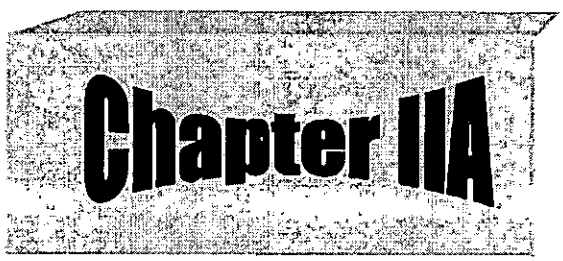


A Novel Synthetic Approach towards N-phenyl-succinimides from γ-lactam-2-carboxylic acid Derivatives by the Dual Oxidant CAN/$NaBrO_3$

IIA.1 Introduction:

A large number of five-member heterocyclic compounds containing a dicarboximide unit (O=CNC=O) have been reported to possess CNS (central nervous system) activity.[1] The simplest member of this class is the succinimides and they are an important class of heterocyclic compounds with numerous applications in different fields.[2]

N-(3, 5-Dichlorophenyl) succinimide (NDPS) was developed as an agricultural fungicide in Japan during the early 1970s (Fujinami *et al.*, 1971, 1972). Although NDPS was a highly efficacious agent, potential health concerns associated with NDPS exposure have limited its usefulness in agriculture. Nonetheless, NDPS is still available in several countries, including the United States. The primary toxicity induced by exposure to NDPS is nephrotoxicity.[3]

The succinimide derivatives also have depressant activity and are used as anticonvulsants, sedatives, and muscle relaxants.[4]

In medicine, they have been used for the treatment of arthritis, tuberculosis, convulsion and epilepsy. They are considered as bioisosteres of hydantoins,[5] a heterocycle widely exploited in the synthesis of combinatorial libraries.[6] In organic synthesis they have been used as valuable reagents and intermediates for the synthesis of natural and unnatural compounds.[7] Recently, succinimide-based pseudopeptides have been shown to stabilize β-turn conformations.[8] It has also been shown that they can be used as irreversible protease inhibitors.[9]

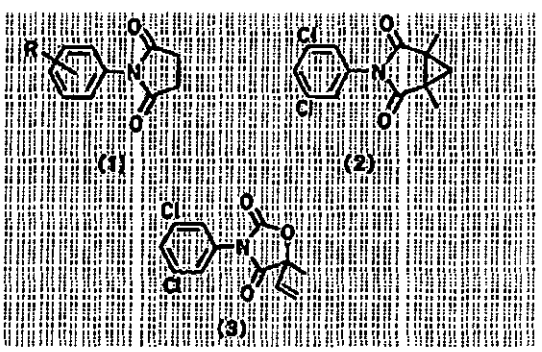
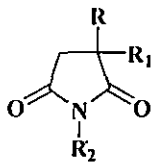


Figure 1

Succinimide derivatives like *N*-phenylsuccinimides **(I),** procymidone **(2),** and vinclozolin **(3)** (Figure 1). show fungicidal activity against ***Sclerotinia sclerotiorum*** and ***Botrytis cinerea.***[10] Phensuximide **(4a),** methsuximide **(4b),** and ethosuximide **(4c)** (Figure 2) are used in the treatment of petit mal epilepsy.[11] The fact that epilepsy is found in 0.5-1.0% of the general population constitutes a major public health problem. Epileptics frequently have a feeling of inferiority and self-consciousness with total withdrawal from society. A further complication for the epileptic is that many of the anticonvulsant agents have some degree of undesirable side effects.

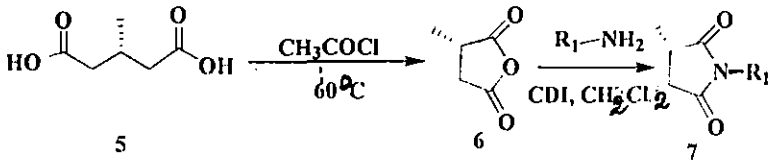


4a, R= C_6H_5; R_1= H ; R_2= CH_3
b, R= C_6H_5; R_1= CH_3 ; R_2= CH_3
c, R= C_2H_5; R_1= CH_3 ; R_2= H

Figure 2

Despite their wide applicability, available routes for the synthesis of imide derivatives are limited. Among them, the dehydrative condensation of an anhydride and an amine at high temperature[12] and then cyclization of the amic acid in the presence of acidic reagents are the typical methods of choice.[13] The direct *N*-alkylation of maleimide with alcohols under Mitsunobu reaction conditions is an alternative method for the synthesis of imide derivatives in reasonably good yield.[14] However, each of these routes has its own synthetic problems when applied to a range of derivatives. Therefore, synthesis of functionalized imide derivatives is still a challenging endeavor.

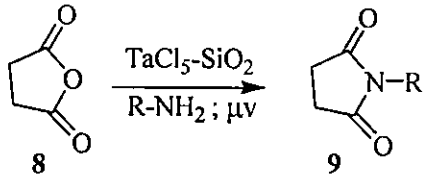
Pohlmann *et al.*[15] had synthesized *N*-substituted succinimides from (S)-(-)-methylsuccinic acid **5**. Treatment of (*S*)-(-)-methylsuccinic acid **5** with acetyl chloride yielded anhydride **6**. The formation of diverse *N*-substituted pyrrolidinediones **7** was achieved by reaction with the appropriate primary amines, hydroxylamines or hydrazines in the presence of *N,N'*-carbonyldiimidazole (CDI) (**Scheme 1**).



R_1 = OBn
CH_3
cyclopropyl
$CH_2CH_2OCH_3$
OCH_2CH_3
$N(CH_3)Cbz$
$N(CH_3)_2$

Scheme 1

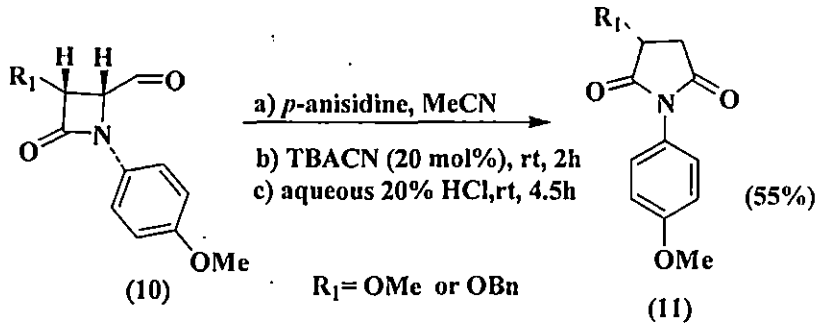
Chandrasekhar *et al.*[16] reported for first time a $TaCl_5$-silica gel catalyzed imide synthesis under microwave irradiation. Succinic anhydride **8** (1 mmol) and benzyleamine (1mmol) were absorbed on activated silica gel (100-200 mesh, dried overnight at 100°C) and stirred at room temperature for 1h under inert atmosphere. To this was added $TaCl_5$-SiO_2 (10 mol %) and mixed thoroughly and irradiated on a microwave oven (448 watt) for 5 min. Purification of the mixture and removal of the volatile furnished *N*-benzyle succinimide **9** (**Scheme 2**).



Scheme 2. Synthesis of Succinimides 9 from succinic anhydride 8.

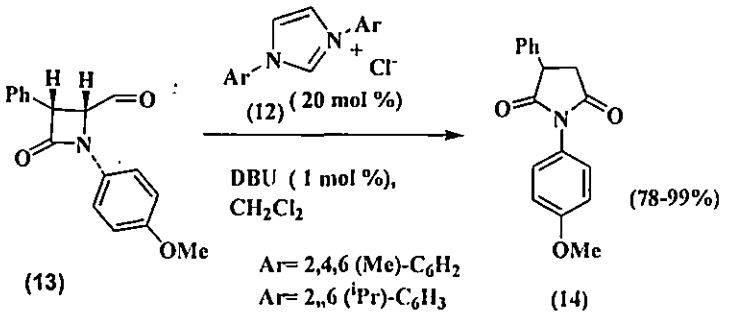
Several groups had also been used *β*-lactam derivatives for the preparation of succinimide derivatives.

Alcaide *et al.*[17] reported that the azetidin-2-ones (*β*-lactam) **10** on treatment with *p*-anisidine and catalytic (20 mol %) amount of tetrabutylammonium cyanide (TBACN) in acetonitrile and subsequent hydrolysis of the reaction mixture in situ with aqueous HCl furnished *N*-aryl succinimide derivatives **11**(**Scheme 3**).



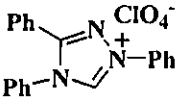
Scheme 3. One-Pot Synthesis of Succinimides 11 from β-Lactam Aldehydes 10.

N-Heterocyclic carbene (NHC) has been employed as an efficient catalyst for ring expansion of 4-formyl-β-lactams, allowing the facile synthesis of succinimide derivatives.[18]



Scheme 4. One-Pot Synthesis of Succinimides 14 from β-Lactam Aldehydes 13.

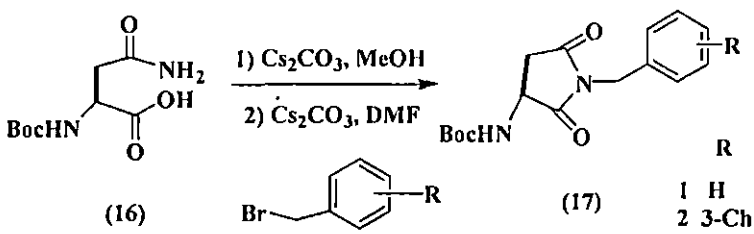
In the presence of 20 mol % of imidazolium chloride **12** and DBU, 4-formyl-β-lactam **13** was smoothly converted to succinimide **14** in 2 h at room temperature in 80% yield (**Scheme 4**).



(15)

Triazolium salt **15** was also a good catalyst, affording **14** in 76% yield.

