SYNTHESIS AND CHARACTRAZATION OF SOME γ- LACTAMS COMPOUNDS BY USING [2+3] CYCLOADDITION REACTION

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Abstract

This study is concerned with the synthesis and characterization of the **γ-**lactams **3(a-f)**, These compounds were prepared by reacting 2-bromobenzoyl chlorides with the appropriate imine **2(a-f)**, in the presence of phenyllithuim in tetrahydrofuran (THF) at 0˚C. Addition of 2-bromobenzoyl chlorides to imines affords N-acyliminium ions as adducts. Subsequent reaction of these adducts with phenyllithium at -5˚C to afford **γ-**lactams **(a-f)** in moderate yields(55-73%).and confirmed these compounds by spectral data IR,UV,^{1}H-NMR and Mass spectra.

Introduction

Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines, are important structural motifs in biologically active natural products that are also found in medicinal leads and approved drugs [1] . γ-lactams is commonly known as Heterocyclic compounds. Heterocyclic organic compounds have a structure that contains in its cyclic structure an heteroatom or more in addition to carbon atoms . The importance of heterocyclic compounds is apparent from the wealth and variety of such compounds that occur naturally or are prepared on a commercial scale by the dye and drug industries. Many of these compounds have important physiological functions in plants and animals.[2] γ-lactams have attracted great attention in recent years because they are valuable building blocks in synthesis and due to the presence of a γ-lactam core in the structure of several biologically active molecules. Theγ-lactams,acquired importance after the introduction of Heliotrope amide[3,4]and bis-avenanthramideB[5,6]are examples of ferulic acid amides that undergo biosynthetic dimerization to produce γ-lactams,whereas lactacystin[7] and salinosporamide[8] emanate from more complex biosyntheses.

The expermental

All solvents were distilled /dried prior to use ,when this seemed necessary by standard methods.all solvent extracts were dried over anhydrous sodium sulphate unless other wise specified.

Preparation of Schiff bases2(a-f)[13,14].

General procedure

the Schiff bases were prepared by heat the mixture of 0.01mole amine with 0.01mole aldehyde ,10 mL of ethanol and one drop of glacial acetic acid was heated in water bath at (70-80˚C) for 30 min.The progress of the reaction was checked by TLC.After completion, the solvent evaporated more than recryastalized from a suitable solvent, as shown in (Table 3-1)

preparation of γ-lactams.[15]

1 2-(4-bromophenyl)-3-(4-chlorophenyl)isoindolin-1- one3a.

2-bromobenzoylchloride(0.8g,1.2mmole, 0.5mL)was added drops to N-(4–Bromophenyl)-4-chlorobenzylidine (2a) (1gm,1mmole) in 40ml THFwas added to this at 0C. The reaction mixture was then stirred for(20 min) after that phenyllithum (0.31gm,0.40ml,1.10mmole) in 10ml THF was added drop wise to reaction mixture at -5^{o}C .the reaction mixture was then stirred for (2h) .then left for 1hour at room temperature . The obtained product was filtered, dried and recrystallized by using ethanol.The

purified yet fully sprayed on TLC and overlying layer in 7:3 hexan:ethylacetate later flying TLC dissolved in dichloro methane and filtered after evaporation of the solvent gets γ–lactam pure(3a).Yield%,=73%.,mp=143-145.,IR(KBr):1654cm^{-1}.^{1}H-NMR (DMSO/CDCl3)δ:3.316ppm(s,1H,C3-H), 7.411-7.728(12H,aromatic proton).,Ms spectra: M+.=398m/z.

Preparation of compounds following the same previous method.

2**: 2-(4-bromophenyl)-3-(4-methoxyphenyl)isoindolin-1-one(3b).**

Yield%,=60%.,mp=135-137.,UV: λmax=288nm., IR(KBr):1654cm-^{1}.^{1}H-NMR(DMSO/CDCl3)δ:2.84ppm(s,3H,OCH3), 3.31ppm(s,1H,C3-H)7.41-7.72(12H,aromatic protons).,Ms spectra: M+.=394m/z.

3 : **2-(4-methylphenyl)-3-(4-chlorophenyl)isoindolin-1-one (3c).**

Yield%,=61%.,mp=130-132.,UV: λmax=290nm., IR(KBr):1653cm-^{1}.^{1}H-NMR(DMSO/CDCl3)δ:2.24ppm(s,3H,

CH3-ph), 3.31ppm(s,1H,C3-H)7.14-7.71(12H,aromatic protons).,Ms spectra: M+.=333m/z.

4 **: 2-(4-methylphenyl)-3-(4-methoxyphenyl) isoindolin-1-one(3d).**

Yield%,=55%.,mp=140-142.,IR(KBr):1672cm-^{1}.,^{1}H-NMR(DMSO/CDCl3) δ:2.273ppm(s,3H,CH3-Ph), 2.98ppm(s,3H,OCH3),3.31ppm(s,1H,C3-H)7.13-7.71(12H,aromatic protons).,Ms spectra: M+.=329m/z**.**

5**: 2,3-(4-chlorophenylisoindoline)-1-one.(3e)**.

Yield%,=66%.,mp=118-120., IR(KBr):1653cm-^{1}.

6:**2-(4-bromophenyl)-3-[4-(dimethylamino)phenyl]isoindolin-1-one(3f).**

Yield%,=72%.,mp=144-146., IR(KBr):1670cm^{-1}.

Results and discussion

Taking a lead from recent earlier studies ,[9,10] we considered to affords

γ-lactams 3(a-d)	Yield (%)	m.p. (°C)	colour
3a	73	143-145	White
3b	60	135-137	White
3c	61	130-132	Whi te
3d	55	140-142	White
3e	66	118-120	White
3f	72	144-146	White

N-acylimini um ions. Consistin g of Addition 2-bromobe nzoyl chlorides to mines. Subsequ ent reaction with

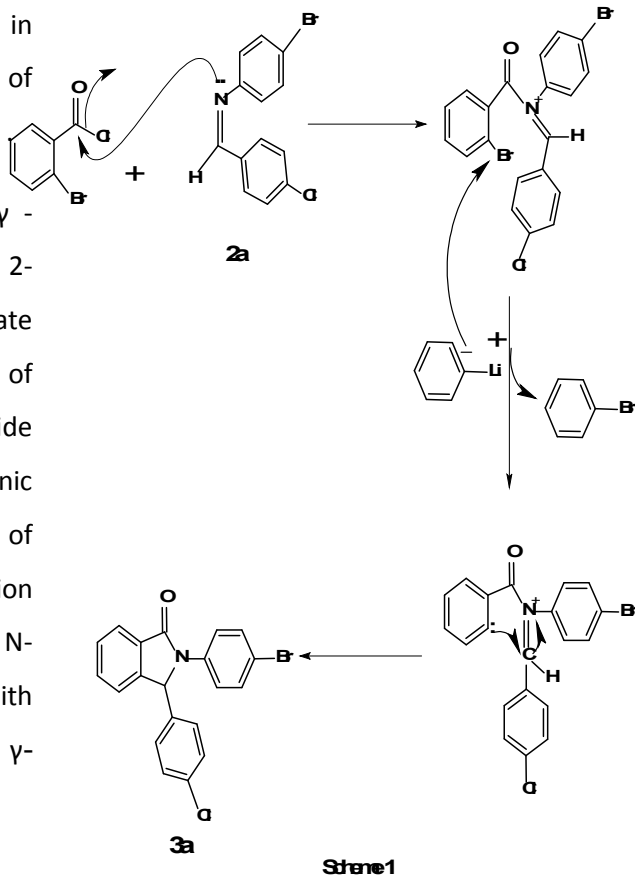
presence phenyllithiumin for the synthesis of γ-lactam**.**

in view of associated biological activity and utility in organic synthesis ,synthesis γ-lactams **3(a-f)** was performed.So,the key step involved the treatment of the imines **2(a-f)** with acid chloride by using phenyllithium in tetrahydrofuran (THF) under the condition required for reaction to afford γ-lactams3(a-f) , as shown in Scheme1.

