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INVESTIGATIONS ON DESIGN AND SYNTHESIS OF NOVEL BIOLOGICALLY ACTIVE ISOINDOLINONE DERIVATIVES THROUGH MICROWAVE AS WELL AS CONVENTIONAL TECHNIQUE

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Abstract: Green multistep synthesis of some new biologically potent Isoindolinone compounds by classical thermal and microwave-irradiation techniques and characterization by the IR, HPLC, H^1-NMR, C^{13} NMR, Mass studies. TSu studies of Isoindolinones are also carried out to predict thermal stability and decomposition phase. Desired Isoindolinones (4a, 4b, 4c) are synthesized through free radical mechanism from azomethine (3) followed through synthesis from ester derivative (2) of 2-carboxy benzaldehyde (1). Biological studies of Isoindolinones have been carried out *in vitro* for antibacterial activity and antifungal activity.

Keywords: Isoindolinone; Azomethine; TSu; Antifungal activity; Antibacterial activity; microwave; conventional.

Introduction

Increase in rapid growth of bacterial and fungal diseases is a major health concern all over the world. Prevention and treatment of these diseases with several anti-bacterial, anti-fungal drugs have decreased the health immunity and damage cells growth, but the number of new diagnosis continues to increase. Therefore, new and more efficient anticancer agents are required against different bacterial or fungal diseases. Isoindolinone derivatives are the biologically active heterocyclic compounds and represents many important classes of therapeutically agents in medicinal chemistry such as- anticonvulsant[1,2,3], anticancer[4,5,6], antioxidant[7,8,9], anti-rheumatoid arthristis[10,11], anti-HIV[12,13].

Some studies have revealed that a group of Isoindolinone derivatives[15] are bioactive natural products and frequently used as anti-inflammatory, anti-bacterial drug. These derivatives act as pharmalogical agents used in the treatment of epileptic seizures. They inhibit bipolar disorder and suppress the rapid and excessive firing of neurons in brain.

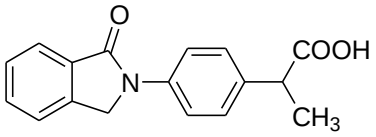


Fig-I:-Indoprofen[16] (Anti-inflammatory)

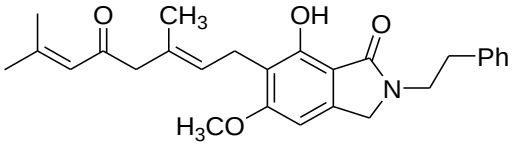


Fig-II:- Hericenone B[17]

Thalidomide[18-19] (Fig-III), a sedative drug possesses more potent cyclooxygenase (COX) inhibiting activity. It is used for the treatment of different diseases like AIDS, myeloma, leprosy.

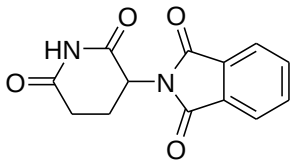


Fig- III

Cyclooxygenase[18] is an enzyme which easily binds with substrate (thalidomide) through its active site and there are two isoforms of COX i.e. COX-1 and COX-2. Out of several isoindolinone compounds (III-a and III-b) show most effective inhibition activity on COX-1 and COX-2.

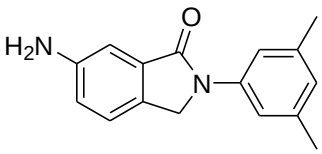


Fig- III-a

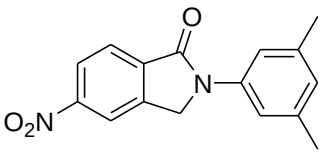
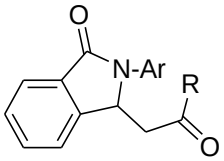


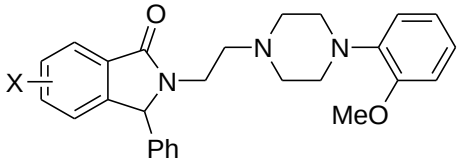
Fig- III-b

Isoindolinones are γ- lactums[19] have large importance in pharmaceuticals such as piracetam oxiracetam, glimepiride etc. It was observed that they also prevent different diseases such as hypertensive vasodilators, cancer, age-related cognitive disorder etc. Some derivatives are given.



R=CH_3, OMe, Ar= -CH_2-C_6H_5 , C_6H_5

Fig-IV:- Anti cancer agent



X= Br, NO_2

Fig-V:- Anxiolytic active

Some N-substituted isoindolinone have resistance activity against tumor cells. World Health Organization (WHO) estimates that near about 10 millions peoples all over the world are affected by cancer. To reduce this diseases compounds[20] (VI: **a-d**) are tested for *in-vitro* anticancer activity against K562, Hep-G2, & HT-29 cells by MTT based assay.

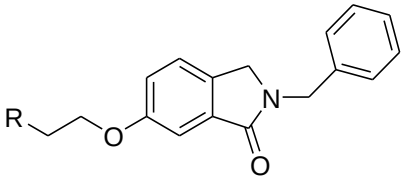
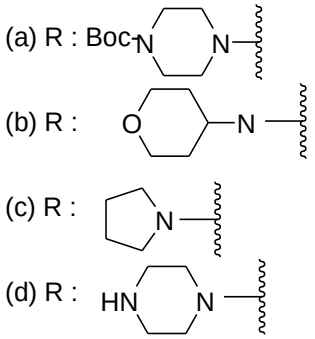


Fig-VI: Anticancer agent



Recently, some isoindolinone scaffolds were published in the literature[21] for the inhibition activity of the MDMZ-P^{53} interaction. MDMZ protein regulates the P^{53} level and maintains the concentration of P^{53} at low level to prevent apoptosis in normal cells. Compounds[22] (VII-a, b, c) showed lower activity for the inhibition of MDMZ protein. These compounds are used to suppress the growth of first stage tumors.