Reaction of *N*-tert-butyloxycarbonylasparagine (Boc-Asn) **16** with 2 equiv of benzyl bromide in presence of cesium carbonate led to *N*-benzyl-3-Boc-amino-pyrrolidin-2,5-dione **17** (*N*-benzyl-3-Boc-aminosuccinimide).[19]



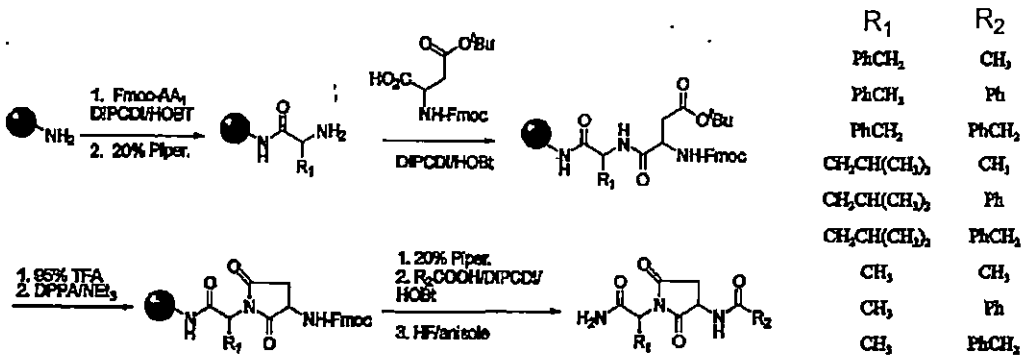
	R	Yields (%)
1	H	70
2	3-Chloro	71
3	4-Fluoro	38
4	4-Cyano	55
5	4-Methoxy carbonyl	67
6	4-Nitro	13

Scheme 5

Cesium carbonate (2.63 mmol) was added to Boc-Asn **16** (0.88 mmol) in 5mL of DMF. The mixture was stirred for 2 days at room temperature to complete the salt formation and then benzyl bromide (2.2 mmol) was added to it. After stirring for 6 h at room temperature, 1-Benzyl-3-Bocaminosuccinimide **17** was isolated in around 70% yield (**Scheme 5**).

Solid phase synthesis of succinimides have also been reported to date.[20]

A 'tea-bag' methodology,[21] for the synthesis of 1,3-disubstituted succinimides is illustrated in **Scheme 6.** The strategy used is based on the intramolecular cyclization of a dipeptide containing aspartic acid in the second position promoted by diphenylphosphorylazide (DPPA) and triethylamine.[22]



R_1	R_2
$PhCH_2$	CH_3
$PhCH_2$	Ph
$PhCH_2$	$PhCH_2$
$CH_2CH(CH_3)_2$	CH_3
$CH_2CH(CH_3)_2$	Ph
$CH_2CH(CH_3)_2$	$PhCH_2$
CH_3	CH_3
CH_3	Ph
CH_3	$PhCH_2$

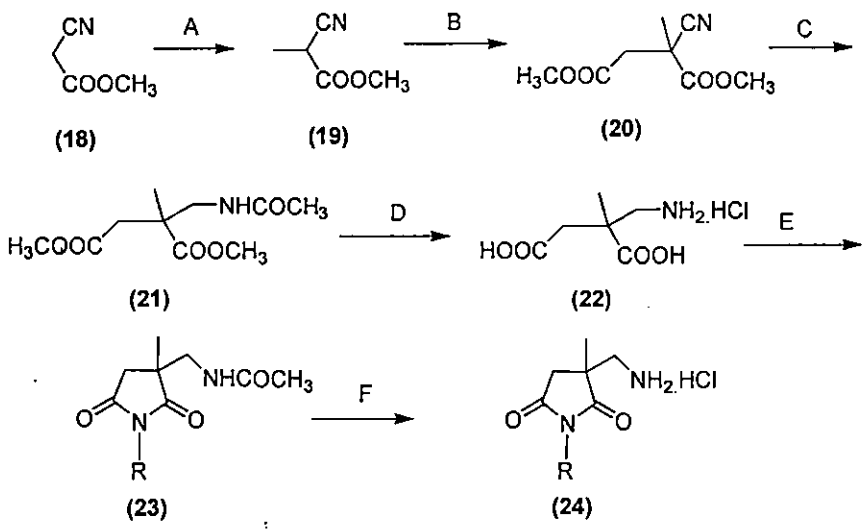
Scheme 6. Solid phase synthesis of 1,3-disubstituted succinimides

After neutralization of the resin (*p*-Methylbenzhydrylamine (MBHA) resin) with 5% diisopropylethylamine (DIPEA) in dichloromethane and washing with DCM, the Fmoc amino acid was coupled using hydroxybenzotriazole (HOBT) and

diisopropylcarbodiimide (DIPCDI,) in dimethylformamide. Removal of the Fmoc group was achieved using 20% piperidine in DMF. The ^{t}Bu ester of the aspartic acid was coupled using the same procedure. Deprotection of the ester with 95% TFA in DCM generates the free carboxylic acid. The cyclization takes place by heating the resin-bound dipeptide at 70°C overnight using a sixfold excess of diphenylphosphorylazide (DPPA) and Et_3N in THF. The Fmoc group was removed and the amine acylated with a carboxylic acid in the presence of DIPCDI and HOBt in DMF. The resin was cleaved with anhydrous HF and anisole (95:5) at 0°C for 1.5 h. The product was extracted with acetic acid (95%) and lyophilized to yield the desired succinimide. AcOH is a good solvent for lyophilizing hydrophobic compounds, since it can be lyophilized at both dilute and high concentrations.

A series of aminomethyl-substituted cyclic imides systems have been prepared by Stratford *et al.*[23] They designed the compounds on the basis of a potential interaction in the γ-aminobutyric acid (GABA) neurotransmitter system and evaluated for anticonvulsant activity (**Scheme 7**).

The route employed for the methyl-substituted succinimides is outlined in Scheme 7. Reductive methylation of methyl cyanoacetate **18** produced crude propionate derivative **19** (which was not further purified due to extensive decomposition on attempted distillation).Treatment of crude **19** with sodium methoxide in methanol, followed by ethyl bromoacetate, provided nitrile diester **20.** Several methods of reduction of nitrile **20** were investigated without success; however, amide **21** was eventually obtained in 89% yield upon hydrogenation over Raney nickel W-2 in acetic anhydride-sodium acetate. Acid-catalyzed hydrolysis then afforded the common intermediate **22** in good yield. Succinimide **23** was prepared by the acetic anhydride dehydration procedure and subsequent hydrolysis of the amide bond by 1N HCl produced the corresponding amino-methyl substituted succinimide derivatives **24**.

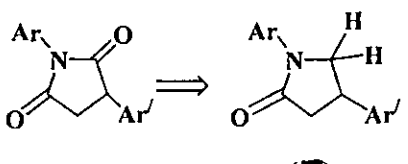


Reaction Condition: **A**= $(CH_2O)_n$, piperidine acetate, 5% Pd/C, H_2; **B**= $BrCH_2CO_2Et$, NaOMe, MeOH; **C**= H_2, Ra-Ni, Ac_2O, NaOAc; **D**= 1 N HCl; **E**= Ac_2O, NaOH, H_2O, R-NH_2, then fuse at 185°C; **F**= 1 N HCl;

Scheme 7

As part of a program aimed at exploring new reactivity patterns for the **γ-lactam nucleus** and subsequent synthetic applications, we now eager to document a catalytic synthesis of pyrrolidine-2,5-diones (succinimides) keeping in mind that modification of the γ-lactam ring is crucial in determining the biological activity of these derivatives.

This can be done only by oxidation of lactam ring **I**. (**Scheme 8**).



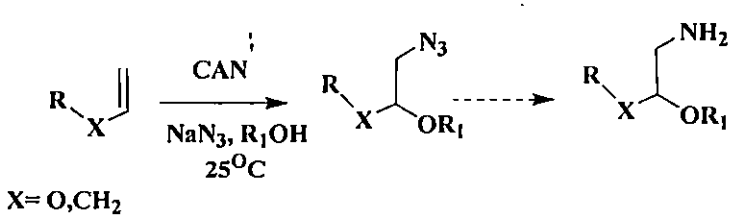
(**I**)

Scheme 8

Cerium(IV) compounds represent some of the most notable oxidants among lanthanide reagents. The most extensively used cerium(IV) reagent in organic chemistry is

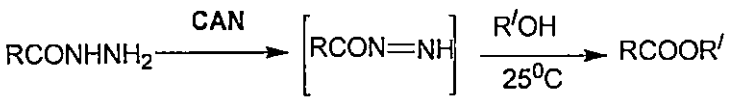
cerium(IV) ammonium nitrate (CAN). In 1936, Smith *et al.*[24] invented the chemical agent ceric ammonium nitrate (CAN), which is also named ammonium cerium(IV) nitrate, ammonium hexanitratocerate(IV), or ammonium nitratocerate(IV). It is prepared from fresh ceric hydrate or oxide in an excess amount of nitric acid and then with a quantitative amount of ammonium salt. Crystallized CAN in orange colour can be obtained by evaporation of the solvent at low temperatures. X-Ray crystallography of CAN shows that cerium(IV) locates at the center of the anion complexed by six bidentate nitrate groups. Thus the formula can be written as $(NH4)_2[Ce(NO_3)_6]$. Being a non-hygroscopic solid, this reagent is readily available in pure form. The reasons for its general acceptance as a one-electron oxidant may be attributed to its large reduction potential value of +1.61 V vs NHE (normal hydrogen electrode), low toxicity, ease of handling, experimental simplicity, and solubility in a number of organic solvents. CAN has proved to be very useful to synthetic organic chemists for over four decades. Its consumption can be judged by colour change from orange to pale yellow or colourless if the substrate and the product are not strongly coloured. The solubility of CAN in water is 1.41 g/ml at 25°C and 2.27 g/ml at 80°C. It is to a smaller extent in polar organic solvents, such as acetic acid, acetonitrile.[25] Because of its extremely limited solubility in common organic solvents, reactions involving CAN are often carried out in mixed water-organic solvents, such as aqueous acetonitrile.

In the Third World, many research groups successfully developed useful transformations by application of this reagent. For example, Chavan and Subbarao[26] developed a CAN-mediated azidoalkoxylation of enol ethers and olefins (**Scheme 9**).



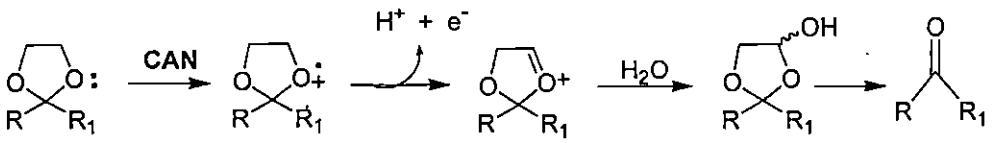
Scheme 9

Polanc *et al.*[27] established a selective conversion of hydrazides to esters by using CAN in the presence of alcohol (**Scheme 10**).