required for this study was prepared by treatment 2-bromobenzoyl chloride with the appropriate imines **2(a-f)** by using phenyllithium as a base in THF at 0 °C. Various imines **2(a-f)** were prepared from

the appropriate aldehydes and amines in methylenechloride in the presence of molecular sieves (4Aº) or in hot ethanol

As mentioned in the beginning, the γ -lactams **3(a-f)** were prepared from 2-bromobenzoyl chloride and appropriate imines **2(a-f)** in presence of phenyllithium.The active acidchloride reacted with imines the double electronic attack of imine on the carbonyl group of acid chloride and leave the chloride ion Which produces intermediate N-acyliminium ions as adducts with presence phenyllithium to afford γ-lactams in moderate yields.



2a

3a

Scheme1

the structures of these γ-lactams were established on basis of spectral data**UV**, **IR,Mass,**^{1}**HNMR** spectra .

These compounds 3b and 3c were characterized by a light white colour and show a strong UV absorption λmax = 288for 3b, λmax = 290 for 3c

in ethanol solvent. Those bands belong to the transitions π-π* The spectra were shown in Figures (3-1) and (3-2)

IR spectra of these compounds **3(a-f)** showed strong stretching absorpition band at 1653-1672cm^{-1}for**(c=o)**as showed figure (3-3),(3-4),(3-5) and(3-6) frequencies of carbonyl groups **(C=O)** depended upon the nature of substituents at adjacent nitrogen atom.

The 1HNMR spectral data of γ-lactams are included most of their spectra are shown in figures (3-7),(3-8).The ^{1}H-NMR spectra of **2-(4-bromophenyl)-3-(4-chlorophenyl)isoindolin-1-one(3a)** showed singlet peak at 3.316 ppm for one proton (*s*,1H, C_3-H). And the^{1}H-NMR spectra of **3a** showed aromatic protons about 13 proton at δ(7.411-7.728) ppm**.**

The 1H-NMR spectra of **2-(4-bromophenyl)-3-(4-methoxyphenyl)isoindolin-1-one(3b).** showed singlet peak for methoxy group at δ 2.846ppm (s,3H,OCH3-Ph) and showed singlet peak at 3.316 ppm for one proton(s,1H, C3-H).and 1H-NMR spectra of 3b showed aromatic protons about 16H at δ(7.412-7.729) ppm.

also the 1H-NMR spectra of **3-(4-chlorophenyl)-2(4-methylphenyl)isoindolin-1-one(3C).** showed singlet peak at 2.241 ppm for methyl group(s,3H,CH3-Ph) and showed singlet peak at 3.318 ppm for one proton (s,1H, C3-H). 1H-NMR spectra of (3c) shows In the aromatic region 16 proton at δ(7.142-7.714) ppm .

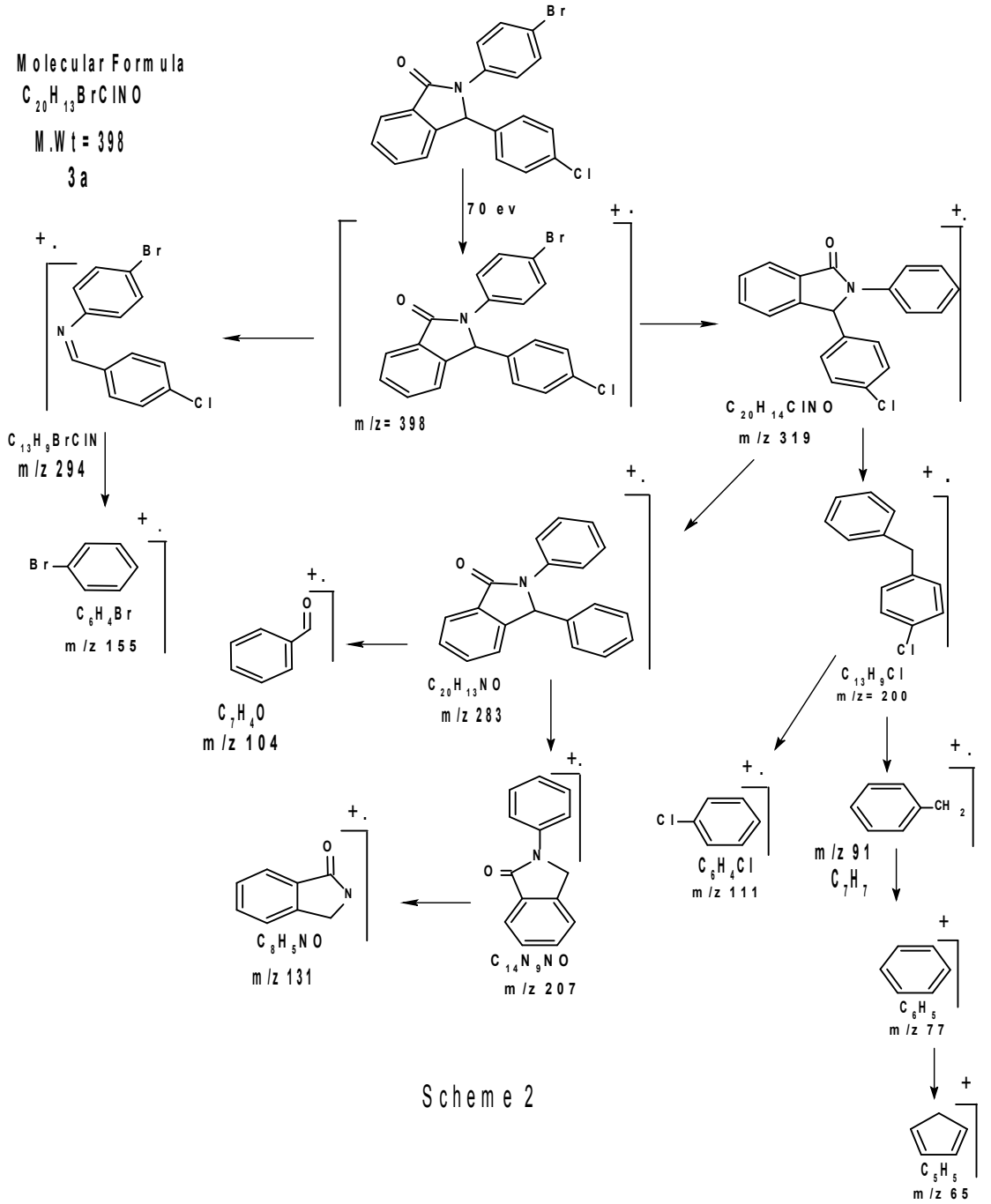
The 1H-NMR spectra of **3-(4-methoxyphenyl)-2-(4-methylphenyl)isoindolin-1-one(3d).**showed singlet peak for methyl group at δ 2.273ppm (s,3H,CH3-Ph) and showed singlet peak at 2.984 ppm for methoxy group (s,3H, OCH3-Ph) also showed singlet peak at 3.314 ppm for one proton (s,1H, C3-H)..and 1H-NMR spectra of 3d showed aromatic protons about 19H at δ(7.139-7.713) ppm.

The mass spectral data of the prepared derivatives are gathered in the figures (3-9),(3-10).