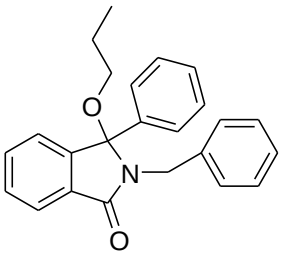


Fig-VII-a

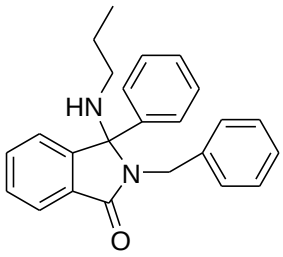


Fig-VII-b

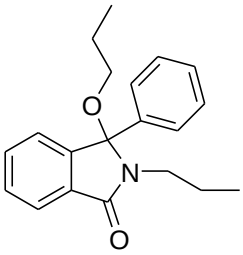


Fig-VII-c

Some new isolindolinone subordinates[23] were integrated as intense histone deacetylase inhibitors Studies uncovered that In vitro, VIII-a and VIII-b showed strong antiproliferative exercises against a few malignancy cell lines, specifically VIII-b, which acted better compared to supported medication chidamide. Morever, compound hindrance and western smudge measure set up VIII-b to be a specific inhibitor for HDAC1-3.

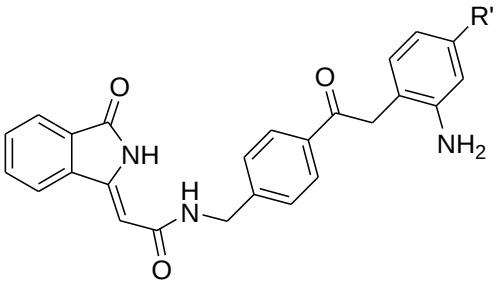


Fig: VIII(a-b)
a: R' - H
b: R' - F

The present work is to develop new chemotherapeutic agents having Isoindolinone nucleus as potential antifungal and antibacterial agent and predict thermal stability during temperature ramping.

EXPERIMENTAL

Chemicals, 2-carboxy benzaldehyde, Triethyl borane, Diphenyl silane, 1, 2-dichloro ethane, Methyl iodide, Ethyl iodide, Isopropyl iodide, silicotungstic acid and others were purchased from Sigma Aldrich, CDH and LOBA and used without purification. Melting points were determined by open capillary tubes on electrical melting pointer. Microwave irradiation was performed under domestic BAJAJ 700 W microwave (model name 1701MT). HPLC analysis was done on SHIMADZU (LC-2010AHT). Analytical thin-layer chromatography (TLC) was done on precoated silica gel 60F-254. Column chromatography was performed on silica gel (60-120 mesh). IR spectra were recorded on Shimadzu FTIR-8400S spectrophotometer. H^1 NMR and C^{13} NMR were done on Bruker Avance II 400 spectroscopy. TSu studies had been done on *H E L*.

GENERAL REACTION SCHEME FOR SYNTHESIS OF PROPOSED ISOINDOLINONE DERIVATIVES:

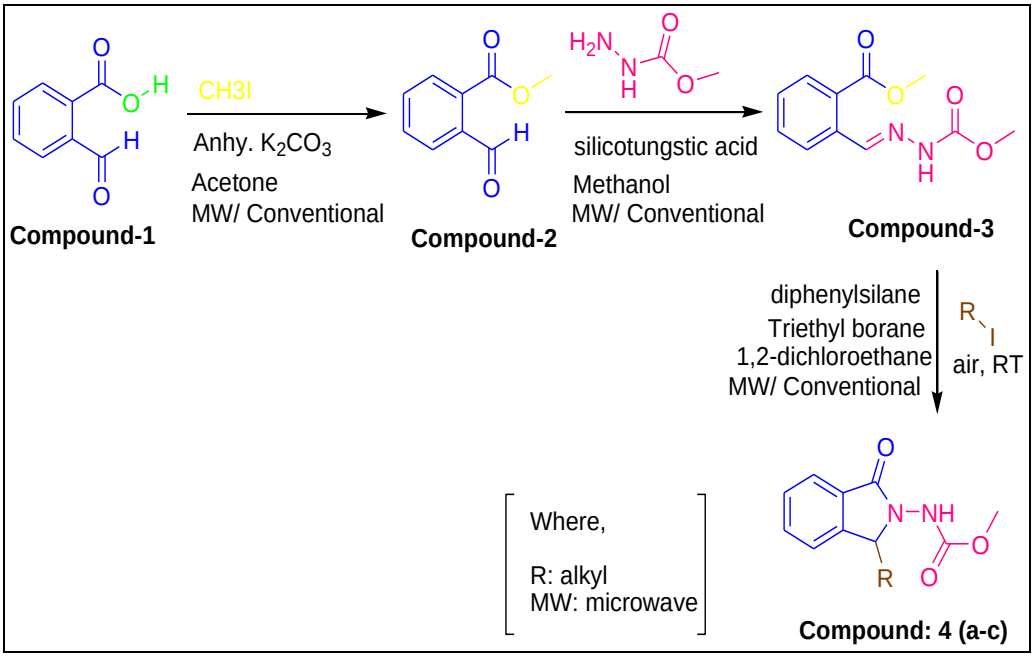


Figure-1: General Reaction Scheme

GENERAL EXPERIMENTAL PROCEDURE

SYNTHESIS OF METHYL 2-FORMYL BENZOATE (COMPOUND-2) FROM 2-CARBOXY BENZALDEHYDE (COMPOUND-1):-

In a 250 ml round bottom flask, methyl iodide (1.136 g, 0.008 moles) was slowly added to a mixture of 2-carboxy benzaldehyde (1.0g, 0.0066 moles) and anhydrous potassium carbonate (1.0 g) in presence of 50 ml anhydrous acetone. The resulting mixture was stirred with refluxing at 40^0C temperature around 8 hours in thermal technique and around 8-9 minutes in microwave strategy. The progress of the reaction was monitored by TLC and stirring was continued till completion of reaction. After completion of reaction, contents were filtered while hot and solvent was evaporated under reduced pressure. A pale yellow liquid was obtained which was washed with 10 ml of diethyl ether to get the pure product (0.91 gm, 0.00554 moles).