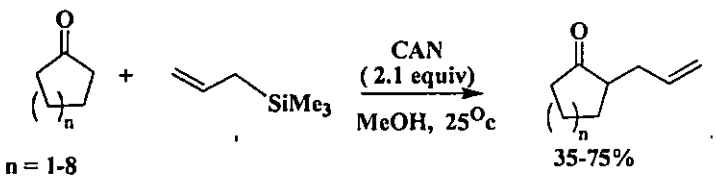
Scheme 10

Markó *et al.*[28] applied CAN as a catalyst in the deprotection of acetals to give the parent ketones (**Scheme 11**).



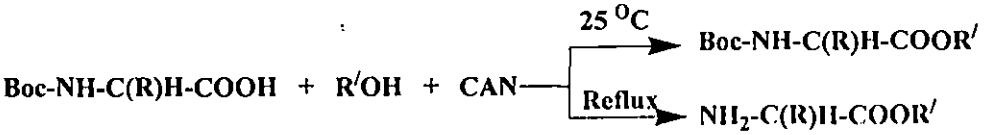
Scheme 11

Use of CAN (2.1 equiv) in methanol allows the conversion of cycloalkanones with five- to eight- and twelve-membered ring to the corresponding monoallylated products in 21–75% yields at 25°C (**Scheme 12**).[29]



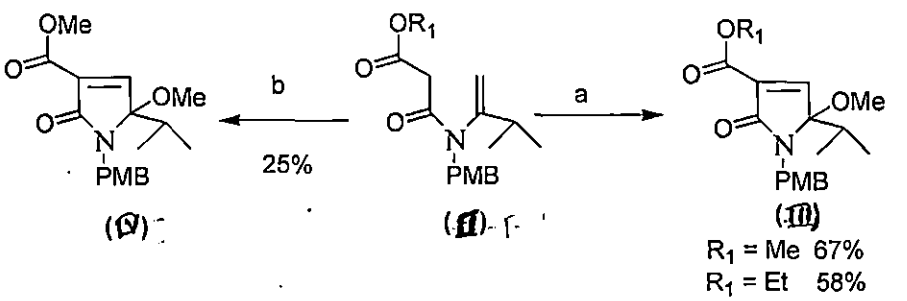
Scheme 12

Esters of *N*-tert-butoxycarbonyl (Boc) amino acids are widely used in peptide chemistry and in preparing several chiral auxiliaries such as *β*-amino alcohols, oxazolidinones, and *α*-amino aldehydes. Reaction of *N*-Boc amino acids with ceric ammonium nitrate in an alcohol as the solvent at room temperature resulted in the esterification of *N*-Boc amino acids with Boc group retention. When the reaction was conducted at reflux temperature, esterification was accompanied with simultaneous removal of the Boc group. Both reactions gave the desired products in good yields (**Scheme 13**).[30]



Scheme 13

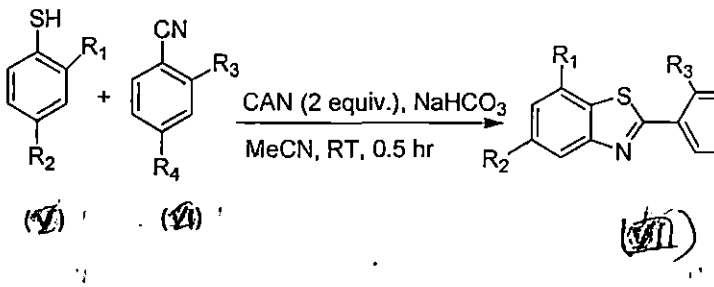
Nair and co-workers[31] have carried out a number of studies to compare the reactivity of $Mn(OAc)_3$ with CAN in the oxidative addition of 1,3-dicarbonyl radicals to unactivated alkenes, and discovered that CAN was often superior to Mn-$(OAc)_3$. More recently, CAN-mediated intermolecular radical reactions in ionic liquids have been reported. Ceric ammonium nitrate mediated the oxidative 5-*endo* radical polar crossover cyclisation reactions of β-enamide esters II to give 5,5-*C,O*-disubstituted-γ-lactams III & IV. Trapping of the intermediate cations leads to 5-hydroxy- or 5-alkoxy-γ-lactams depending upon the reaction conditions (**Scheme 14**).[32]



***a* Reagents and conditions:** (a) 4 equiv of CAN, MeOH, rt, 20 min; (b) 4 equiv of CAN, MeOH, reflux,

Scheme 14

The benzothiazole nucleus is of particular interest especially within the realm of medicinal chemistry. Many useful therapeutic agents contain the benzothiazole moiety. Ceric ammonium nitrate (CAN), an excellent one-electron oxidant, could be employed for radical generation and subsequent cyclization. Thiophenols V were treated with aromatic nitriles VI in the presence of ceric ammonium nitrate, and as envisaged the reactions proceed smoothly to afford the corresponding 2-arylbenzothiazoles VII in excellent yield (**Scheme 15**).[33]



R_1	R_2	R_3	R_4	yield (%)
H	H	H	H	95
H	CH_3	H	CH_3	90
H	H	H	CH_3O	95
H	CH_3	CH_3O	CH_3O	89
CH_3	H	H	NO_2	85
F	H	Cl	H	80
Br	H	H	CN	96
H	CF_3	I	H	80

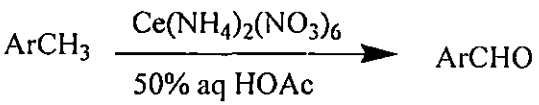
Scheme 15

Ceric ammonium nitrate [CAN] has also been utilized extensively for a variety of oxidative transformations. As might be expected for very powerful one-electron oxidants, the chemistry of oxidation by Ce(IV) was dominated by radical and radical cation chemistry.[34]

In 1965 Trahanovsky *et al.* showed that benzyl alcohols underwent oxidation to benzaldehydes in excellent yields using CAN in 50% aqueous acetic acid (**Scheme 16**).[35]

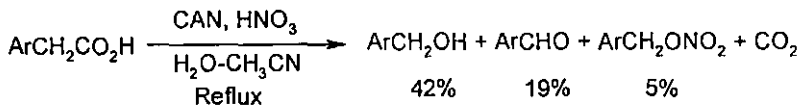
Scheme 16

The side-chain oxidation of toluene to benzaldehyde by CAN was also reported (**Scheme 17**).[36, 37]



Scheme 17

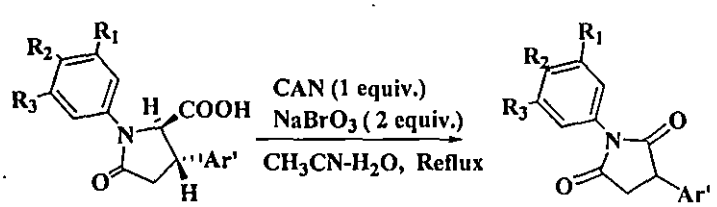
Trahanovsky *et al.*[38] also reported that substituted phenylacetic acids were readily decarboxylated when treated with CAN in refluxing aqueous acetonitrile solutions containing nitric acid to give the corresponding benzyl alcohol, benzaldehyde, benzyl nitrate and carbon dioxide (**Scheme 18**).



Scheme 18

IIA.2.1. Present Work:

The development of efficient synthetic methodologies, which allow for the incorporation of important pharmacophores into biologically interesting molecular architectures, is of considerable significance from the standpoint of the medicinal and organic chemistry and keeping in view of above usefulness of CAN as single electron oxidant, we became interested in exploring its reactivity toward our laboratory made γ-lactam derivatives. Thus the γ-lactam-carboxylic acids **25** when treated with CAN–$NaBrO_3$ in acetonitrile–water (1:1; v/v) at 80 °C it furnished exclusively the 1,3-diaryl succinimides **26** in high yields (**Scheme 19, Table 1**).[39]



(25) **(26)**

Scheme 19. Decarboxylative oxidation of γ-lactam-2-carboxylic acids

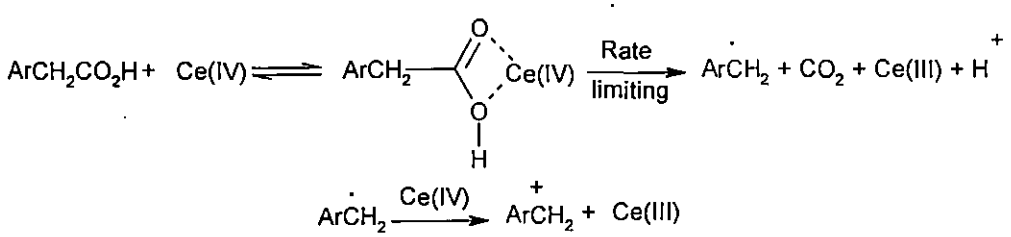
Except for oxalic, malonic and α-hydroxycarboxylic acids, carboxylic acids are resistant to oxidation with cerium(IV). In our case CAN–$NaBrO_3$ acts as a dual oxidant although the cerium(IV) ion is the actual reagent. Cerium(IV) has a high oxidation potential of +1.61 V compared to the NHE (normal hydrogen electrode),[38] and acts as a single electron oxidant. The oxidation by Ce(IV)/BrO_3^- occurred via a radical cation in the above reaction.

Table 1: Synthesis of *N*-arylsuccinimides 26 from γ-lactam-2-carboxylic acids 25[a,b]

Substrate *N*-aryl- γ-lactam-2-carboxylic acid		Product *N*-arylsuccinimide	Yield (%)
25a.	R_1=R_3=H, R_2 =Cl	26a	87
25b.	R_1=R_3=H, R_2 = F	26b	76
25c	R_1=R_3=H, R_2 = Br	26c	70
25d	R_1=R_3=H, R_2 =CH_3	26d	80
25e	R_1=R_3=R_2=H	26e	90
25f	R_1 = Cl, R_2 = F, R_3=H	26f	76

[a] **Reagents and conditions**: All the reactions were carried out with 1 equiv of CAN, and 2 equiv of $NaBrO_3$ in CH_3CN–H_2O (1:1, v/v) at 80°C. [b] In all cases Ar' is phenyl.