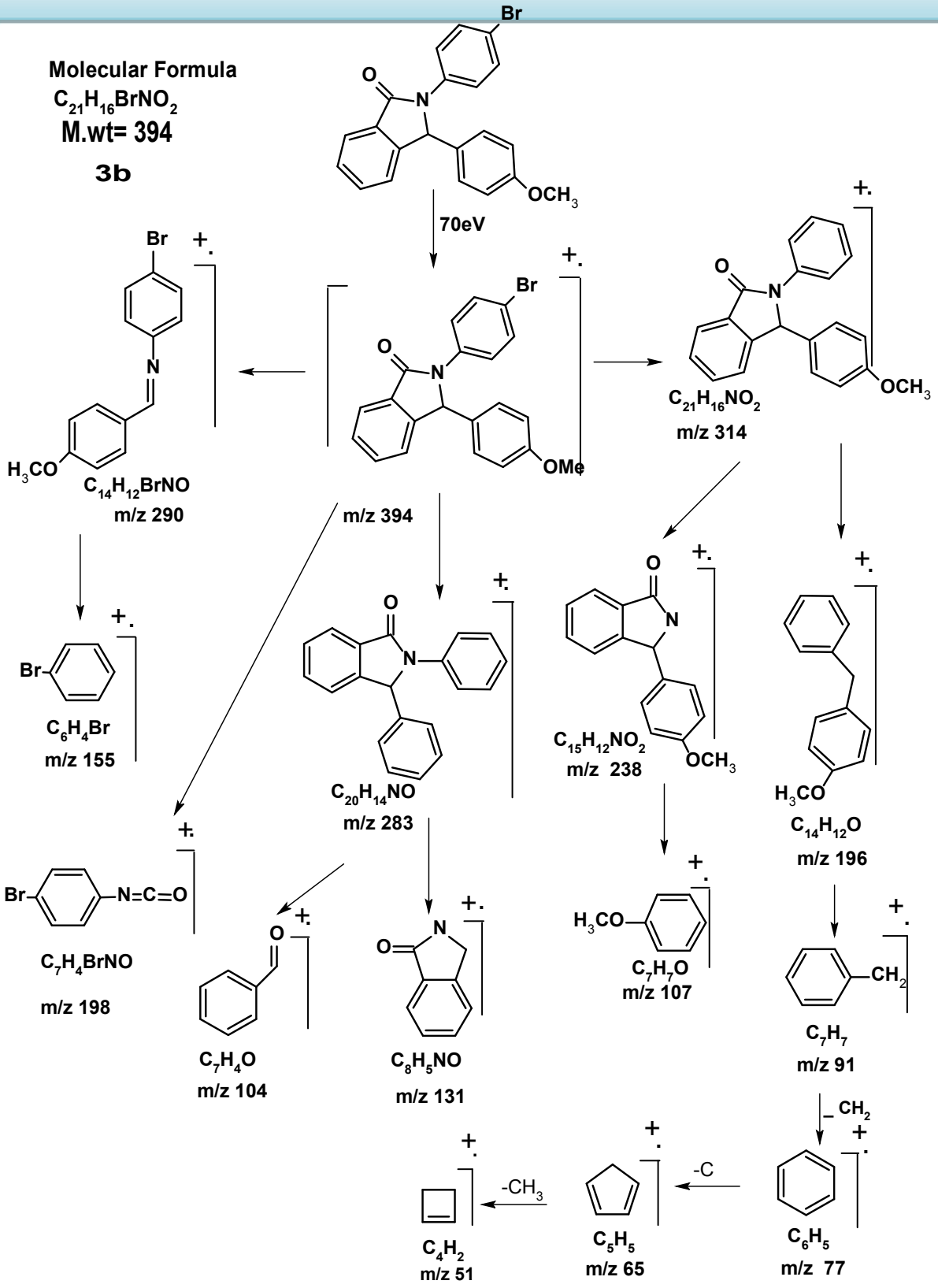
The mass spectra of compound 3a,3b,3c and 3d showed the molecular ion peak corresponding to the particular compound M 398m/z,394 m/z,333 m/z and 329m/z.The fragmentation of 3a showed isocyantes peak in 198m/z , imine peak in 294m/z and Appearance peak of γ-lactam ring merged with benzen ring in 131m/z. Also fragmentation of 3b showed isocyantes peak in 198m/z , imine peak in 290m/z and showed peak of γ-lactam ring merged with benzen ring in 131m/z.

The mass spectra of 3c showed isocyantes peak in 133m/z , imine peak in 229m/z and showed peak of γ-lactam in 131m/z .

Finally The fragmentation of 3d showed isocyantes peak in 133m/z , imine peak in 225m/z and peak of γ-lactam ring merged with benzen ring in 131m/z. Also, all compounds3(a-d) show packs of trobeleom ion in 91m/z and the benzene ring in 77m/z. the fragmentation mechanism of compounds 3(a-d) is shown below[11,12]in Schemes 2,3,4and 5.