SYNTHESIS OF 2-(METHYL-HYDRAZONO-METHYL)-BENZOIC ACID METHYL ESTER (COMPOUND-3) FROM METHYL 2-FORMYL BENZOATE (COMPOUND-2):-

In a 250 ml round bottom flask, methyl hydrazinocarboxylate (1.1057 g, 0.01443 moles) was added in dry methanol (50 ml) in presence of silicotungstic acid (catalyst, 0.05 g). The reaction mixture was stirred at room temperature for 15-20 minutes. After 20 minutes methyl 2-formyl benzoate (1.55 g, 0.00944 moles) was added to the reaction mixture. The resulting mixture was starred at room temperature around 3 hours in thermal technique and around 6-7 minutes in microwave strategy. The progress of the reaction was monitored by TLC and stirring was continued till completion of reaction. After completion of reaction, solvent was evaporated under reduced pressure. A white solid was obtained which was subjected to column chromatography (flash chromatography using silica 60-120, column packed in hexane) using hexane ethyl acetate 1:1 to get the pure product. This pure product was further purified with pure hexane dissolving in chloroform to get the recrystalized product (2.01 gm, 0.0085 moles).

FREE RADICAL MECHANISM OF ISOINDOLINONE SYNTHESIS

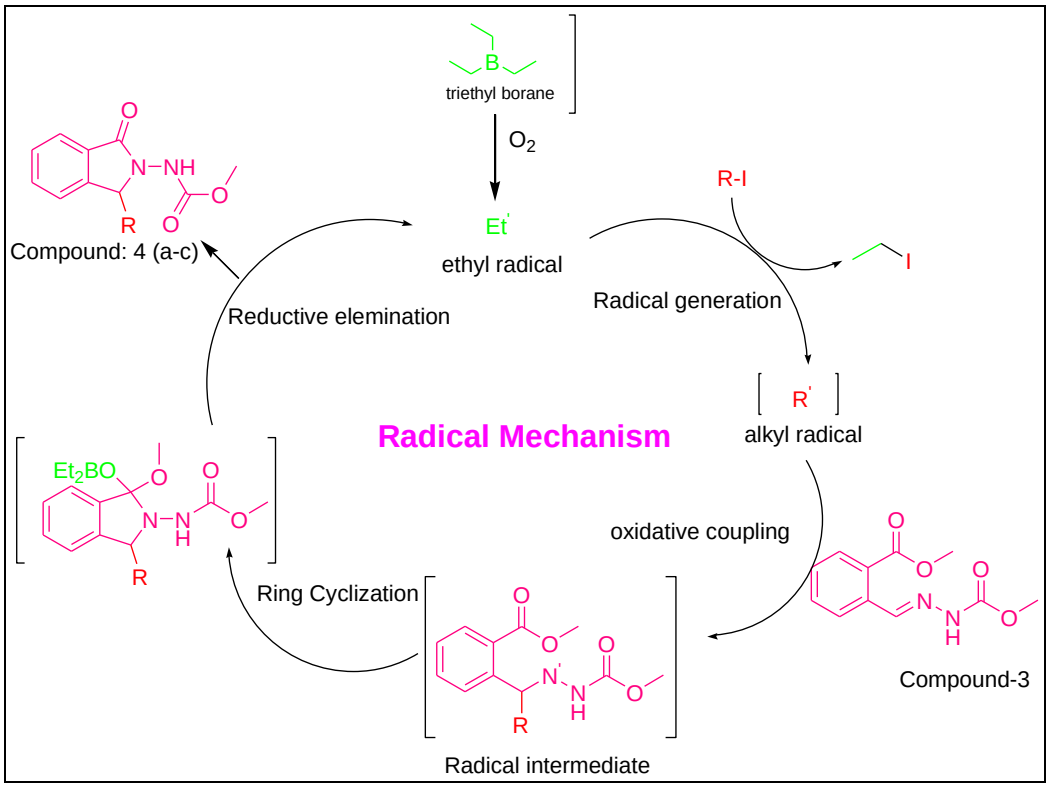


Figure-2: Probable free radical path of Isoindolinone synthesis

SYNTHESIS OF METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4a) FROM 2-(METHYL-HYDRAZONO-METHYL)-BENZOIC ACID METHYL ESTER:-

To a solution of 2-(Methyl-hydrazono-methyl)-benzoic acid methyl ester (200 mg, 0.8466 m mmoles) and diphenylsilane (0.157 ml, 1.0 eq) in 1,2-dichloroethane (15.0 ml) was added methyl iodide (0.1589 ml, 3.0 eq diluted with 1.0 ml of 1,2-dichloroethane) under nitrogen, to this Triethyl borane (0.1224 ml, 1.0 eq) was added strictly under nitrogen, the contents were stirred vigorously at room temperature and air was inserted through needle around 10 hours in thermal technique and around 8-9 minutes in microwave strategy. The progress of reaction was monitored by TLC and stirring was continued till completion of reaction. After completion of reaction, solvent was evaporated under reduced pressure, and the crude mass was subjected to column chromatography (flash chromatography using silica 60-120, column packed in hexane) using hexane ethyl acetate 1:1 to get the pure product. After elution of column 146 mg pure product was isolated.

