2	A2	49.7 ± 2.6***	39.76	434 ± 9.0^{ns}
3	A3	16.4 ± 3.1***	69.45	421 ± 16.0^{ns}
4	A4	10.89 ± 0.7***	86.45	425 ± 14.0^{ns}
5	A5	26.78 ± 1.6***	71.57	445 ±14.0^{ns}
6	Control	90.6±3.2	0.0	508±12
7	Desipramine	21.6±1.5	79.27	470±19

Data analysed by one-way ANOVA followed by Dunnett's test. n = 5; dose = 100 mg/kg. Values are represented as mean ± S.E.M. Values are significant at ***P < 0.001, compared with control group. ns: not significant (P < 0.05) as compared to vehicle-treated group.

6.0 RESULT AND DISCUSSION

The synthesized compounds have been purified by column chromatography technique. The purified compounds are then screened for their anti-depressant activity using forced swim test model on mice. The synthesized compounds show significant anti-depressant activity. Out five synthesized derivative of 1,5 benzodiazepine series the compound A3, A4 and A5 shows significant anti-depressant activity. The compounds were synthesized by using Michael addition reaction the structural features included like 1,5-benzodiazepine ring, electron donating substituents are responsible for showing activity.

7.0 CONCLUSION

The 1,5-Benzodiazepine derivatives was synthesized by Michael addition reaction using chalcones and OPD. The synthesized compounds were tested for their anti-depressant activity using Forced Swim Test model and Desipramine as a standard drug. The compounds on further toxicity studies can be explored as a lead for the future development of Benzodiazepines as a potential anti-depressant drugs. The Benzodiazepine nucleus is responsible to show anti-depressant activity.

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