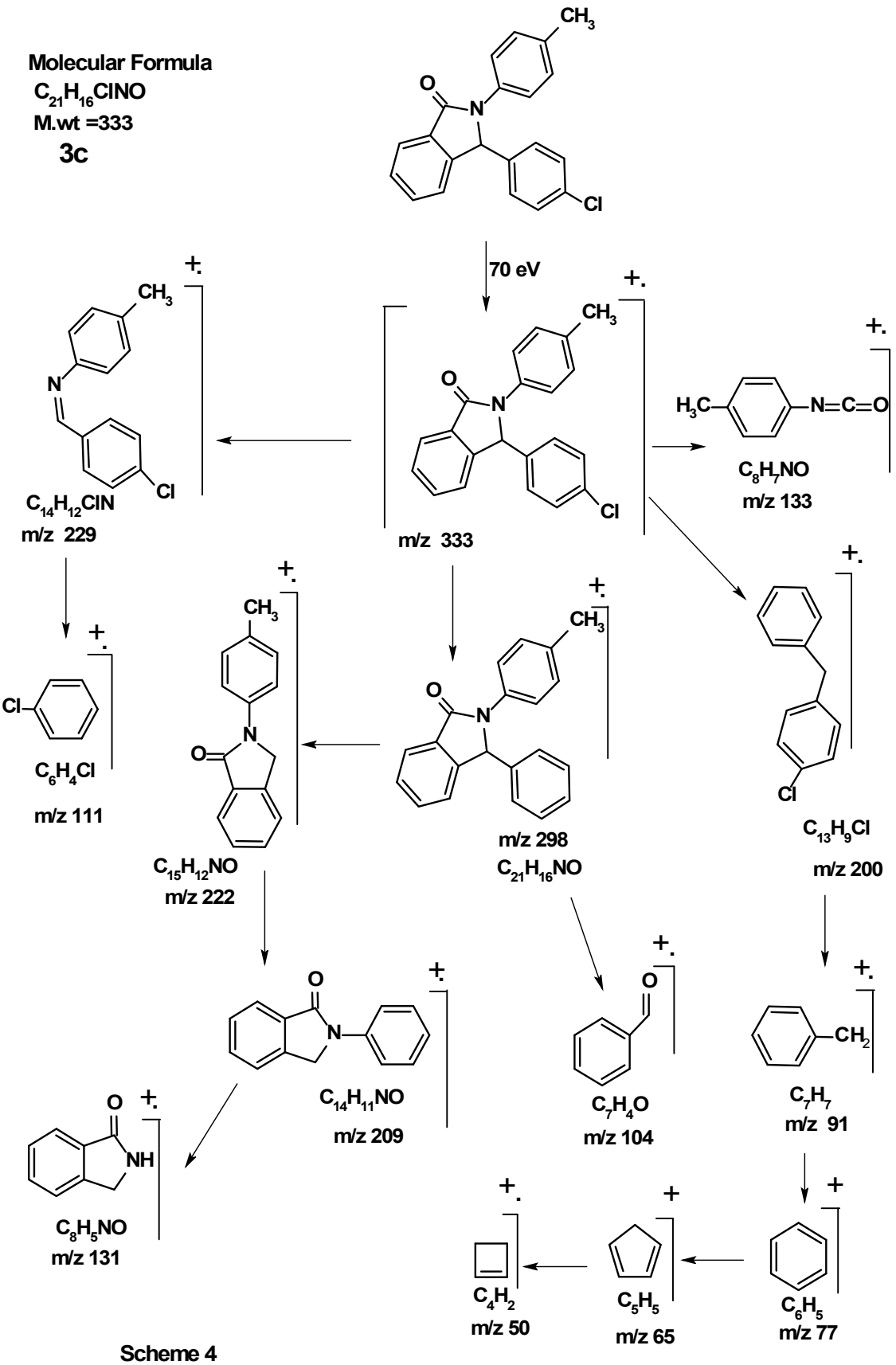


Scheme 2

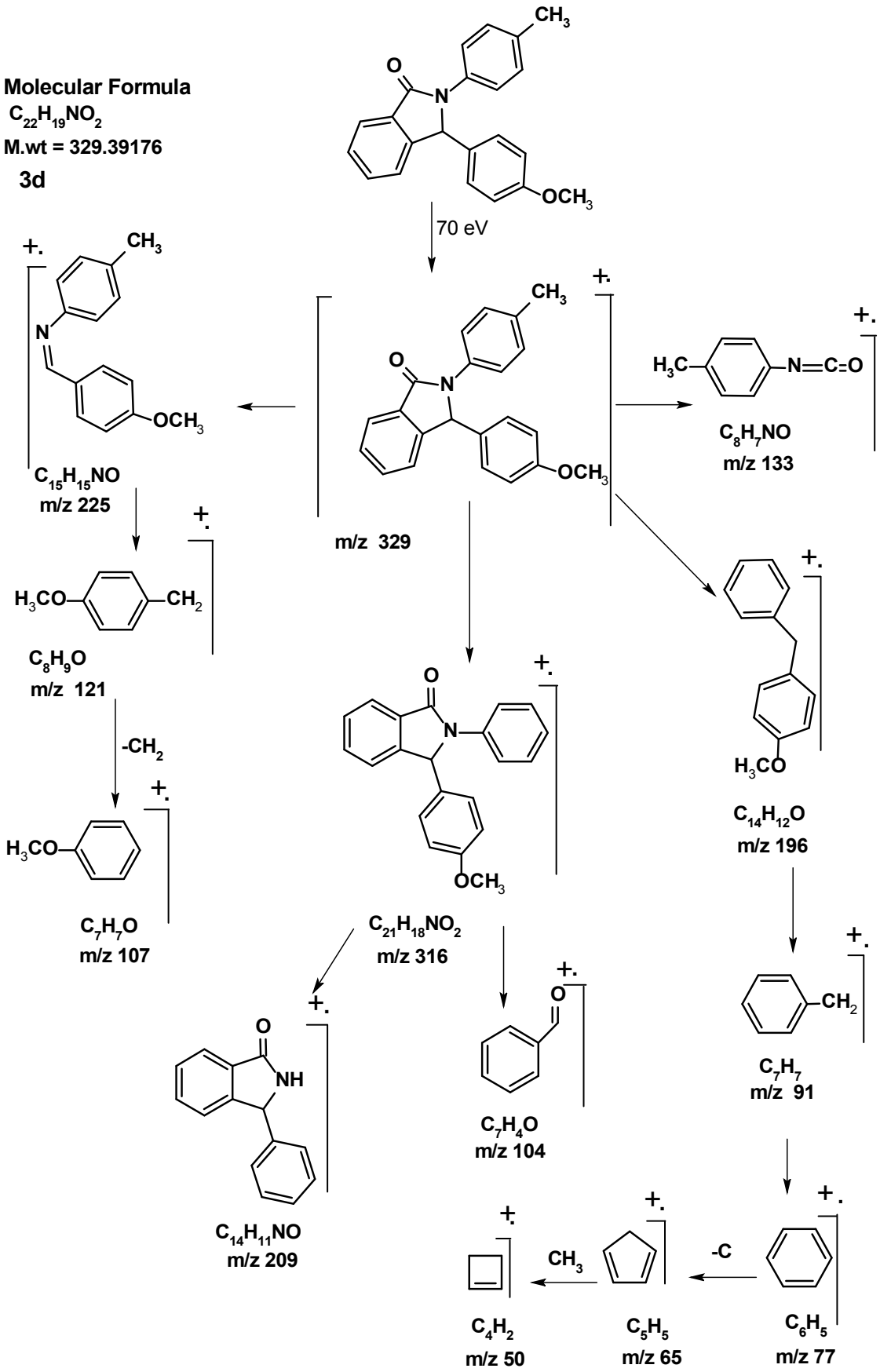

Molecular Formula
C21H16BrNO2
M.wt= 394
3b
70eV
m/z 394
C14H12BrNO
m/z 290
C21H16NO2
m/z 314
C6H4Br
m/z 155
C20H14NO
m/z 283
C15H12NO2
m/z 238
C14H12O
m/z 196
C7H4BrNO
m/z 198
C7H4O
m/z 104
C8H5NO
m/z 131
C7H7O
m/z 107
C7H7
m/z 91
C4H2
m/z 51
C5H5
m/z 65
C6H5
m/z 77
-CH3
-C
-CH2

Scheme 3

Scheme4


Molecular Formula
C21H16ClNO
M.wt =333
3c
70 eV
m/z 333
C14H12ClN
m/z 229
C8H7NO
m/z 133
C6H4Cl
m/z 111
C15H12NO
m/z 222
m/z 298
C21H16NO
C13H9Cl
m/z 200
C14H11NO
m/z 209
C7H4O
m/z 104
C7H7
m/z 91
C8H5NO
m/z 131
C4H2
m/z 50
C5H5
m/z 65
C6H5
m/z 77

Scheme 4


Molecular Formula
C22H19NO2
M.wt = 329.39176
3d
70 eV
m/z 329
C15H15NO
m/z 225
C8H9O
m/z 121
C7H7O
m/z 107
-CH2
C8H7NO
m/z 133
C14H12O
m/z 196
C7H7
m/z 91
C21H18NO2
m/z 316
C7H4O
m/z 104
C14H11NO
m/z 209
C6H5
m/z 77
C5H5
m/z 65
C4H2
m/z 50
-C
CH3

