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‘SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF BENZIMIDAZOLE WITH ISOINDOLINE DERIVATIVES BY LEUCKART REACTION”

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ABSTRACT:

Some new benzimidazoles with iso indoline (JV1-JV5) have been synthesized by Leuckart reaction using microwave irradiation. Synthesis of1,4 aryl 1H benzimidazole-2yl alkyl-1H isoindol-1,3-dione compounds by using different aldehydes. The structures of newly synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H NMR, and MASS spectroscopy. The in vitro Anthelmintic activity of the synthesized compounds was studied by using Eudrilluseuginae earth worms. Albendazole was used as standard drug.

KEYWORDS:

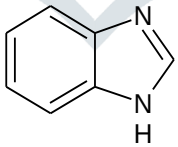
Benzimidazole with isoindoline derivatives, leuckart reaction, microwave irradiation, Anthelmintic activity

INTRODUCTION

Medicinal chemistry of drug synthesis involves, structure modification for optimization of their activity and other physical properties and total and semi synthesis for a thorough scrutiny of structure activity relationship. The techniques of molecular graphics and computational chemistry have provided novel chemical structure that have led to new drugs with potent medicinal activates.

BENZIMIDAZOLE

The heterocyclic compound Benzimidazole derivatives are formed by the fusion of benzene and imidazole ring.

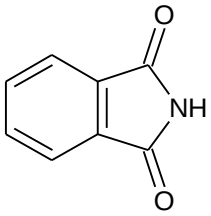


The imidazole core is a common moiety in a large number of natural products and pharmacologically active compounds.

On the basis of various literature surveys Benzimidazole derivatives shows various pharmacological activities like antifungal, antibacterial activity, anti-inflammatory activity, anti -tubercular activity, antidepressant activity, anticancer activity, antiviral activity. Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, they are remarkably effective compounds with respect to their inhibitory activity as well as their selectivity.(13)

Benzimidazole as ‘‘lead’’ molecule, binds with other heterocyclic act by intercalation or block cell growth by inhibit the enzymes directly responsible for the formation of nucleic acids. This inhibition is believed to prevent DNA transcription, which ultimately leads to cell death, which explains the use of these drugs to treat cancer.(11)

ISOINDOLINE



The literature survey shows that indoline and isoindoline derivatives which have a wide range of biological activities such as antimicrobial, antibacterial, anti-inflammatory, antihistamine, antioxidant, antiproliferative, acetylcholinesterase inhibitors, inhibitor of human neuronal nitric oxide synthase.Out of the above mentioned heterocyclics, indole and benzimidazole derivatives comprise the ring system in a number of many drugs to name a few omeprazole, albendazole, indomethazine, indoprofen, etc(16)

MECHANISM:

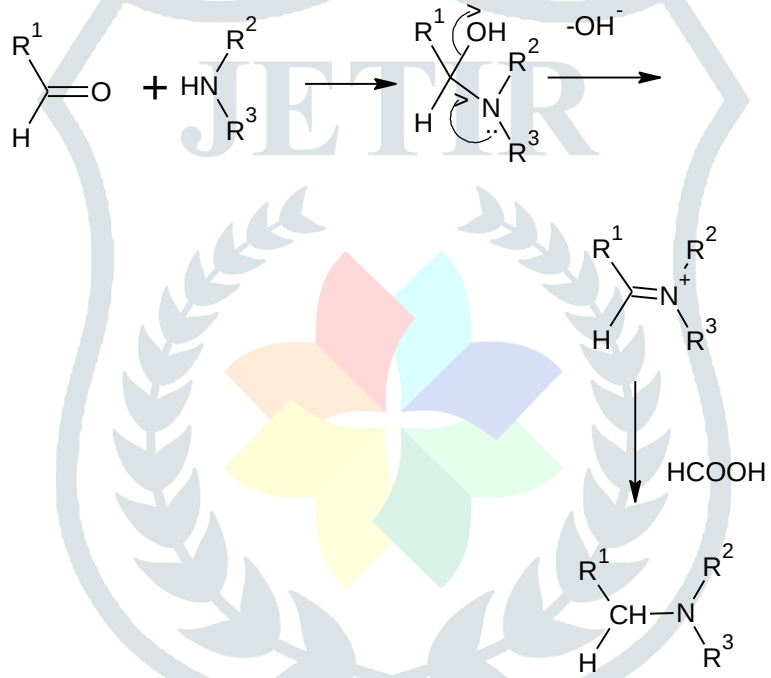
Amine reacts with aldehyde to give iminium ion.