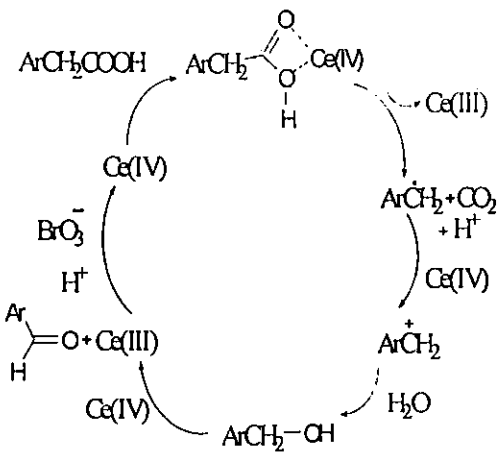
In 1974, Trahanovsky *et al.*[38] proposed a mechanism for the CAN mediated decarboxylative oxidation of substituted phenyl acetic acids (**Scheme 20**).



Scheme 20

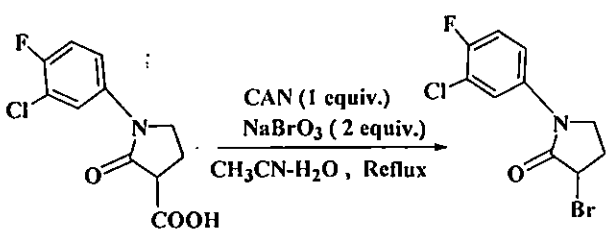
However, the mechanism of the reaction is uncertain, and we were unable to isolate any intermediate, although a plausible mechanism may be written as depicted in (**Scheme 21**).[39]

The standard electrode potential, E^0(CeIV/CeIII) is unknown. The formal potential for equal concentrations of cerium(IV) and cerium(III) varies considerably with the nature and concentration of the acidic medium. Cerium-(III) is converted to cerium(IV) by the BrO_3^- ion in the reaction medium, also the BrO_3^- ion can oxidize the alcohol formed during the course of the reaction.[40] The electronic configurations of Ce^{III} and Ce^{IV} are $[Xe]4f^1$ and $[Xe]4f^0$ where Xe represents the xenon configuration. The stability of the vacant f shell accounts for the ability of cerium to exist in the Ce^{IV} oxidation state.[34]



Scheme 21. Mechanistic pathway

The pleasing outcome of the above reaction prompted us to extend this method to include other γ-lactam carboxylic acid derivatives. And when we changed the position of the carboxylic acid group of γ-lactam carboxylic acid and performed the same reaction we got the decarboxylative bromination product instead of decarboxylative oxidation product. Thus by reaction of 1-(3-Chloro-4-floro-phenyl)-2-oxo-pyrrolidine-3-carboxylic acid (**27**)[41] with CAN-$NaBrO_3$ in acetonitrile- water (1:1; v/v) at 80°C furnished 3-Bromo-1-(3-Chloro-4-floro-phenyl)-pyrrolidine-2-one **28** in 60% yield (**Scheme 22**).



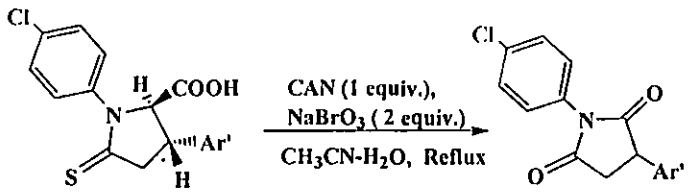
(27) (28)

Scheme 22: Decarboxylative bromination of γ-lactam- 3-carboxylic acids

We presume this reaction proceed through free radical pathway. The Br radical formed by the reaction between HOBr and H^+ [$HOBr + H^+ + e^- = Br + H_2O$][42], undergoes

Markownikoff addition to the enol tautomer of the substrate.[43] This is a strong proof in favour of the above mentioned CAN mediated decarboxylative pathway through radical mechanism.

To further test the generality of this reaction we next investigated the reaction on γ-thio-lactam-2-carboxylic acid (**29**) and surprisingly we isolated the product (**26a**) in about 63% yield (**Scheme 23**)



(29) **(26a)**

Scheme 23: Decarboxylative oxidation of γ-thio--lactam-2-carboxylic acids

In conclusion, we have developed a novel and simple method for the decarboxylative oxidation of γ-lactamcarboxylic acids to *N*-arylsuccinimides in one step and in good yields. And we are able to isolate two different products with the same reagents and same reaction condition by changing only the position of acid group in γ-lactam carboxylic acids. This procedure demonstrates the potential of the CAN–$NaBrO_3$ reagent system as a decarboxylative oxidating agent in refluxing acetonitrile–water as solvent. The synthesis allows oxidation under mild conditions using low cost reagents. The experimental simplicity of the reaction opens new opportunities for the use of this reaction in synthetic and industrial processes.

IIA.3 **Experimental :**

General procedure for the synthesis of 1,3-diaryl succinimide (26) from *N*-Aryl γ-lactam-2-carboxylic acid (25):

In a round bottom flask containing γ-lactam-2-carboxylic acid (1 mmol) in acetonirile (10 mL) a mixture of ceric ammonium nitrate (1 mmol) and $NaBrO_3$(2 mmol) in water (15 mL) was added and stirred for 15 minutes at room temperature. After that the reaction mixture was refluxed for 6-8 hours (depending on completion of the reaction monitored by TLC), it was then cooled to room temperature. Solvent was evaporated out under vacuum and the residue was extracted with CH_2Cl_2, the combined organic layer was washed successively with H_20, 10% $NaHCO_3$ solution and then finally again with H_20. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product thus obtained was re-crystallized from ethyl acetate-petroleum ether mixture.

General procedure for the synthesis of 3-Bromo-1-(3-Chloro-4-floro-phenyl)-pyrrolidine-2-one (28):

In a solution of γ-lactam-3-carboxylic acid (1 mmol) in acetonirile (10 mL) a mixture of ceric ammonium nitrate (1 mmol) and $NaBrO_3$ (2 mmol) in water (15 mL) was added and stirred for 15 minutes at room temperature. After that the reaction mixture was refluxed for 6 hours (monitored by TLC), it was then cooled to room temperature. Solvent was evaporated out under vacuum and the residue was extracted with CH_2Cl_2, the combined organic layer was washed successively with H_20, 10% $NaHCO_3$ solution and then finally again with H_20. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product thus obtained was re-crystallized from ethyl acetate-petroleum ether mixture.

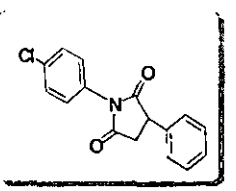
General procedure for the synthesis of 1,3-diaryl succinimide (26) from *N*-Aryl-thio γ-lactam-2-carboxylic acid (29):

In a round bottom flask containing thio-γ-lactam-2-carboxylic acid (1 mmol) in acetonirile (10 mL) a mixture of ceric ammonium nitrate (1 mmol) and $NaBrO_3$ (2 mmol) in water (15 mL) was added and stirred for 6 hours at room temperature (monitored by TLC). Solvent was evaporated out under vacuum and the residue was extracted with CH_2Cl_2, the combined organic layer was washed successively with H_20, 10% $NaHCO_3$ solution and then finally again with H_20. After drying the organic layer with Na_2SO_4, the solvent was evaporated under reduced pressure. The crude product thus obtained was re-crystallized from ethyl acetate-petroleum ether mixture.

Physical properties and Spectral Data of respective Compounds:

1-(4-Chloro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA,26a) :

Light yellow solid; mp 158-162 ^{0}C.



IR ($CHCl_3$): ν_{max} 1718, 1685, 1560 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.90-3.02 (dd, J = 4.91, 18.56 Hz, 1H), 3.29-3.35 (dd, J = 4.52, 8.81 Hz, 1H), 4.15 (q, J = 4.95 Hz, 1H), 7.13-7.54(m, 9H).

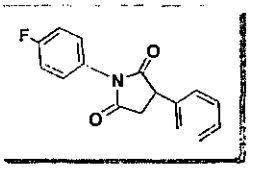
^{13}C NMR ($CDCl_3$, 50 MHz) δ: 36.96; 45.76; 127.24 (2C); 127.56 (2C); 127.98; 129.15 (2C); 129.21 (2C); 130.24; 134.26; 134.76; 174.75; 176.33;

ESI-MS for $C_{16}H_{12}NO_2Cl$ [M], [M+H$^+$] = 286.071(100%).

HRMS (ESI) Cal for $C_{16}H_{12}NO_2Cl$ [M+H$^+$] 286.063 found 286.06.

1-(4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26b) :

Light yellow solid, mp 136-140 ^{0}C,



IR ($CHCl_3$): ν_{max} 1717, 1655, 1509 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.94-3.05 (dd, *J* = 4.87, 18.56 Hz, 1H), 3.31-3.45 (dd, *J* = 9.46 Hz, 18.69 Hz, 1H), 4.19 (q, *J* = 4.86 Hz, 1H); 7.12-7.51 (m, 9H);

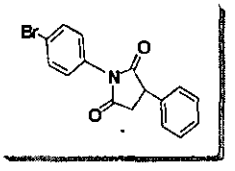
^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.12, 45.91, 115.98, 116.44, 127.33 (2C), 128.14, 128.20, 128.37, 129.15, 129.31 (2C), 132.43, 136.93, 175.04, 176.5,

ESI-MS for $C_{16}H_{12}NO_2F$ [M], [M+H$^+$] = 270.088 (100 %).

HRMS (ESI) Cal for $C_{16}H_{12}NO_2F$ [M+H$^+$] 270.085 found 270.089.

1-(4-Bromo-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26c):

Light yellow solid, mp 155-158^{0}C,



IR ($CHCl_3$): ν_{max} 1718, 1655, 1508 cm^{-1}

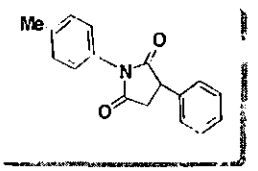
^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.95-3.07 (dd, *J* = 4.94 and 18.61 Hz, 1H), 3.31-3.46 (dd, *J* = 9.6 and 18.57 Hz, 1H), 4.19(q, *J* = 4.73 Hz, 1H), 7.22-7.45 (m, 7H), 7.59-7.65 (m, 2H),

^{13}C NMR ($CDCl_3$, 50 MHz) δ 37.07; 45.87; 122.45; 127.30 (2C); 127.87 (2C); 128.10; 129.79 (2C); 130.81; 133.75 (2C); 136.78, 174.69; 176.25;

ESI-MS for $C_{16}H_{12}NO_2Br$ [M], [M+H$^+$] = 330.020(^{79}Br), 332.020(^{81}Br).