Scheme 9

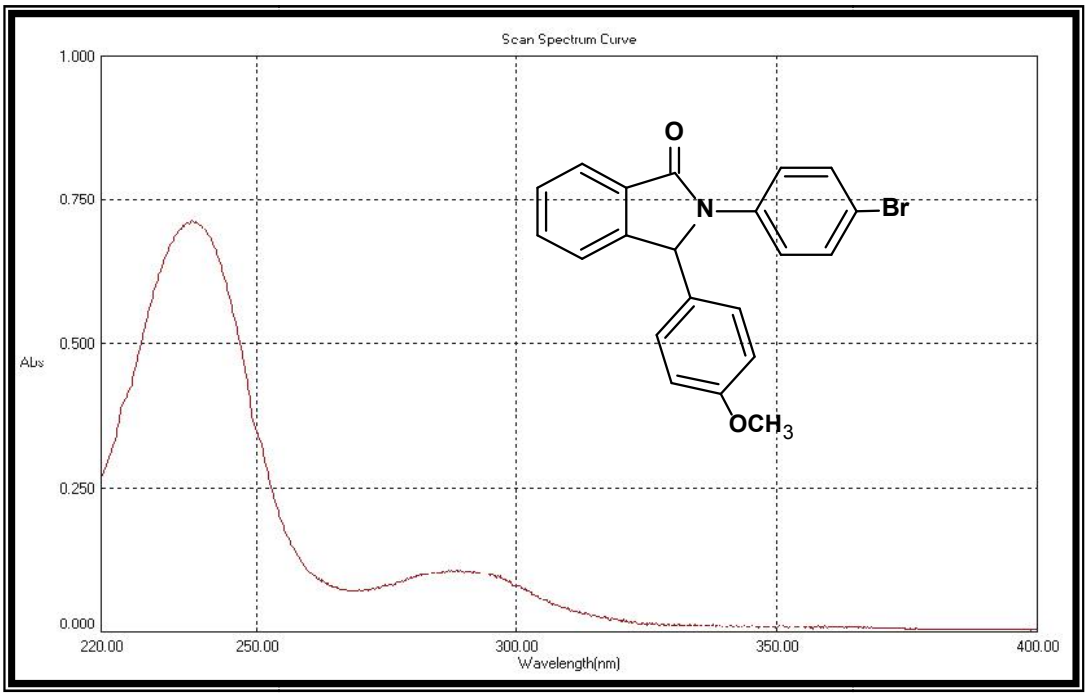


Figure (3-1) :**UV** spectrum of 2-(4-bromophenyl)-3-(4- methoxyphenyl)isoindolin-1-one **(3b)**.

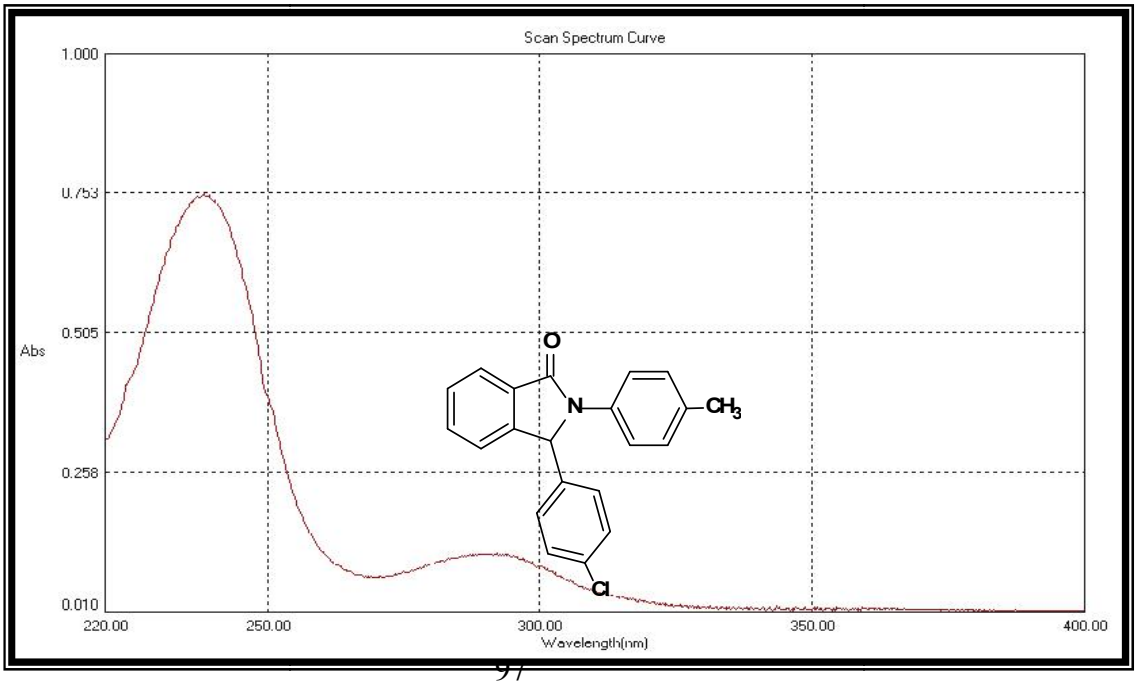
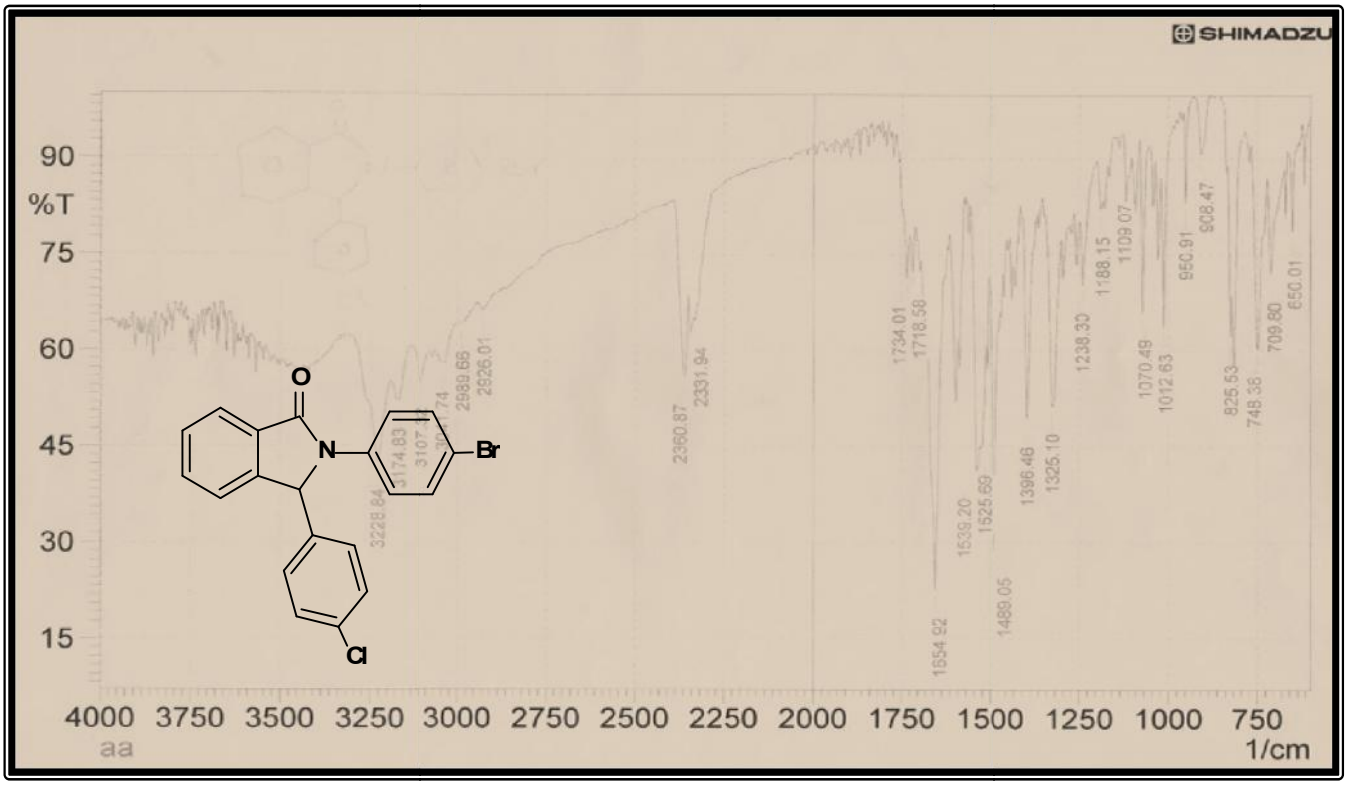
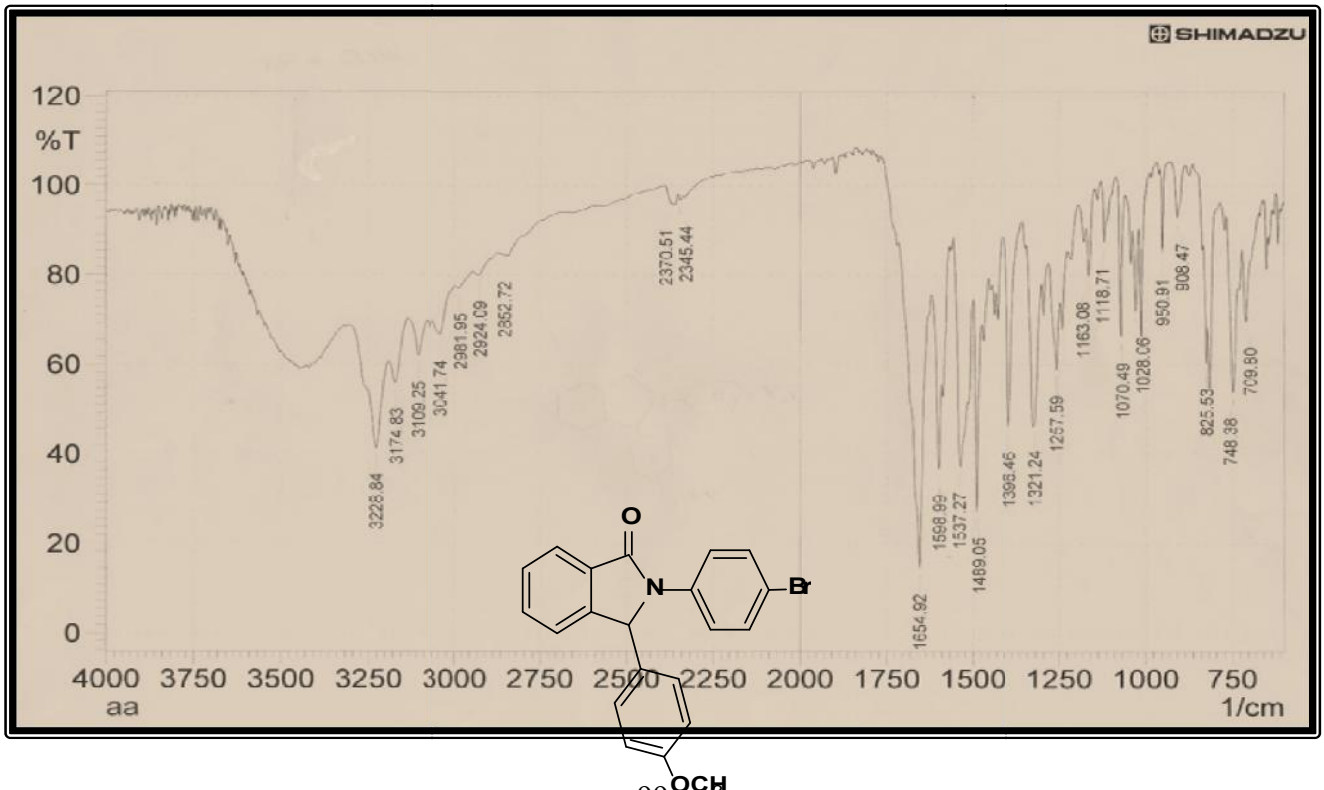