The iminium ion then react with formic acid to give methylated ammonium ion and release CO_2 gas, where formic acid act as a reducing agent or hydride transfer reagent.

This CO_2 gas leads the synthesis process to the next level of synthesis.

In this stage ammonium ion gets deprotonated to form final methylated amine product.

If reaction occurs with primary amine same process follows twice to reach the tertiary amine as a final product(28)



METHODS AND METRIALS

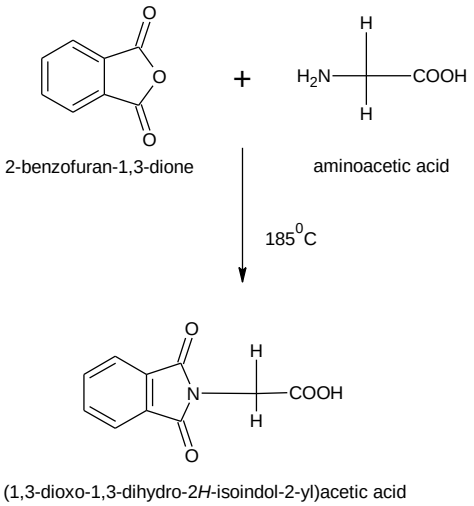
INSTRUMENTS AND MATERIALS

Microwave irradiation was carried out in a microwave oven (IFB-3way system, 23sc1, 2450 MHz) with power output of 800W. The reaction was monitored by TLC (Thin layer chromatography). The melting points of the synthesized compounds were estimated by open capillary tube method. IR spectra were recorded on Perkin-Elmer FT spectrophotometer used KBr disc the ranges of 4000-400 cm^{-1}. 1 H NMR spectra were recorded on Bruker 400 ultra-shield NMR spectrometer operating at 400MHz.For FT-NMR, DMSO is used as a solvent and chemical shift values were recorded in unit δ (ppm). Analytical grade chemicals were used for synthesized compounds.

STEP :1

SYNTHESIS OF 2-GLYCYL ISOINDOLE-1,3 DIONE

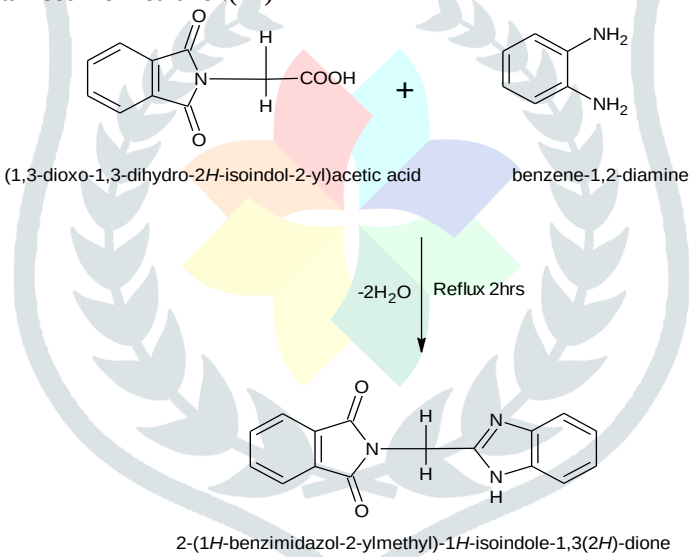
Weighed equimolecular quantity of pthalic anhydride and glycine in a beaker were kept in a heated sand bath (180-185^{0}C). The melted mixture was stirred continually during the first five minutes and any solid Pthalic anhydride which sublimed into the melted reaction mixture till there was complete fusion occurs. The melted mixture was kept aside, undisturbed for 5 minutes observe the liquid mass solidified. The white solid obtained was then recrystallized from ethanol.(16)



STEP:2

SYNTHESIS OF 2-METHYL BENZIMIDAZOLYL -ISOINDOLE-1, 3-DIONE

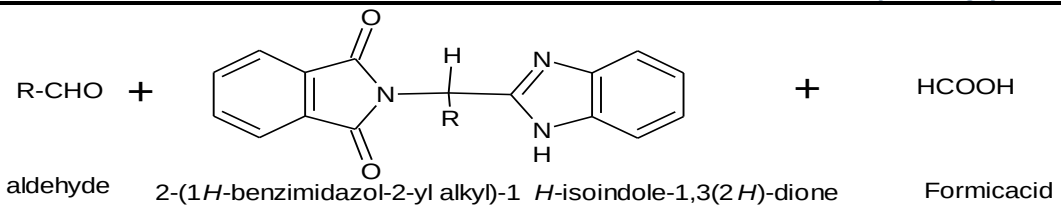
The 0.1 molar quantity of (1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)acetic acid and 0.1 molar of orthophenylene diamine were refluxed in 30 ml of 4N HCl for two hours. The solution was cooling gave a precipitate which was filtered with ice cold water, dried and then recrystallised from ethanol.(11)