1-(p-Tolyl)-3-phenyl-pyrrolidine-2,5-dione(IIA.26d):

Light yellow solid, mp 145-147^{0}C (lit mp 142 ^{0}C)[18],



IR ($CHCl_3$): ν_{max} 1732, 1598, 1505 cm^{-1}

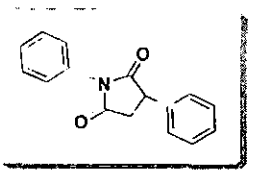
^{1}H NMR ($CDCl_3$,200 MHz) δ 2.39 (S, 3H), 2.92-3.03 (dd, *J* = 4.80 and 18.53 Hz, 1H), 3.30-3.44 (dd, *J* = 9.54 and 18.53 Hz, 1H), 4.18 (q, *J* = 4.75 Hz, 1H); 7.03-7.50 (m, 9H),

^{13}C NMR ($CDCl_3$, 50 MHz) δ 21.05; 37.10; 45.81; 126.12 (2C); 126.79 (2C); 127.24; 129.11 (2C); 129.52 (2C); 137.07; 138.66; 152.53, 175.24; 176.70;

ESI-MS for $C_{17}H_{15}NO_2$ [M], [M+H$^+$] = 266.105.

1,3-Diphenyl-pyrrolidine-2,5-dione (IIA.26e):

Light yellow solid, mp 135-138 ^{0}C (lit mp 140 ^{0}C)[18],



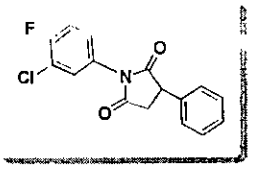
IR ($CHCl_3$): ν_{max} 1711, 1490 cm^{-1}

^{1}HNMR ($CDCl_3$, 200 MHz) δ 2.98-3.04 (dd, *J* = 4.00 and 18.40, 1H), 3.35-3.42 (dd, *J* = 9.6 and 18.4, 1H), 4.20 (q, *J* = 4.8, 1H), 7.12 -7.43 (m, 5H), 7.47 -7.55 (m, 3H), 7.6-7.62 (d, *J* = 8, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 37.05; 45.85; 122.47; 126.38; 127.27 (2C); 127.84 (2C); 128.10; 129.25 (2C): 132.38 (2C); 136.73; 174.71; 176.24;

ESI-MS for $C_{16}H_{13}NO_2$ [M], [M+H$^+$] = 252.109.

1-(3-Chloro-4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione(IIA.26f):



Yellow viscous dense liquid

IR ($CHCl_3$): ν_{max} 1718, 1654, 1500 cm^{-1}

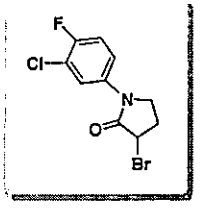
^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.94-3.06 (dd, *J* = 4.92, 18.71 Hz, 1H), 3.31-3.40 (dd, *J*.= 9.58, 18.60 Hz, 1H), 4.18 (t, *J* = 4.83 Hz, 1H); 7.20-7.47 (m, 8H);

^{13}C NMR ($CDCl_3$, 50 MHz) δ: 37.02; 45.87; 116.75; 117.20; 121.53; 121.90; 126.29; 126.43; 127.30; 127.74; 128.23; 128.82; 129.04; 129.92; 136.62; 155.26; 160.26; 174.64; 176.20;

ESI-MS for $C_{16}H_{11}NO_2F$ [M], [M+H$^+$] = 304.055.

3-Bromo-1-(3-Chloro-4-Fluoro-phenyl)-pyrrolidine-2-one (IIA.28):

Blackis white solid, mp 93-97 ^{0}C,



IR ($CHCl_3$): ν_{max} 1702, 1500 cm^{-1}

^{1}H NMR ($CDCl_3$, 200 MHz).δ 2.38-2.52 (m, 1H), 3.31-3.40 (2.64-2.82 (m, 1H), 3.71-3.83 (m, 1H), 3.98-4.07 (m, 1H) 4.56 (dd, *J* = 5.82, 13.78 Hz, 1H), 7.1-7.22 (m, 1H), 7.45-7.55 (m, 1H), 7.74-7.78 (m, 1H)

^{13}C NMR ($CDCl_3$, 50 MHz) δ, 29.72, 44.66, 46.70, 116.49, 116.71, 119.52, 119.58; 122.13; 135.41, 154.03, 154.50, 169.55,

ESI-MS for $C_{10}H_8NOBrClF$ [M], [M+H$^+$] = 292.02 (^{79}Br), 294.025 (^{81}Br).

HRMS (ESI) Cal for $C_{10}H_8NOBrClF$ [M+H$^+$] 291.9462 (^{79}Br), 293.9441 (^{81}Br), found 291.9460 (^{79}Br), 293.9409 (^{81}Br).

IIA.4 References :

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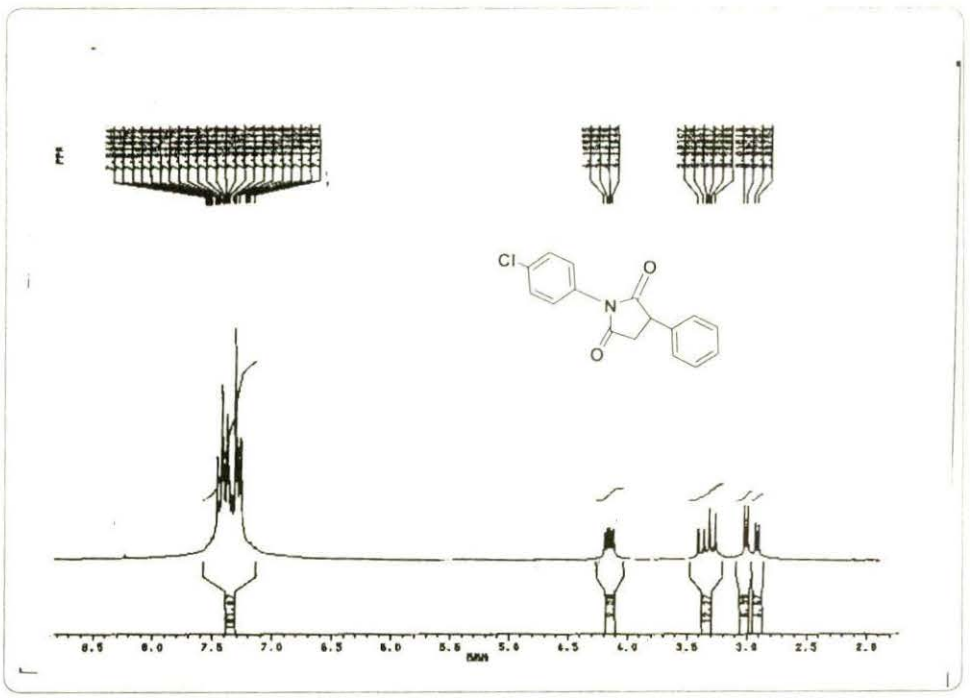
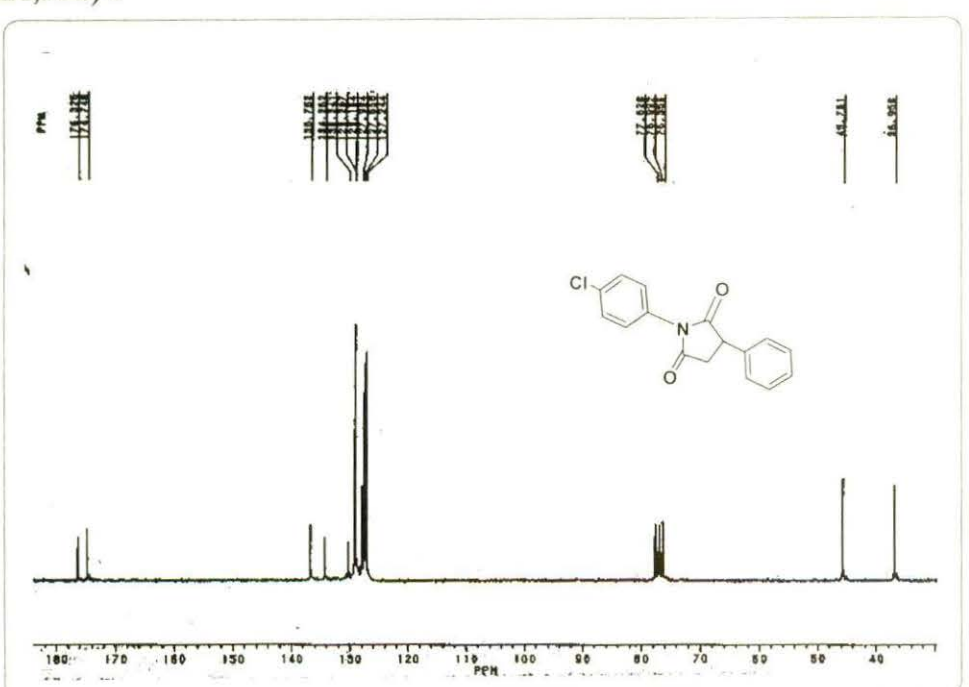
Selected spectra