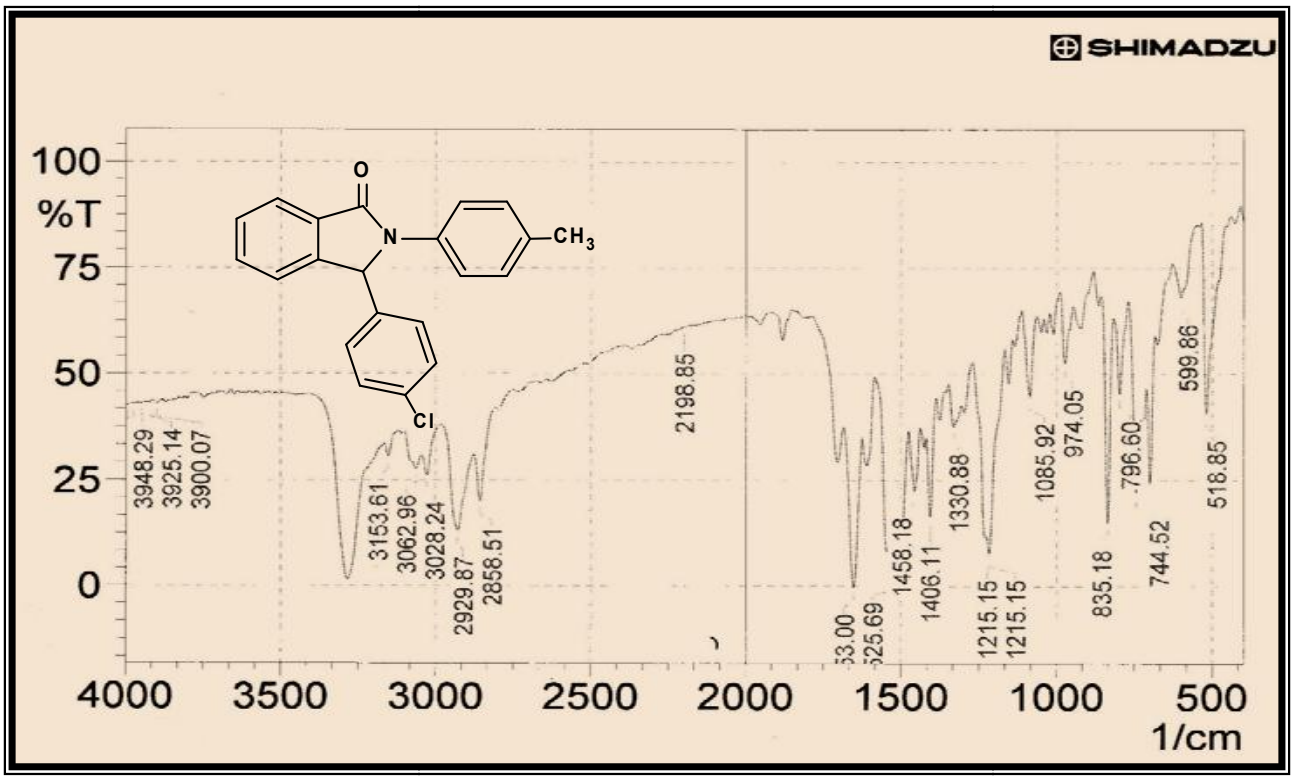
Figure (3-2) :**UV** spectrum of 3-(4-chlorophenyl)-2-(4-methylphenyl)isoindolin-1-one **(3c).**