SYNTHESIS OF METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4b) FROM 2-(METHYL-HYDRAZONO-METHYL)-BENZOIC ACID METHYL ESTER:-

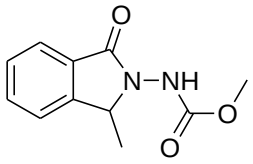
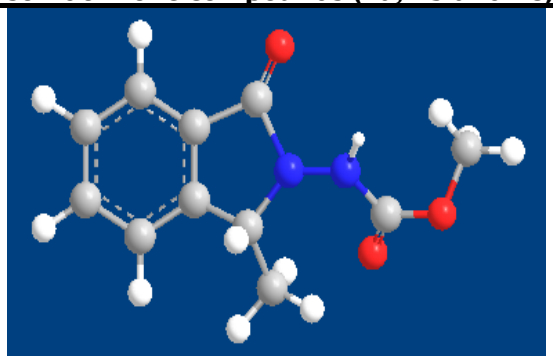
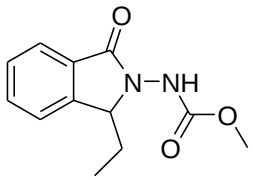
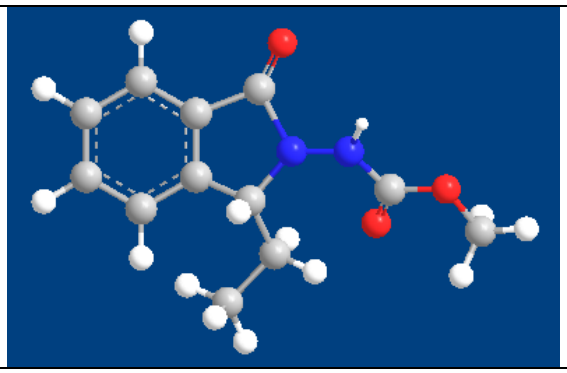
To a solution of 2-(Methyl-hydrazono-methyl)-benzoic acid methyl ester (200 mg, 0.8466 m moles) and diphenylsilane (0.156 ml, 1.0 eq) in 1,2-dichloroethane (15.0 ml) was added ethyl iodide (0.2042 ml, 3.0 eq diluted with 1.0 ml of 1,2-dichloroethane) under nitrogen, to this Triethyl borane (0.1224 ml, 1.0 eq) was added strictly under nitrogen, the contents were stirred vigorously at room temperature and air was inserted through needle around 10 hours in thermal

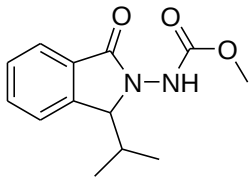
technique and around 9-10 minutes in microwave strategy. The progress of reaction was monitored by TLC and stirring was continued till completion of reaction. After completion of reaction, solvent was evaporated under reduced pressure, and the crude mass was subjected to column chromatography (flash chromatography using silica 60-120, column packed in hexane) using hexane ethyl acetate 1:1 to get the pure product. After elution of column 171mg pure product was isolated.

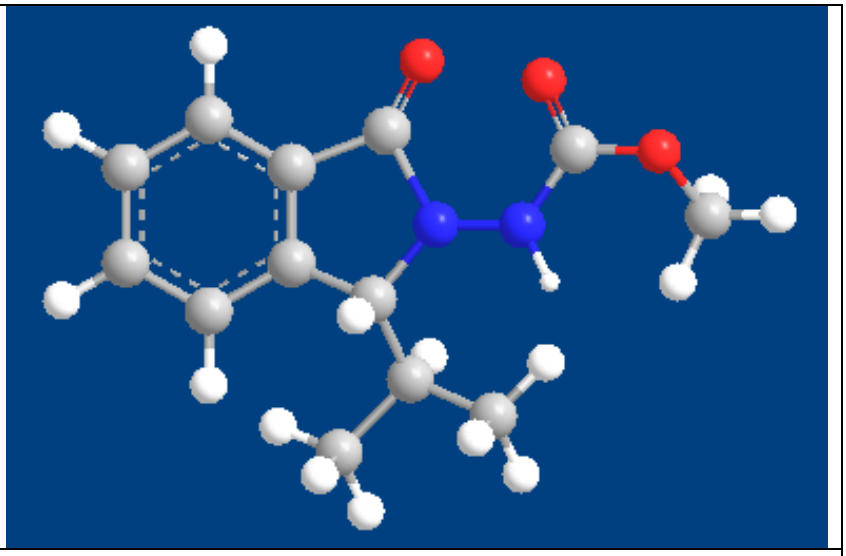
SYNTHESIS OF METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4c) FROM 2-(METHYL-HYDRAZONO-METHYL)-BENZOIC ACID METHYL ESTER:-

To a solution of 2-(Methyl-hydrazono-methyl)-benzoic acid methyl ester (200 mg, 0.8466 m moles) and diphenylsilane (0.157 ml, 1.0 eq) in 1,2-dichloroethane (15.0 ml) was added isopropyl iodide (0.254 ml, 3.0 eq diluted with 1.0 ml of 1,2-dichloroethane) under nitrogen, to this Triethyl borane (0.1224 ml, 1.0 eq) was added strictly under nitrogen, the contents were stirred vigorously at room temperature and air was inserted through needle around 10 hours in thermal technique and around 11-12 minutes in microwave strategy. The progress of reaction was monitored by TLC and stirring was continued till completion of reaction. After completion of reaction, solvent was evaporated under reduced pressure, and the crude mass was subjected to column chromatography (flash chromatography using silica 60-120, column packed in hexane) using hexane ethyl acetate 1:1 to get the pure product. After elution of column 174 mg pure product was isolated.