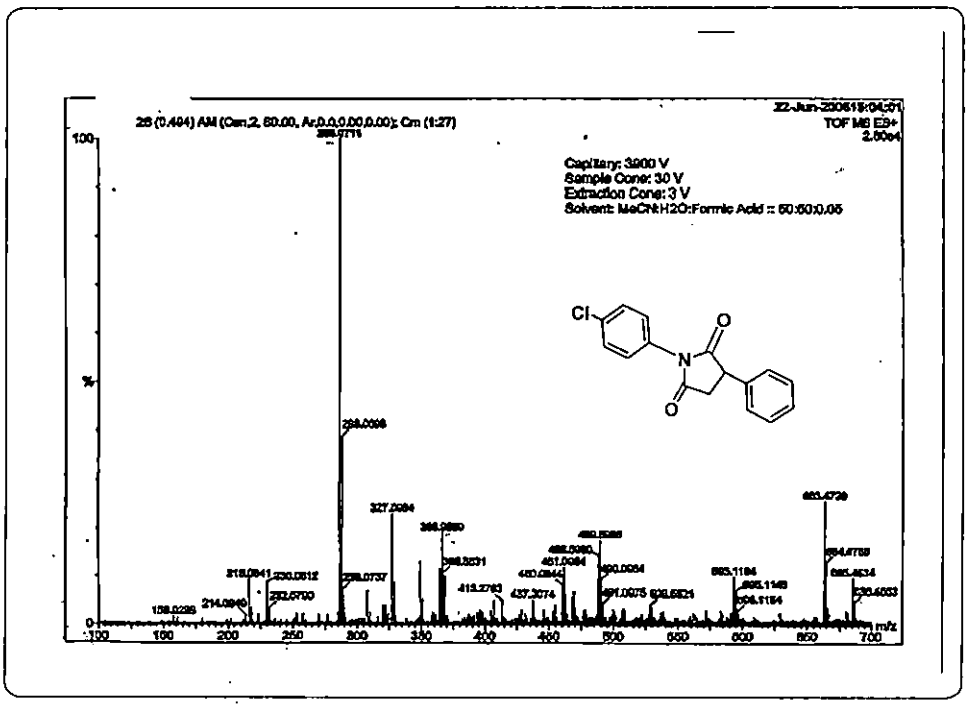
^{1}H NMR ($CDCl_3$, 200 MHz) of 1-(4-Chloro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA,26a) :



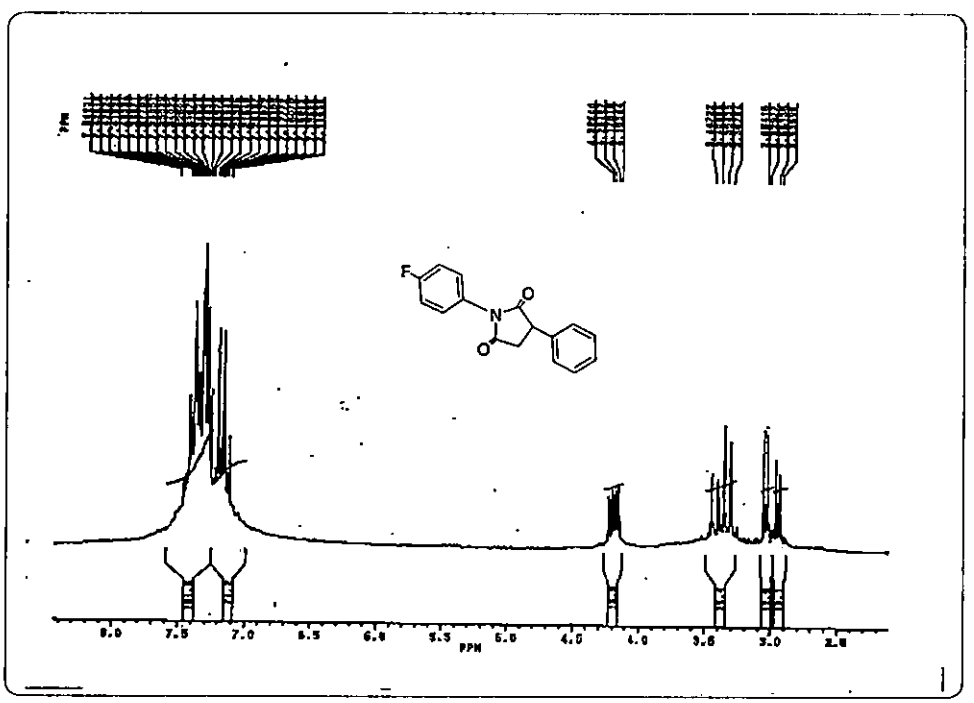
^{13}C NMR ($CDCl_3$, 50 MHz) of 1-(4-Chloro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA,26a) :



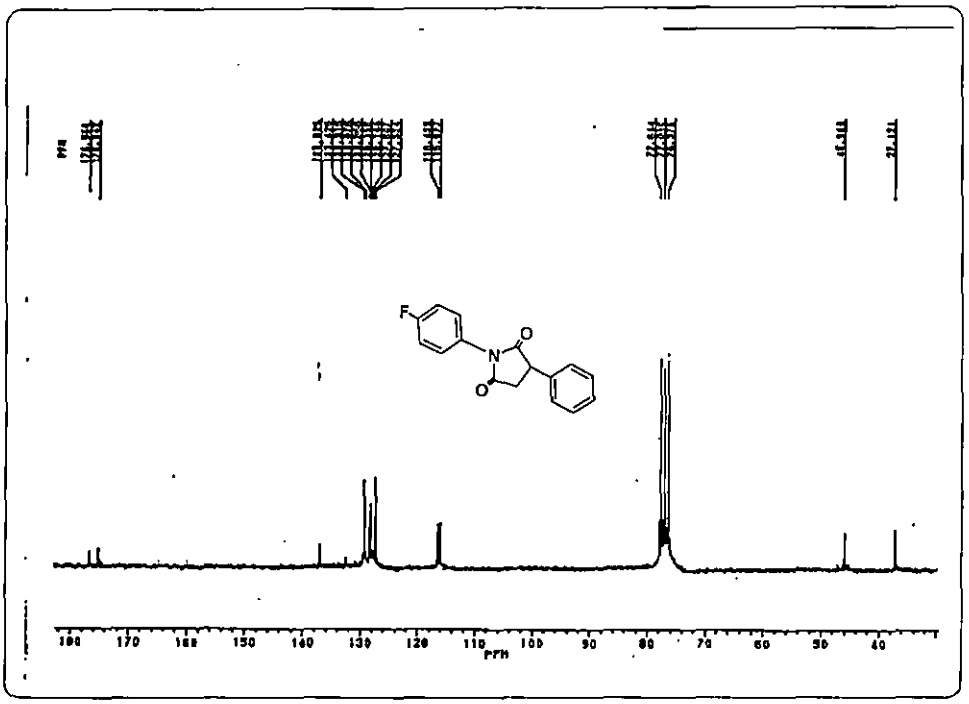
ESI-MS [M+H$^+$] of 1-(4-Chloro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA,26a) :



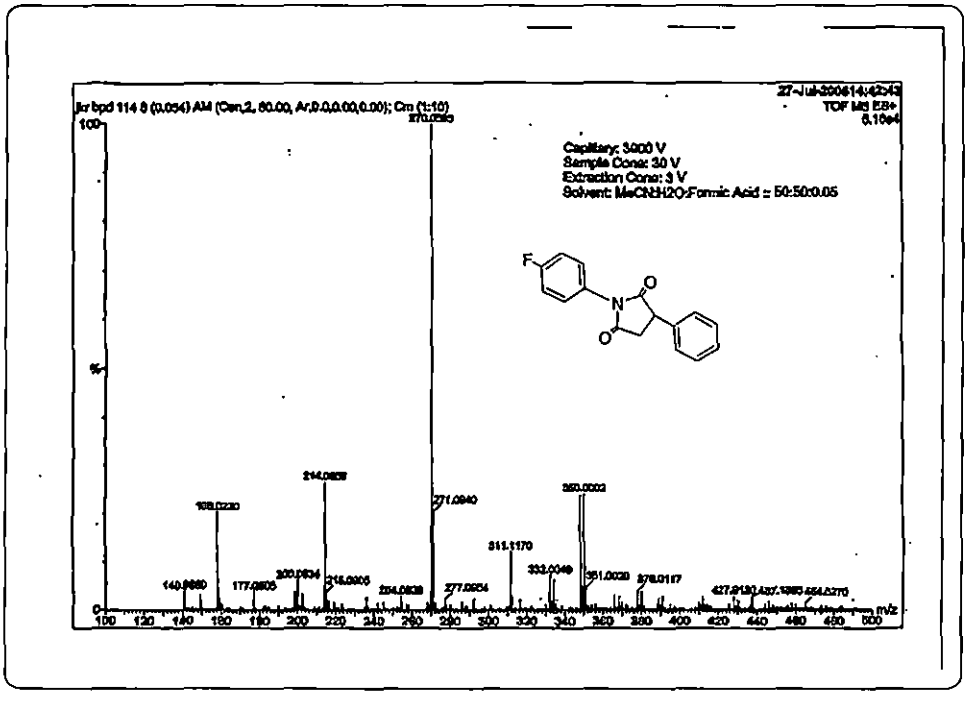
^{1}HNMR ($CDCl_3$, 200 MHz) of 1-(4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26b) :



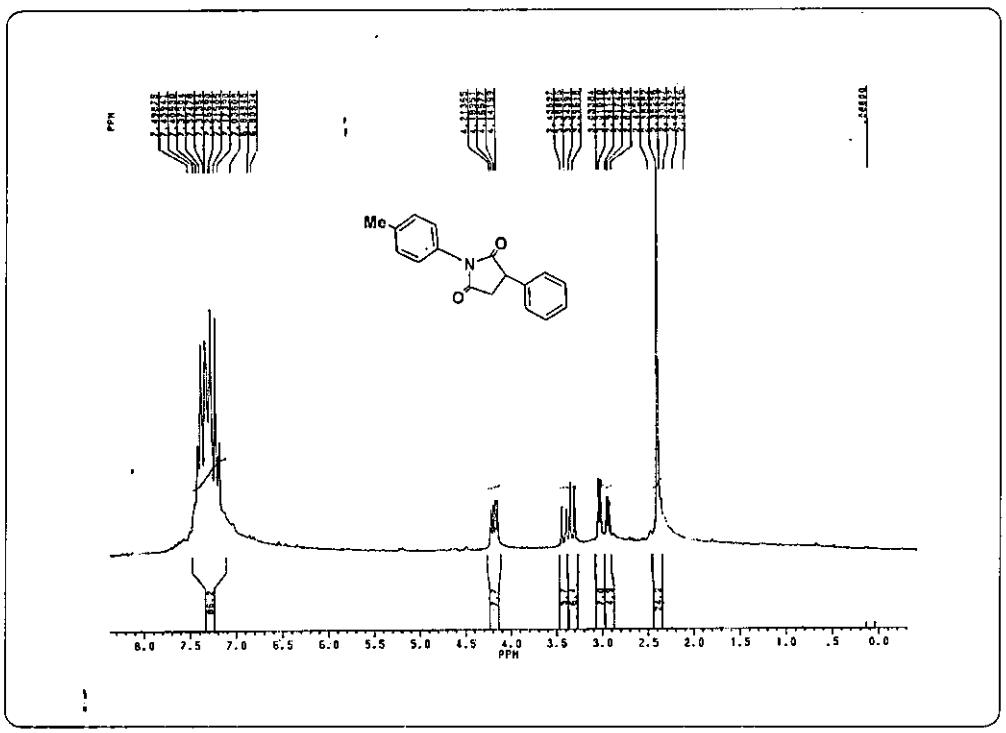
^{13}C NMR ($CDCl_3$, 50 MHz) of 1-(4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26b) :