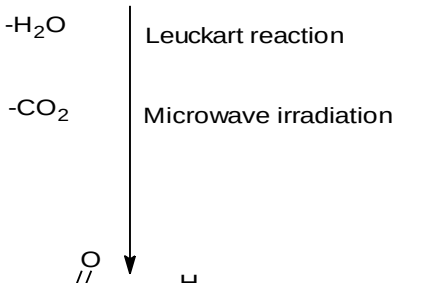


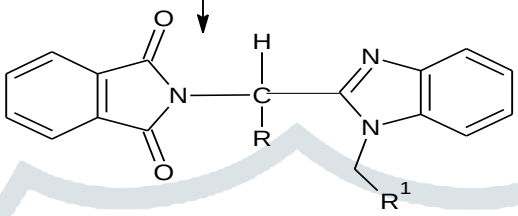
STEP:3

SYNTHESIS OF 2-{[1-(4-ARYL)-1*H*-BENZIMIDAZOL-2-YL] METHYL}-1*H*-ISOINDOLE-1,3(2*H*)-DIONE

Aldehyde (0.1M) and 2-(1*H*-benzimidazol-2-ylmethyl)-1*H*-isoindole-1,3(2*H*)-dione(0.1M) and formic acid(0.1M)) was irradiated in microwave at 80◦C for 5minutes in equimolar quantities. The solution was obtained and then cooled in ice bath until the crystals are formed. The crude product was obtained and washed with ice cold water and air dried.(19)







2-{[1-(4-aryl)-1 *H*-benzimidazol-2-yl]alkyl}-1 *H*-isoindole-1,3(2 *H*)-dione

R_1
C6H5-Cl,
C6H5OCH3,
C6H5-OH,
C6H5-NCH3
C4H4O

SPECTRAL DATA OF SYNTHESIZED COMPOUNDS

JV1 Compound 2-{[1-(4-chlorobenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR: C-H str (Ar)3047 cm^{-1},C=C str (Ar)1547 cm^{-1}, N-C= O str 1717 cm^{-1},C=N str1603 cm^{-1},C- N str1217 cm^{-1},CH_2str2849 cm^{-1},C-H bend1458 cm^{-1}, Ar-Cl623 cm^{-1}

1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.6,d,4H2NCH_2 4.6, m,4H ArH 7.8

MASS (m/e):401.84

JV2 Compound 2-{[1-(4-methoxybenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3049 cm^{-1},C=C str (Ar)1508 cm^{-1},^{N}-C= O str1763 cm^{-1},C=N str1609 cm^{-1},C- N str1248 cm^{-1},CH_2str2876 cm^{-1},C-H bend 1439 cm^{-1},$OCH_3$2837 cm^{-1}

1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.7,d,4H2NCH_2 4.9, m,4H ArH 7.8, s,3H OCH_3 6.6

MASS (m/e):397.42

JV3 Compound 2-{[1-(2-hydroxybenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3032 cm^{-1},C=C str (Ar)1587 cm^{-1},N-C= O str1772 cm^{-1},C=N str1454 cm^{-1},C- N str1244 cm^{-1},CH_2str2939 cm^{-1},C-H bend 1436 cm^{-1},OH 3593 cm^{-1}

1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.7,d,4H2NCH_2 4.4, m,4H ArH 7.8, s 1H OH 4.9

MASS (m/e):383.39

JV4 Compound 2-{[1-(4-dimethylaminobenzyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3030 cm^{-1},C=C str (Ar)1535 cm^{-1},^{N}-C= O str1711 cm^{-1},C=N str1604 cm^{-1},C- N str1271 cm^{-1},CH_2str2934 cm^{-1},C-H bend 1425 cm^{-1},$N(CH_3)_2$1385cm^{-1}

1HNMR(DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.6,d,4H2NCH_2 4.4, m,4H ArH 7.8,s6H $N(CH_3)_2$ 2.2

MASS (m/e):410.46

JV5 Compound 2-{[1-(furan-2-ylmethyl)-1*H*-benzimidazol-2-yl] methyl}-1*H*-isoindole-1,3(2*H*)-dione