Ball sticks Structure of the Isoindolinone compounds (4a, 4b and 4c)

	
2-Acetyl- METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	
	
METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	





METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE

RESULT AND DISCUSSION

COMPARISON BETWEEN THERMAL AND MICROWAVE METHODS

A comparison between thermal and microwave method is given in **Table A.**

Table A: Comparison between thermal and microwave methods

Synthesized Compounds	Yield (%)		Solvent used (mL)		Time	
	Thermal method	Microwave Method	Thermal Method	Microwave method	Thermal method (hrs)	Microwave method (min)
Fig-2	83.22%	90.52%	50	10	8	9
Fig-3	90.12%	93.59%	50	10	3	6
Fig-4a	78.65%	86.87%	15	2	10	8
Fig-4b	86.58%	89.22%	15	1.5	10	10
Fig-4c	83.11%	91.47%	15	2.0	10	12

METHYL 2-FORMYL BENZOATE (2): 99.792% HPLC purity**,** Melting point of compound-2 shows 40.41-40.46°C. LC-MS data shows m/e 165.13 (m+1).The IR data of compound-2 gives a sharp peak at 1720.56 cm^{-1} for C=O of aldehyde and ester moiety, two distinct peaks at 2955.04 cm^{-1} and 2906.82 cm^{-1} for sp^2 C-H and sp^3 C-H respectively. Aromatic C=C peaks were also observed at 1589.40 cm^{-1} region. ^{1}H-NMR ($CDCl_3$) spectra gives different signals w.r.t TMS (Trimethyl Silane) as reference. There were sharp signal at 3.9733 (s, 3H, 2*OMe), 10.6079 (s, 1H, Aldehyde) and 7.63-7.97 (m, 4H, Aromatic & 1H). C^{13}-NMR

($CDCl_3$) 134.4, 133.4, 129.7, 136.6, 132.4, 130.3, 166.1, 51.4, 191.2. Anal. Calcd for ($C_9H_8O_3$): C 65.85; H 4.91; Found C 65.72; H 4.88.

2-(METHYL-HYDRAZONO-METHYL)-BENZOIC ACID METHYL ESTER (3): 99.88% HPLC purity**,** Melting point of compound-2 shows 58.14-58.65°C. LC-MS data shows m/e 237.13 (m+1). The IR data of compound-**3** gives a sharp peak at 1664.62 cm^{-1} for C=O of imine and ester moiety, two distinct peaks at 3032.27 cm^{-1} and 2949.26 cm^{-1} for sp^2 C-H and sp^3 C-H respectively. Aromatic C=C peaks were also observed at 1550.82 cm^{-1} region and NH peak was observed at 3163.36 cm^{-1}.
^{1}H-NMR ($CDCl_3$) spectra gives different signals w.r.t TMS (Trimethyl Silane) as reference. There was a sharp signal(s) at 3.39 ppm for 6H of 2*OMe group. NH showed a sharp signal (s) at 12.61 ppm. And 7.63-7.65 ppm (m, 3H, Aromatic), 8.25-8.29 ppm (m, 2H, Aromatic) and CH signals were observed. C^{13}-NMR ($CDCl_3$) 131.1, 133.5, 133.9, 129.0, 131.6, 130.2, 166.1, 51.2, 143.1, 154.2, 49.2. Anal. Calcd for ($C_{11}H_{12}N_2O_4$): C 55.93; H 5.12; N 11.86. Found C 55.91; H 5.09; N 11.81.

METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4a): 99.53 % HPLC purity. Melting point of compound-2 shows 196.1-196.15°C. LC-MS data shows m/e 221.21 (m+1). The IR data of this compound gives a sharp peak at 1726.35 cm^{-1} for C=O, two distinct peaks at 3010.98 cm^{-1} and 2956.97 cm^{-1} for sp^2 C-H and sp^3 C-H respectively. Aromatic C=C peak was observed at 1429.30 cm^{-1} region and NH peak was observed at 3064.99 cm^{-1}. ^{1}H-NMR ($CDCl_3$) spectra gives different signals w.r.t TMS (Trimethyl Silane) as reference. δ 3.64 ppm (s, 3H,-OMe group), 8.01 ppm (s, 1H, NH), 1.55 ppm (d, 3H, CH_3), 5.10 ppm (m, 1H, methine), 7.21-7.98 ppm(m, 4H, aromatic) C^{13}-NMR ($CDCl_3$) 126.7, 132.1, 127.4, 145.2, 130.5, 127.4, 49.5, 160.5, 16.2, 156.4, 49.2. Anal. Calcd for ($C_{11}H_{12}N_2O_3$): C 59.99; H 5.49; N 12.72. Found C 59.22; H 5.41; N 12.81.

METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4b): 99.01 % HPLC purity. Melting point of compound-2 shows 207.11-207.12°C. LC-MS data shows m/e 235.51 (m+1). The IR data of this compound gives a sharp peak at 1662.69 cm^{-1} for C=O, two distinct peaks at 3009.05 cm^{-1} and 2893.32 cm^{-1} for sp^2 C-H and sp^3 C-H respectively. Aromatic C=C peak was observed at 1429.30 cm^{-1} region and NH peak was observed at 3047.63 cm^{-1}. ^{1}H-NMR ($CDCl_3$) spectra gives different signals w.r.t TMS (Trimethyl Silane) as reference. δ 3.68 ppm (s, 3H,-OMe group), 8.05 ppm (s, 1H, NH), 0.98 ppm (t, 3H, CH_3), 1.84 ppm (m, 2H,-CH_2-), 4.82 ppm (t, 1H, methine), 7.22-7.89 ppm (m, 4H, aromatic). C^{13}-NMR ($CDCl_3$) 126.5, 131.9, 128.5, 142.2, 131.3, 127.5, 56.9. 160.7, 22.7, 49.5, 8.2, 156.5. Anal. Calcd for ($C_{12}H_{14}N_2O_3$): C 61.53; H 6.02; N 11.96. Found C 61.42; H 6.05; N 10.99.

METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4c): 99.09 % HPLC purity. Melting point of compound-2 shows 203.2-203.7°C. LC-MS data shows m/e 249.56 (m+1). The IR data of this compound gives a sharp peak at 1662.69 cm^{-1} for C=O, two distinct peaks at 3034.13 cm^{-1} and 2945.40 cm^{-1} for sp^2 C-H and sp^3 C-H respectively. Aromatic C=C peak was observed at 1477.52 cm^{-1} region and NH peak was observed at 3165.29 cm^{-1}. ^{1}H-NMR ($CDCl_3$) spectra gives different signals w.r.t TMS (Trimethyl Silane) as reference. δ 3.67 ppm (s, 3H,-OMe group), 8.04 ppm (s, 1H, NH), 0.99 ppm (d, 6H, i-pr), 2.84 ppm (m, 1H,- CH-), 4.76 ppm (d, 1H, methine), 7.20-7.99 ppm (m, 4H, aromatic). C^{13}-NMR ($CDCl_3$) 124.9, 131.5, 128.2, 144.5, 131.6, 126.4, 63.6, 160.7, 28.2, 156.7, 49.2, 17.5, 17.5. Anal. Calcd for ($C_{13}H_{16}N_2O_3$): C 62.89; H 6.50; N 11.28; O 19.33. Found C 62.44; H 5.95; N 11.22; O 20.01.

THERMAL STABILITY ANALYSIS OF COMPOUNDS 4(a-c):

The TSu enables rapid screenings of compounds on same platform inform temperature vs pressure plotting.

METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4a): Sample showed mild exothermic at 193°C and after that decomposition was observed. During temperature ramping no pressure onset was observed. Residual pressure confirmed the absence of non-condensable gas generation.

Onset temperature (°C)	Onset Pressure (Bar)	Max Temperature rate	Maximum pressure reached	Max pressure rate	Residual pressure at 40°C	Phase Transformation (°C)
Not Observed	Not Observed	4.9°C/min at 230°C	5 bar (abs)	0.1 bar/min at 207°C	1.3 bar (abs)	-

Where abs: absolute pressure

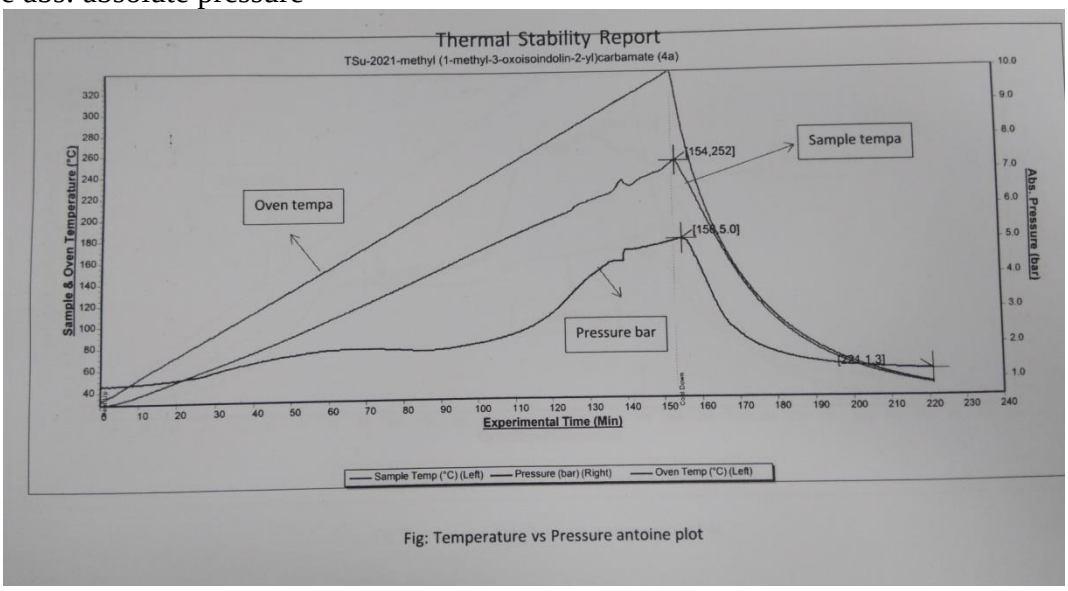


Figure-3: TSu plot of 4a

METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4b): Sample showed mild exothermic at 225°C and after that decomposition was observed. During temperature ramping 171°C light pressure onset was observed. Residual pressure confirmed the absence of non-condensable gas generation.

Onset temperature (°C)	Onset Pressure (Bar)	Max Temperature rate	Maximum pressure reached	Max pressure rate	Residual pressure at 40°C	Phase Transformation (°C)
Mild exotherm at 225°C	Light pressure observed from 171°C	2.3°C/min at 245°C	16.8 bar (abs)	0.52 bar/min at 207°C	1.3 bar (abs)	142°C