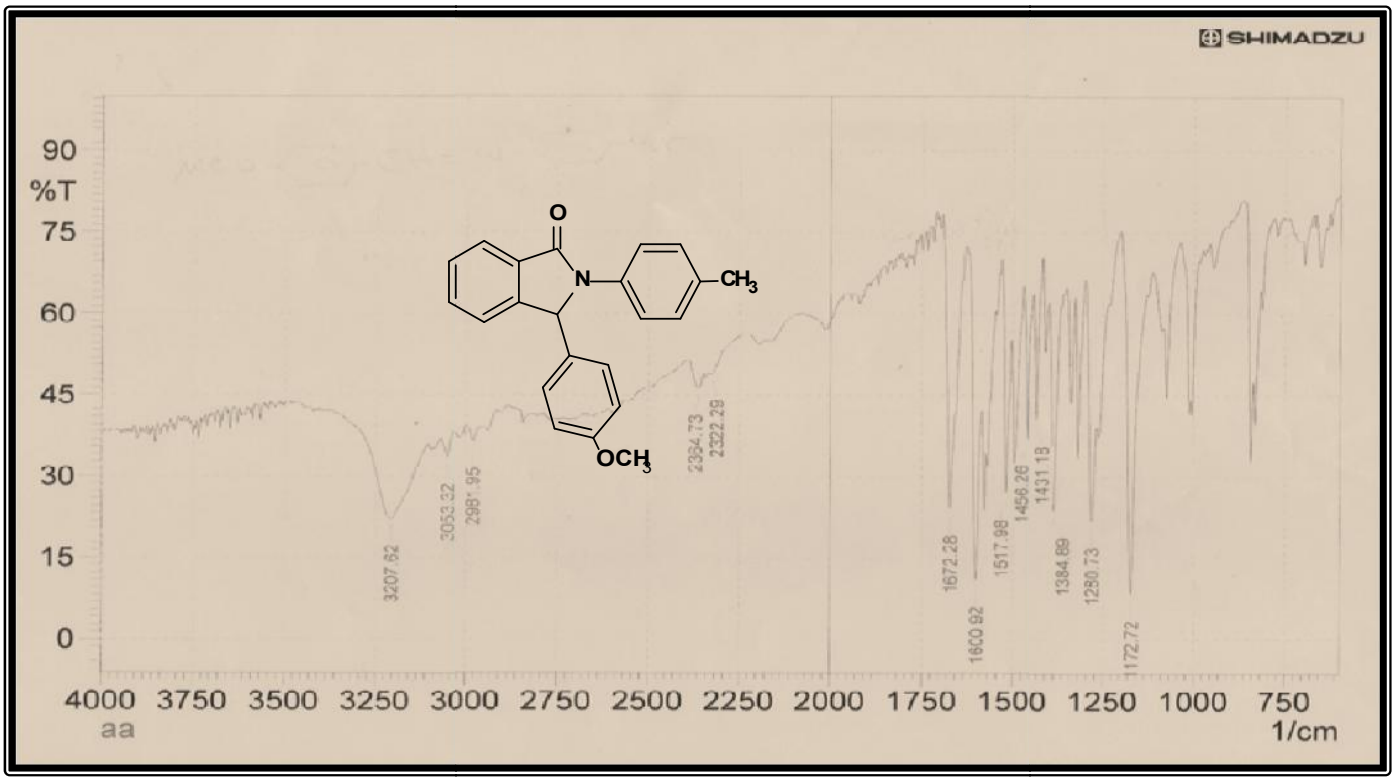
Figure(3-3):**FT-IR** spectrum of 2-(4-bromophenyl)-3-(4-chlorophenyl)isoindolin-1-one**(3a).**



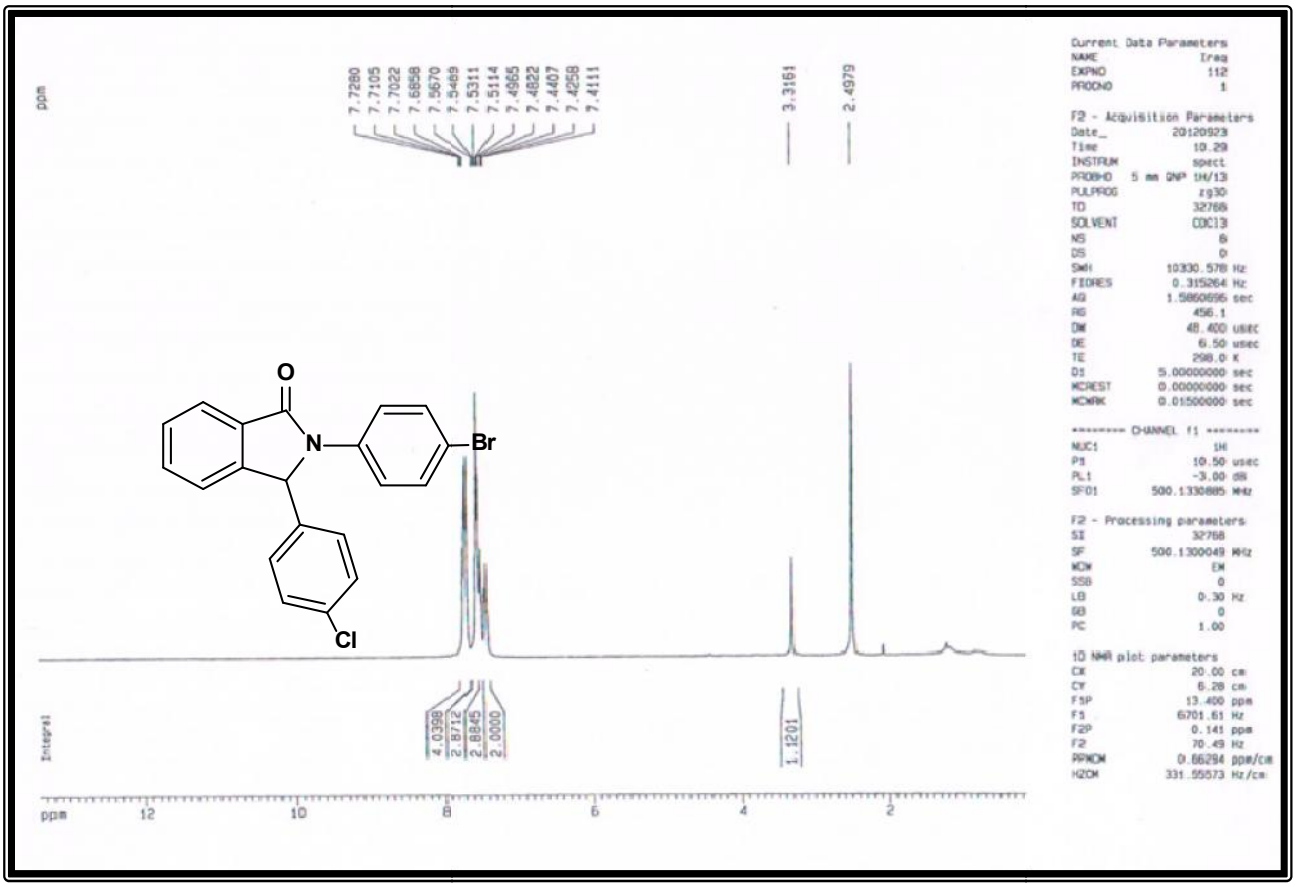
Figure(3-4):**FT-IR** spectrum of 2-(4-bromophenyl)- 3-(4-methoxyphenyl)isoindolin-1-one **(3b).**

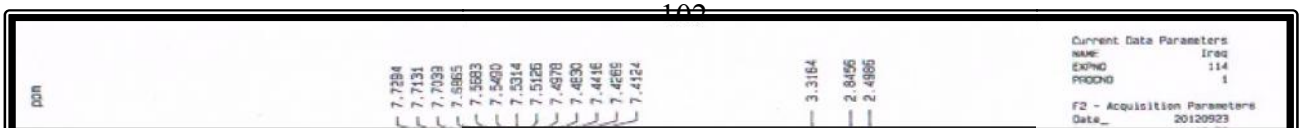


Figure(3-5):**FT-IR** spectrum of 3-(4-chlorophenyl)-2-(4-methylphenyl)isoindolin-1-one (3c).