IR:C-H str (Ar)3049 cm^{-1},C=C str (Ar)1510 cm^{-1},^{N}-C= O str1775 cm^{-1},C=N str1630 cm^{-1},C- N str1215 cm^{-1},CH_2str2853 cm^{-1},C-H bend 1425 cm^{-1},CO 1273 cm^{-1}

1HNMR (DMSO,80MHz,$^{\delta}$,ppm: m,8H ArH 7.5,d,4H2NCH_2 4.5, m,3H ArH 7.8

MASS (m/e):357.36

Physical data analysis

Table no:1

Compoud Code	Solubiliy	Appearance/ Colour	Percenge Yield
JV1	$CHCl_3$, DMSO	SOLID/PALE YELLOW	73.56%
JV2	$CHCl_3$, DMSO	SOLID/ ORANGE	67.50%
JV3	$CHCl_3$, DMSO	SOLID/PALE YELLOW	71.27%
JV4	$CHCl_3$, DMSO	SOLID/RED	75.60%
JV5	$CHCl_3$, DMSO	SOLID/BLACK	58.26%

The melting point of synthesized compounds

Table no: 2

S.No	Compound	Melting Point ^{0}c
1	JV1	248
2	JV2	256
3	JV3	244
4	JV4	240
5	JV5	247

Rf value ofsynthesised compounds

Table No:3

Compound Code	R_f Value
JV1	0.55
JV2	0.60
JV3	0.44
JV4	0.43
JV5	0.37

BIOLOGICAL EVALUATION

INVITRO ANTHELMINTIC ACTIVITY

Anthelmintic are drugs that have the capability of ridding the body of parasitic worms or helminthes. The anthelmintic activity of the synthesized compounds was studied by using earth worms.

Earth worms -Eudrilluseuginae (purple colour)
Solvent - DMSO
Control - Normal saline
Standard - Albendazole
Sample - Synthesised compounds JV1-JV5

PROCEDURE

The synthesised compounds were tested for anthelmintic activity by in-vitro bioassay method. The earth worms Eudrilluseuginae of 7.5-9cm in length and 0.2-0.3 cm width were used for the invitro anthelmintic activity due to its anatomical and physiological resemblance with the intestinal worm parasites of human beings. The earth worms of nearly equal size (8±1cm) were selected randomly than washed thoroughly with normal saline solution to remove all fecal and adhering materials before they were released in to petridishes which containing drug in 15 ml of normal saline solution. The worms were divided into the control, standard and tested compounds groups of five earth worms in each group. All the synthesized tested compounds and the standard drug solution were freshly prepared before commencement of the experiments. The control group petridish contains 0.5ml of DMSO in 14.5ml of normal saline.

The standard drug albendazole and tested compounds were prepared at a doses level of 50,100,150mg by dissolving in minimum quantity, about 0.5ml of DMSO and the volume was diluted to 15 ml with normal saline, then poured into petridishes. The five earth worms were placed in each petridishes at room temperature and time taken for the induction of complete paralysis and time taken for death of individual earth worms was noted. The time taken for worms to become motionless and do not revive even in normal saline was noted as paralysis time. The death time was ascertained by applying external stimuli unless placing the individual worms in warm water at 50^0C which stimulate and induce movement of worms, if alive. The mean paralysis time and mean death time were calculated for each tested concentrations of the synthesised compounds.(8)

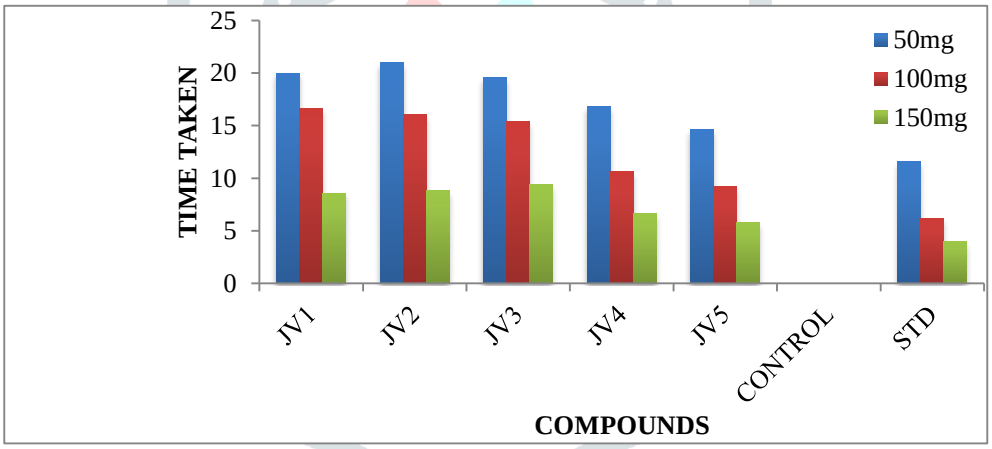
invitro anthemintic activity of synthesised compounds