Where abs: absolute pressure

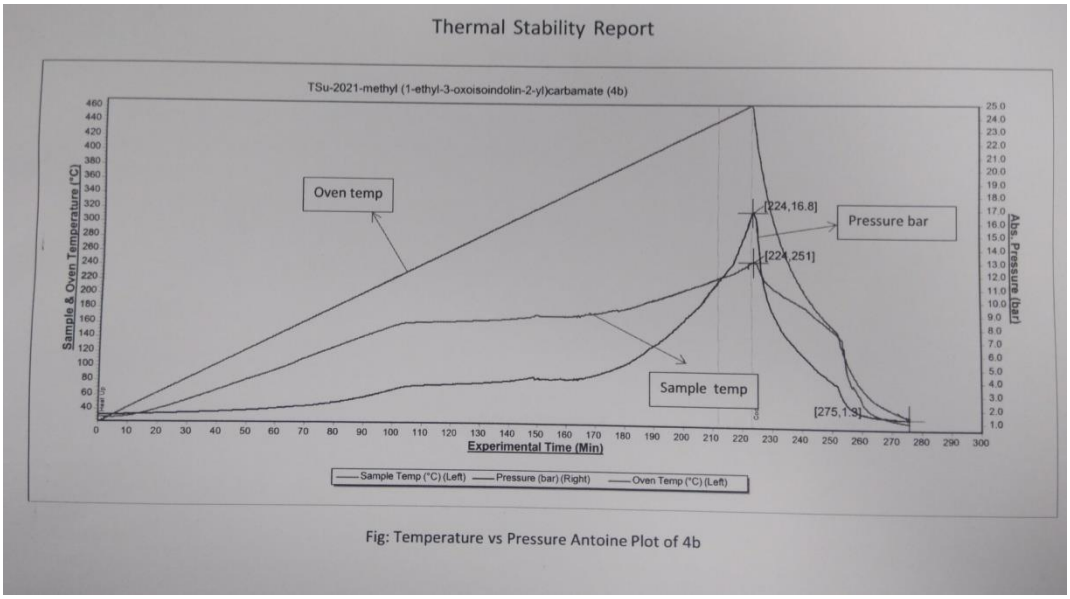


Figure-4: TSu plot of 4b

METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE (4c): Sample showed mild exothermic at 235°C and after that decomposition was observed. During temperature ramping no pressure onset was observed. Residual pressure confirmed the absence of non-condensable gas generation.

Onset temperature (°C)	Onset Pressure (Bar)	Max Temperature rate	Maximum pressure reached	Max pressure rate	Residual pressure at 40°C	Phase Transformation (°C)
Not observed	Not observed	15.1°C/min at 245°C	12.4 bar (abs)	0.5 bar/min at 207°C	1.7 bar (abs)	175°C

Where abs: absolute pressure

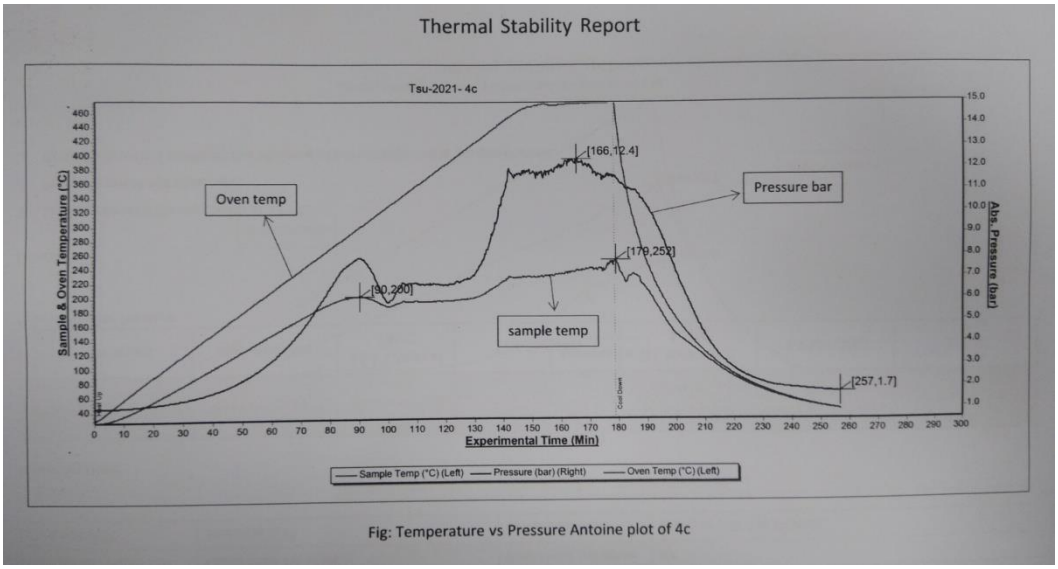


Figure-5: TSu plot of 4c

Antimicrobial assay

Calculation of minimum inhibitory concentration (MIC) of isoindolinone derivatives were done on selected fungi, *Candida albicans* and *Aspergillus niger* and two bacteria, Gram-positive (*Bacillus subtilis),* and Gram-negative (*Escherichia coli* and the MIC esteems determined for the isoindolinones as demonstrated in (Table 5). The outcomes demonstrated that Isoindolinones were the most dynamic in repressing the development of the tried creatures between 16-26 µg/mL MIC esteems for chosen microscopic organisms and parasites. It has also been proposed that the ultimate action of the compounds is the denaturation of one or more proteins of the cell as a result of which normal cellular processes are impaired and deactivation of various cellular enzymes that play a vital role in different metabolic pathways of these microorganisms.

MIC values of antifungal activity of Isoindolinone Derivatives

The MIC values for derivatives are given in **Table** B

Table B: MIC (µg/mL) values for Isoindolinone derivatives

Synthesized compounds	*Candida albicans*	*Aspergillus niger*
METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	22.0±0.1	22.0±0.4
METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	24.0±0.2	24.0±0.1
METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE	26.0±0.1	26.0±0.3
Fluconazole	13±0.2	13±0.2

MIC values for antibacterial activity of Isoindolinone Derivatives

The MIC values for isoindolinone derivatives are given in **Table C**

Table C: MIC (µg/mL) values for isoindolinone derivatives complexes

Synthesized compounds	***Bacillus subtilis***	***Escherichia coli***
METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	20.0±0.1	18.0±0.3
METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	24.0±0.2	17.0±0.2
METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE	22.0±0.1	20.0±0.2
Streptomycin	12±0.3	09±0.1

Antifungal studies

Bio efficacies of the synthesized isoindolinone derivatives were checked in vitro. The in vitro antifungal exercises[24] of compounds have been considered in contrast to two pathogenic organisms, Candida albicans and Aspergillus niger utilizing by the agar plate technique. The antifungal screening information of compounds was compared with the standard (Fluconazole) (Table-D).