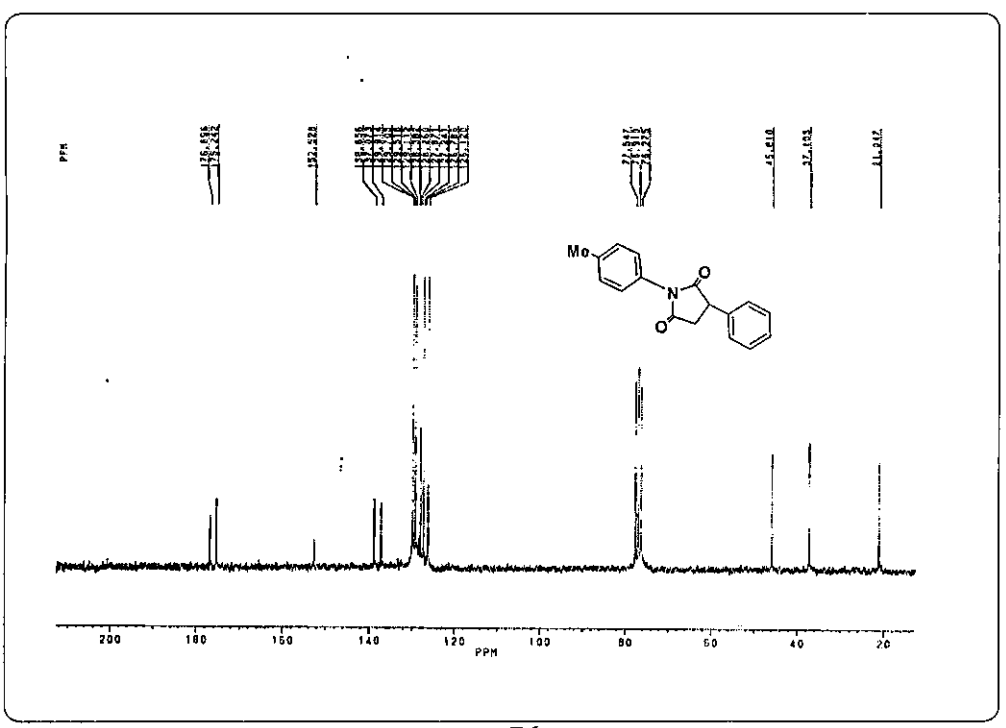
ESI-MS [$M+H^+$] of 1-(4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26b) :



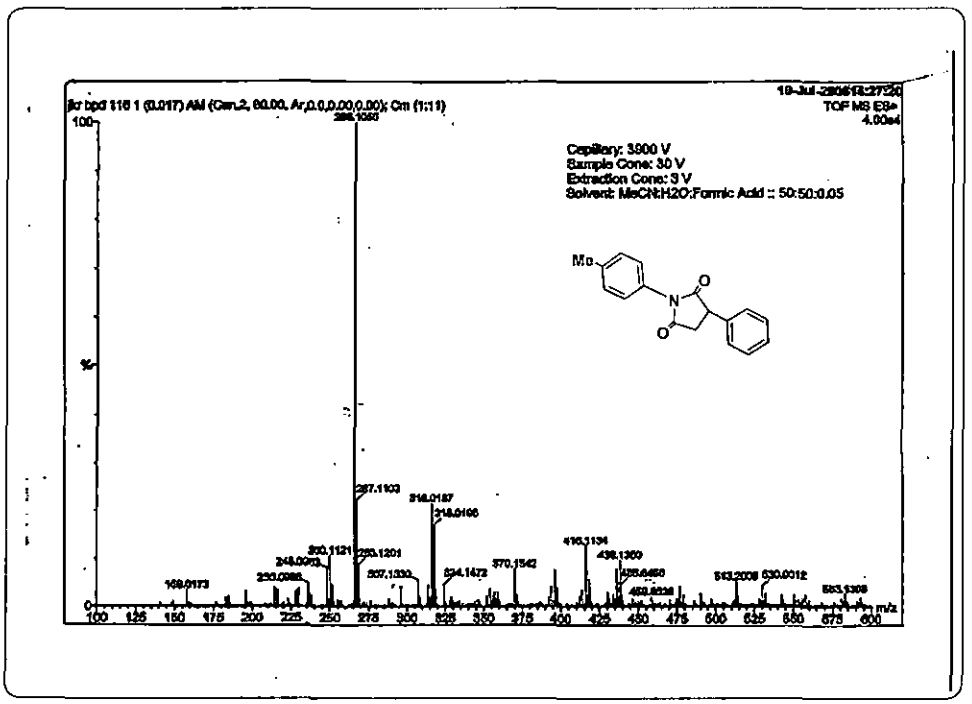
^{1}H NMR ($CDCl_3$, 200 MHz) of 1-(p-Tolyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26d):



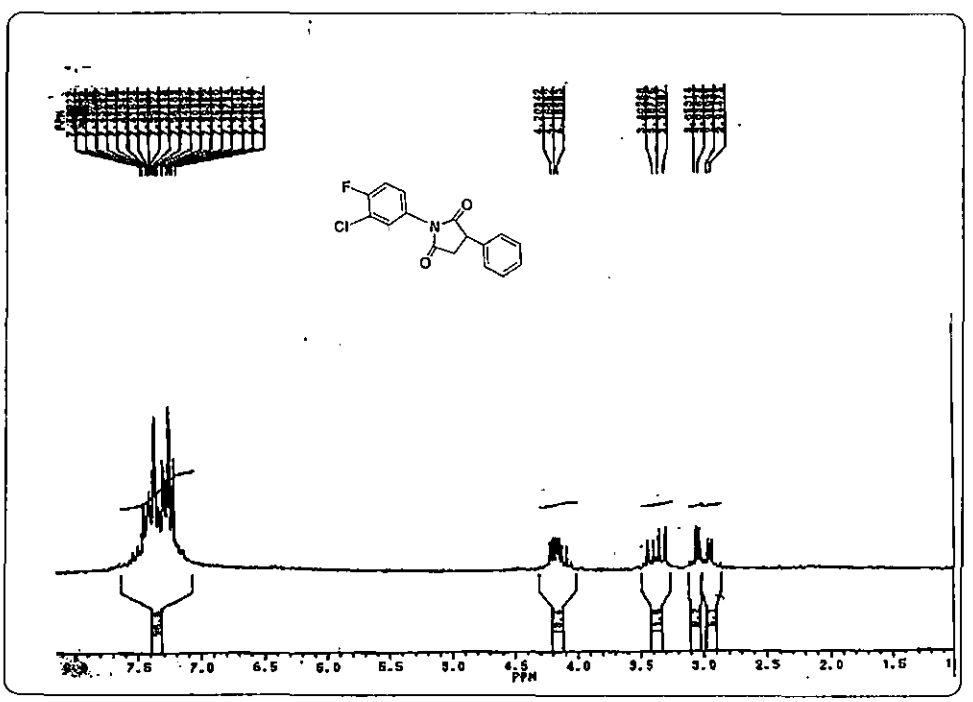
^{13}C NMR ($CDCl_3$, 50 MHz) of 1-(p-Tolyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26d):



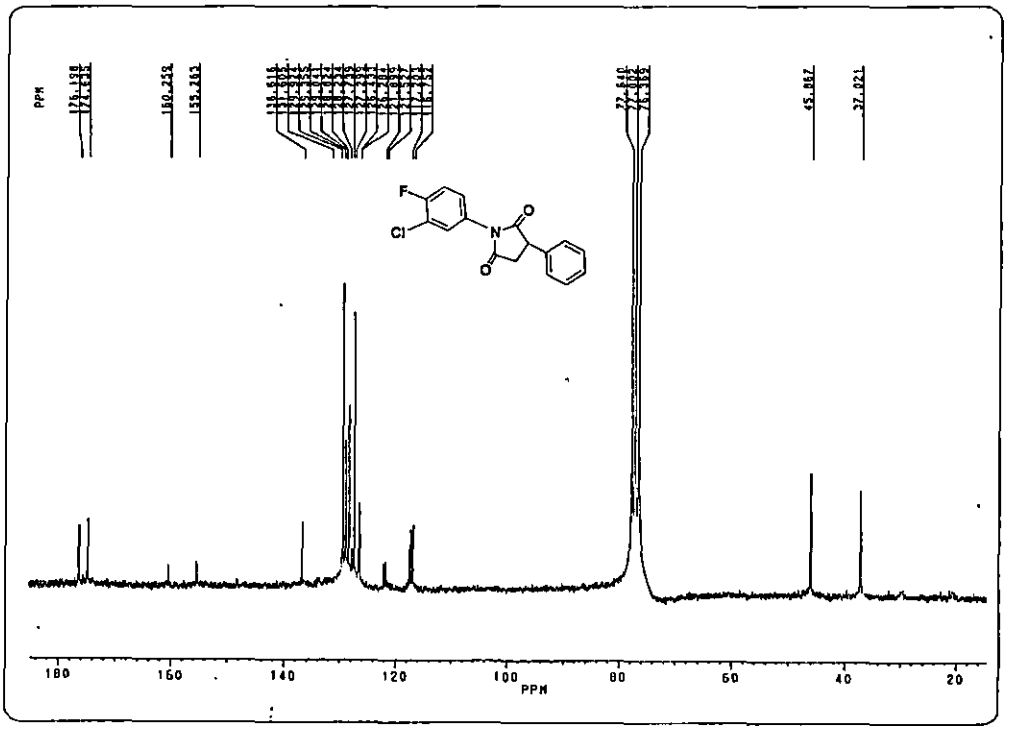
ESI-MS [M+H$^+$] of 1-(p-Tolyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26d):