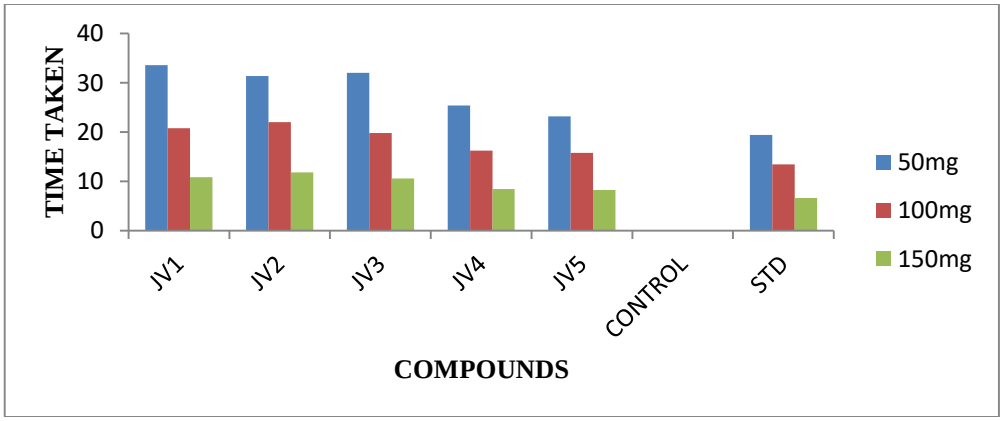
Table no:4

Compoud Code	Time Taken For Paralysis (P)			Time Taken For Death (D)		
	50mg/ group	100mg/ Group	150mg/ Group	50mg/ Group	100mg/group	150mg/ group
JV1	20±0.93	16.6±0.51	8.6±0.24	33.6±1.03	20.8±0.58	10.8±0.58
JV2	21 ±0.71	16 ±0.89	8.8±0.37	31.4±0.93	22±0.95	11.0±1.04
JV3	19.6±0.92	15.4±0.75	9.4±0.24	32±0.71	19.8±0.37	10.6±0.60
JV4	16.8±0.58	10.6±0.51	6.6±0.51	25.4±1.08	16.2±0.58	8.4±0.40
JV5	14.6±0.51	9.2±0.37	5.8±0.37	23.2±0.86	15.8±0.73	8.2±0.37
CONTROL	R	R	R	R	R	R
STD	11.6±0.51	6.2±0.37	4±0.32	19.4±0.51	13.4±0.51	6.6±0.51

ANTHELMINTIC ACTIVITY AGAINST EUDRILLUSEUGINAE (EARTH WORM)

TIME TAKEN FOR PARALYSIS





INVITRO ANTHELMINTIC ACTIVITY OF COMPOUNDS-JV5

PARALYSIS OF COMPOUND-JV5 DEATH OF COMPOUND JV5

RESULT AND DISCUSSION

The structure, and properties of synthesized compounds were determined by using various software such as chemdraw and chemsketch. The compounds JV1-JV5were synthesized by using microwave irradiation.The compounds were synthesized by "Leuckart reaction" which shows good percentage yield, melting point and solubility of the compounds are determined and shown in Table no:1,&2.The compounds are monitored by TLC and R_f value was calculated and shown in Table no:3.The compounds were confirmed by spectral analytical data. The anthelmintic activity was performed by using Eudrillus euginae earth worm. The standard drug albendazole and tested compounds were prepared at a doses level of 50,100,150mg.The results of Time taken for paralysis and Time taken for death were shown in Table no:4. All the synthesized compounds showed comparable activity with standard albendazole drug.

CONCLUSION

Synthetic work: The present study describes the synthesis of benzimidazole with isoindoline derivatives by leuckart reaction using microwave irradiation. The reaction having lesser time reaction and yield higher percentage of products. All synthesized compounds were found to be good anthelmintic activity. The furfuraldehyde, dimethyl amino benzaldehyde substituted synthesized compounds JV4, JV5 having good anthelmintic activity as compared to standard drug Albendazole.

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