Table D: Antifungal screening data for isoindolinone derivatives

Synthesized compounds	**% Inhibition after 120 hrs**					
	Candida albicans		***Aspergillusniger***		***Alternariaalternata***	
	100 ppm	**200 ppm**	**100 ppm**	**200 ppm**	**100 ppm**	**200 ppm**

METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	27	39	29	41	30	45
METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	36	48	31	49	36	49
METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE	65	66	61	69	64	69
Fluconazole	71	76	67	89	85	95

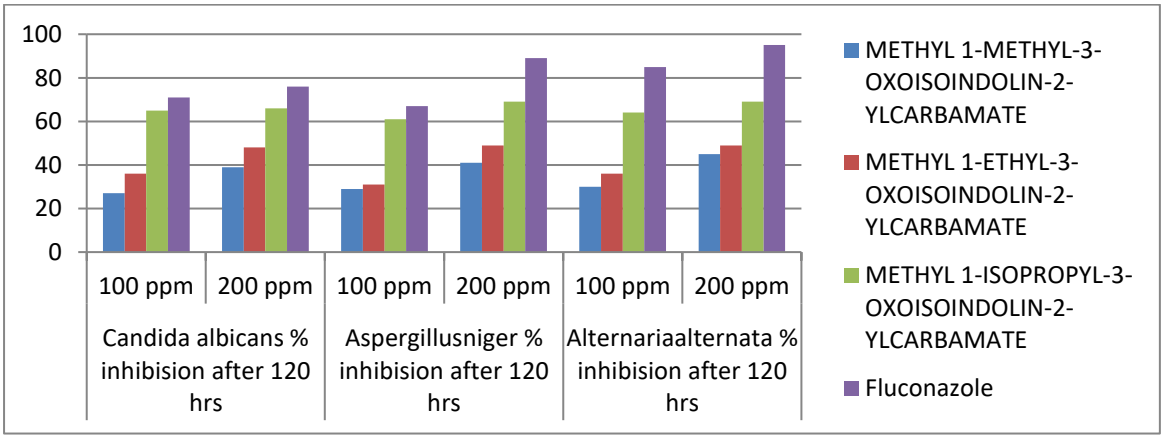


Figure-6: plot of antifungal screening data of Isoindolinone Derivatives

Antibacterial screening

In vitro antibacterial screening[25-26] is generally performed by plate dissemination method for essential determination of the compounds as restorative specialists. The antibacterial action of the isoindolinone compounds were thought about in contrast to of two microbes including Gram-positive (Bacillus subtilis)[27] and Gram-negative (Escherichia coli)[28]. The breadths of the zone of restraint created by the mixtures were contrasted and the standard anti-infection (Streptomycin). The zone of inhibition consequently conformed to each disc containing the test compounds were estimated precisely in mm (Table-E).

Table-E: Antibacterial screening data for Isoindolinone Derivatives

Synthesized compounds	**% Inhibition after 48 hrs**					
	Bacillus subtilis		**Eschirichia coli**		**Staphylococcus aureus**	
	500ppm	**1000ppm**	**500ppm**	**1000 ppm**	**500 ppm**	**1000 ppm**
METHYL 1-METHYL-3-	13	14	14	16	16	19

OXOISOINDOLIN-2-YLCARBAMATE						
METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE	13	17	16	15	17	18
METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE	15	19	17	22	20	23
Streptomycin	16	24	17	22	25	27

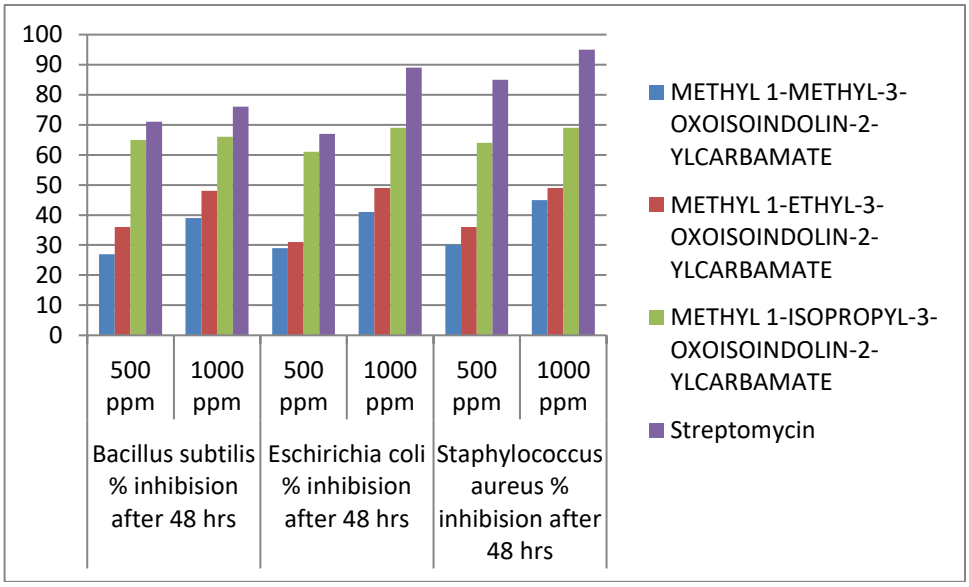


Figure-7: plot of Antibacterial screening data of Isoindolinone Derivatives

Conclusions

Microwave (MW) irradiation is an efficient and environmentally-benign method to accomplish various organic syntheses to afford products in higher yields in shorter reaction periods. The current outcomes showed that varieties of the replacement and the heterocyclic moieties prompted striking changes in the pharmacological, physical and biochemical properties. As it was normal, compound 4c I,e METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE had the most striking nature to antifungal and antibacterial activity than 4a I,e METHYL 1-METHYL-3-OXOISOINDOLIN-2-YLCARBAMATE and 4b I,e METHYL 1-ETHYL-3-OXOISOINDOLIN-2-YLCARBAMATE. Thermal stability data also prevailed that METHYL 1-ISOPROPYL-3-OXOISOINDOLIN-2-YLCARBAMATE was showed low decomposition rate at higher temperature ramp.

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