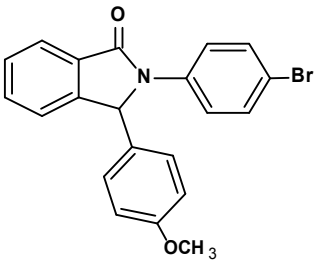


Figure(3-6):**FT-IR** spectrum of 3-(4-methoxyphenyl)-2-(4-methylphenyl)isoindolin-1-one**(3d).**

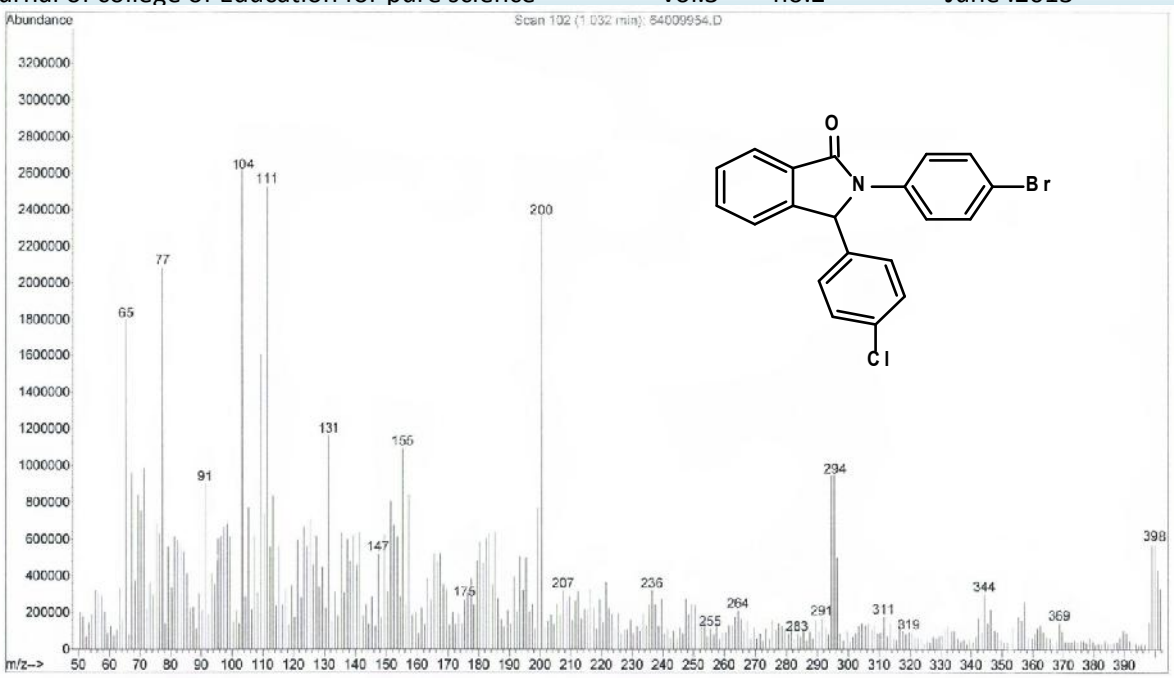




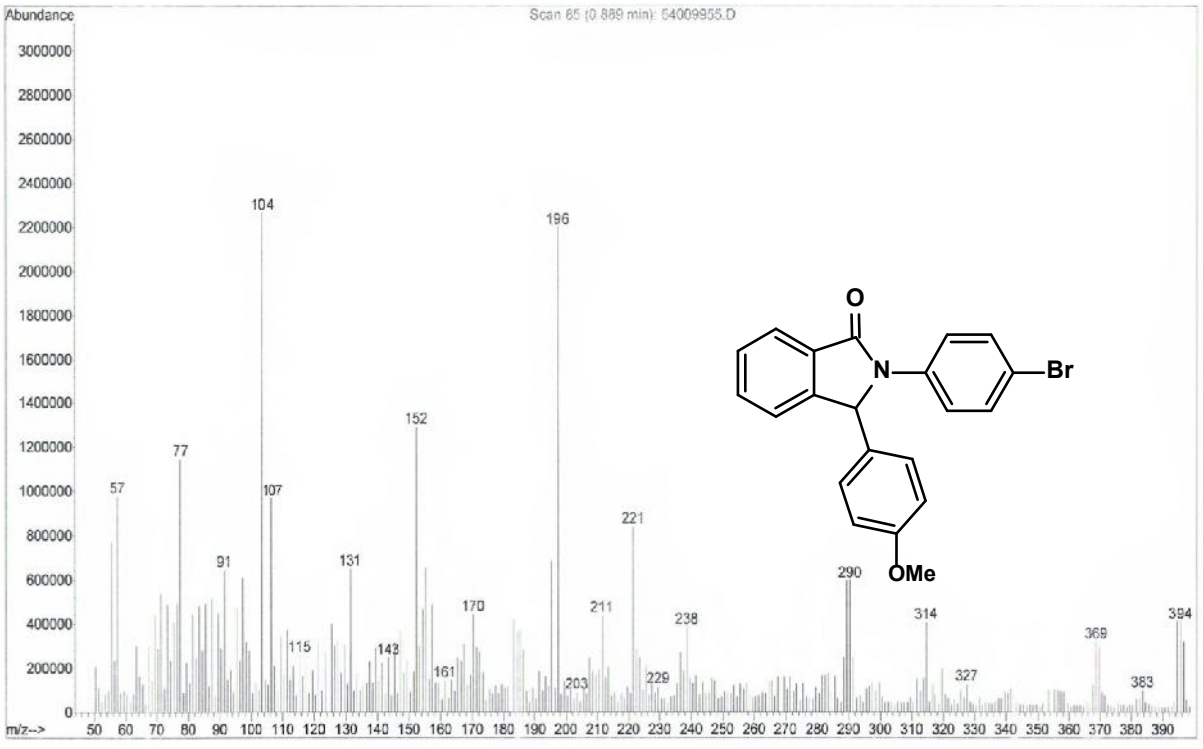
Figure(3-7):^{1} **H NMAR** spectrum of 2-(4-bromophenyl)-3-(4-chlorophenyl)isoindolin-1-one**(3a).**



Figure(3-8):^{1} **H NMAR** spectrum of 2-(4-bromophenyl)-3-(4-methoxyphenyl)isoindolin-1-one **(3b)**



Figure(3.9): **Mass** spectrum of 2-(4-bromophenyl)-3-(4-chlorophenyl)isoindolin-1-one**(3a).**



Figure(3.10): **Mass** spectrum of 2-(4-bromophenyl)-3-(4-methoxyphenyl)isoindolin-1-one**(3b).**

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تخليق وتشخيص بعض مركبات الكاما-لاكتام باستخدام تفاعل الاضافه الحلقيه من نوع [3+2]

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الملخص

تضمنت الدراسة تخليق و تشخيص بعض مركبات γ-لاكتام التي تم تحضيرها من تفاعل حامض 2-بروموبنزويل كلورايد مع بعض قواعد شيف المحضرة بأستخدام تتراهايدروفيوران الجاف كمذيب عند درجة 0C° حيث ينتج مركب بوطي ن-اسايل امونيوم ايون والذي يتفاعل مع الفنيل ليثيوم بدرجة حرارة 5C- ليعطي مركبات γ-لاكتام المقابله 3(a-f) وبحصيلة بلغت 55-73%.وشخصت تلك المركبات باستخدام الأطياف تحت الحمراء وفوق البنفسجية وطيف بروتون الرنين النووي المغناطيسي وطيف الكتله.