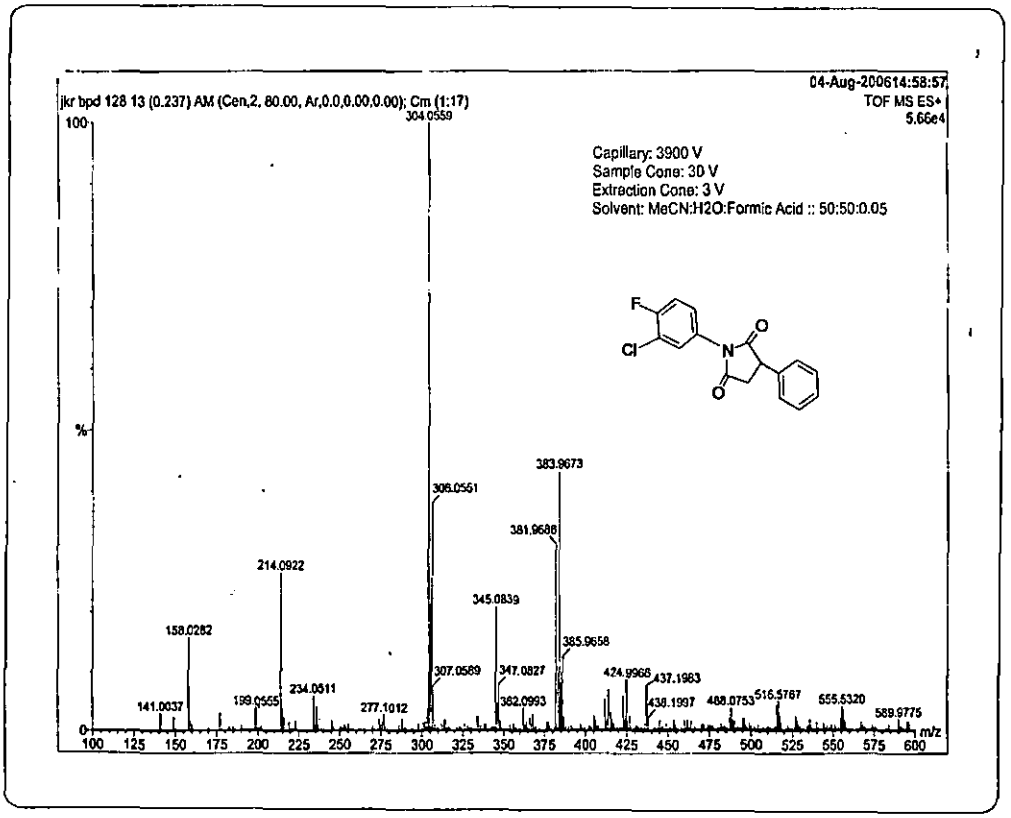
^{1}H NMR ($CDCl_3$, 200 MHz) of 1-(3-Chloro-4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26f):



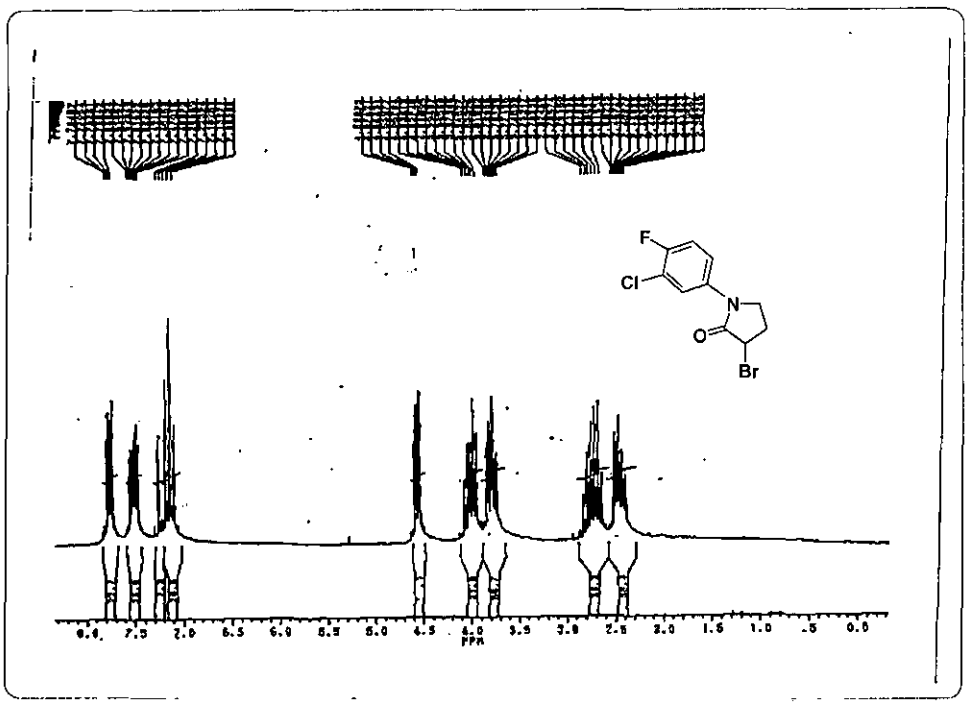
^{13}C NMR ($CDCl_3$, 50 MHz) of 1-(3-Chloro-4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26f):



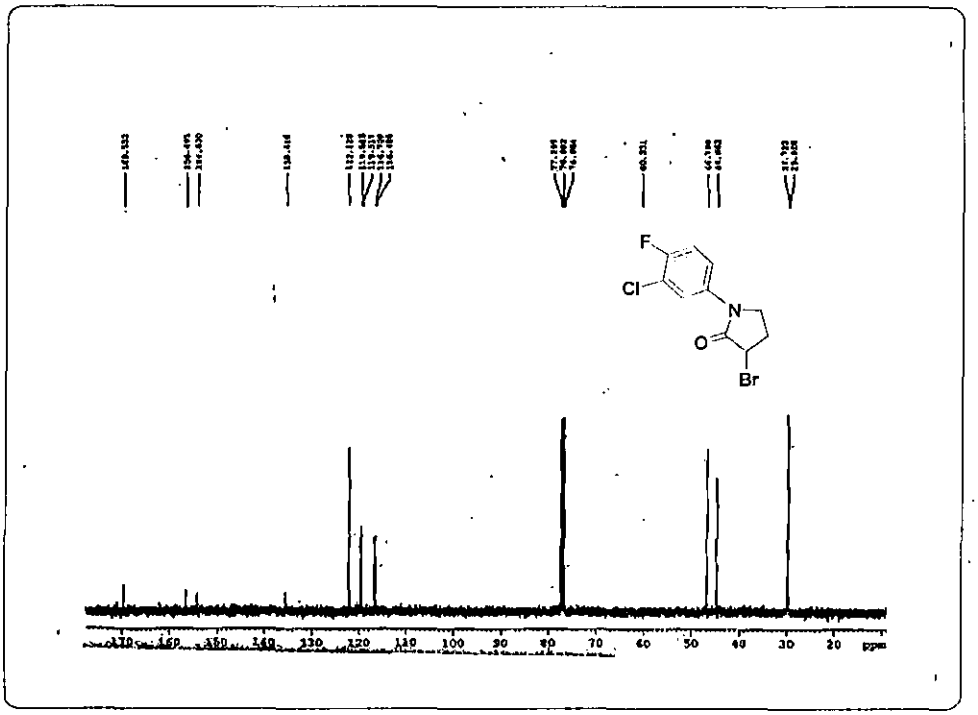
ESI-MS [M+H^+] of 1-(3-Chloro-4-Fluoro-phenyl)-3-phenyl-pyrrolidine-2,5-dione (IIA.26f):



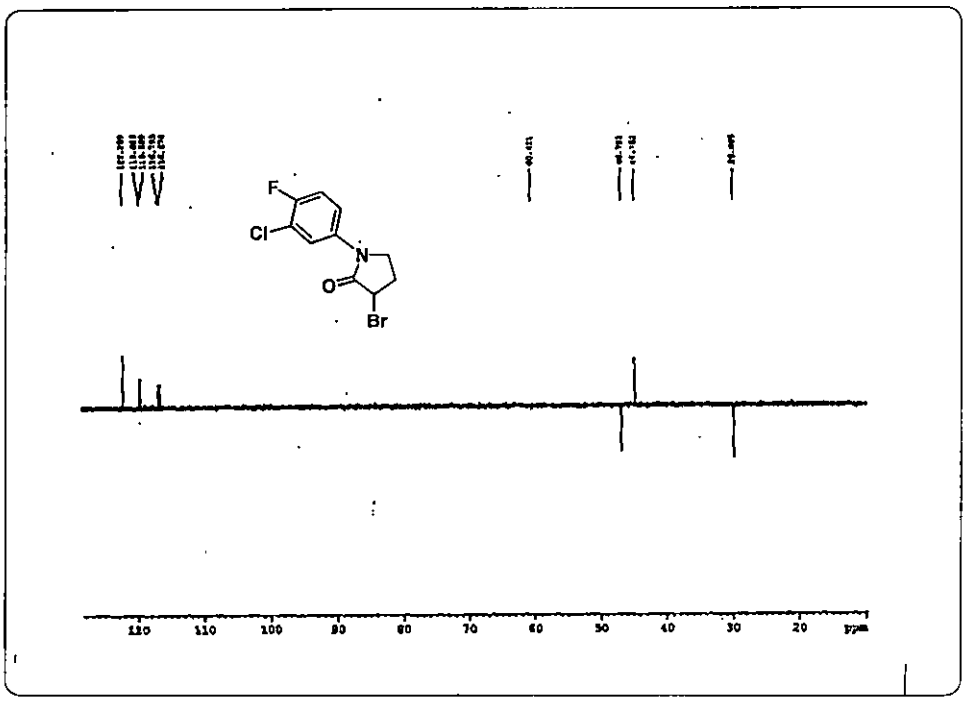
^{1}H NMR ($CDCl_3$, 200 MHz) of 3-Bromo-1-(3-Chloro-4-Fluoro-phenyl)-pyrrolidine-2-one (IIA.28):



^{13}C NMR ($CDCl_3$, 50 MHz) of 3-Bromo-1-(3-Chloro-4-Fluoro-phenyl)-pyrrolidine-2-one (IIA.28):



DEPT-135 of 3-Bromo-1-(3-Chloro-4-Fluoro-phenyl)-pyrrolidine-2-one (IIA.28):



ESI-MS [M+H$^+$] of 3-Bromo-1-(3-Chloro-4-Fluoro-phenyl)-pyrrolidine-2-one (IIA.28):