

DOKUZ EYLÜL UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

**SYNTHESIS OF POTENTIAL ANTIBACTERIAL
CARBAZOLE MOIETY BEARING β -LACTAM
DERIVATIVES**

by
César Eduardo GUTIÉRREZ QUEVEDO

July, 2017
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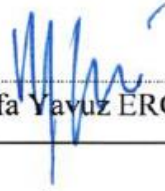
**A Thesis Submitted to the Graduate School of Natural and Applied Sciences of
Dokuz Eylül University
In Partial Fulfillment of the Requirements for the Degree of
Master of Science in Chemistry**

**by
César Eduardo GUTIÉRREZ QUEVEDO**

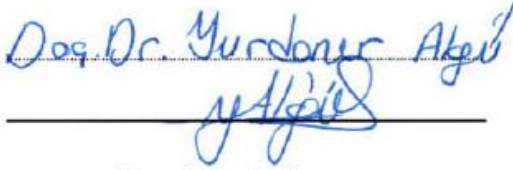
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M.Sc. EXAMINATION RESULT FORM

We have read the thesis entitled “SYNTHESIS OF POTENTIAL ANTIBACTERIAL CARBAZOLE MOIETY BEARING β -LACTAM DERIVATIVES” completed by Cesar Eduardo GUTIERREZ QUEVEDO under supervision of Prof. Dr. Mustafa Yavuz ERGÜN and we certify that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.


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César Eduardo GUTIÉRREZ QUEVEDO

SYNTHESIS OF POTENTIAL ANTIBACTERIAL CARBAZOLE MOIETY BEARING β -LACTAM DERIVATIVES

ABSTRACT

Carbazoles are interesting key compounds in the development and improve of antitumors, antibiotics, antihistaminics, antioxidatives, anti-inflammatorie, phychotropic agents, etc. since their selectivity (activity) can be influenced by substituents.

In this context, carbazole skeleton allows an enhancement of the potent antibacterial activity in β -lactam (2-azetidinone) rings attached in systems like penicillin, aztreonam, nocardicin, etc. and led to obtain synthons with diverse pharmacological activities.

Here, we intended to synthesize and characterize a series of novel 9-methyl-9*H*-carbazole compounds with azetidinone moieties, using condensation and ketene–imine cycloaddition type reactions. The synthesized compounds were identified and characterized by Infrared spectroscopy and Nuclear Magnetic Resonance spectroscopy.

Keywords: Carbazole, β -lactam, antibacterial

POTANSİYEL ANTİBAKTERİYEL AKTİFLİĞE SAHİP KARBAZOL GRUBU İÇEREN β -LAKTAM TÜREVLERİNİN SENTEZİ

ÖZ

Karbazoller; seçiciliklerinin ve aktivitelerinin sübstituentlerle kolayca değiştirilebilmeleri sayesinde antitümör, antibiyotik, antihistaminik, antioksidatif, anti-inflamatuar ve psikotropik ajanların geliştirilmesinde ilgi çeken kilit bileşiklerdir.

Karbazol iskeleti, penisilin, aztreonam ve nocardicin gibi β -laktam bağlı sistemlerin antibakteriyel aktivitesinin artmasına yardımcı olur ve çeşitli biyolojik aktivitelere sahip olmasını sağlar.

Bu çalışmada, kondenzasyon ve keten–imin siklokatılma tipi reaksiyonları kullanarak, laktam yapısal içeren yeni bir 9-metil-9*H*-karbazol bileşikleri serisi, sentezleme ve karakterize etmeyi amaçladık. Sentezlenen bileşikler IR ve Nükleer Manyetik Rezonans spektroskopisi ile tanımlandı ve karakterize edildi.

Anahtar kelimeler: Karbazol, β -laktam, antibakteriyel

CONTENTS

	Page
THESIS EXAMINATION RESULT FORM	ii
ACKNOWLEDGMENTS	iii
ABSTRACT	iv
ÖZ	v
LIST OF FIGURES	ix
LIST OF TABLES	xii
 CHAPTER ONE - INTRODUCTION	 1
1.1 Overview of the Carbazole Compounds	1
1.2 Biological and Pharmacological Activities of Carbazoles	1
1.2.1 Anti-tumor and Anticancer Agents	1
1.2.2 Cardiovascular, Analgesic/Anti-inflammatory and Anti-pyretic Agents	4
1.2.3 Antioxidant, Metabolic Disorders and Lowering Agents	5
1.2.4 Antiviral Agents	7
1.2.5 Antibacterial and Antifungal Agents	7
1.3 Overview of β -lactam Compounds	11
1.4 Biological and Pharmacological Activities of β -lactam Compounds	14
1.4.1 Anti-tumor and Anticancer Agents	14
1.4.2 Analgesic/Anti-inflammatory and Anti-pyretic Agents	15
1.4.3 Antihyperlipidemic Agents	17
1.4.4 Antidepressant and Anticonvulsant Agents	18
1.4.5 Antibacterial and Antifungal Agents	19
1.5 State of Research	23
1.5.1 Synthesis of the Amine Carbazole	23
1.5.2 Synthesis of the Aldehyde Carbazole	26
1.5.3 Synthesis of the Schiff Bases	29

1.5.4 Synthesis of Lactams	31
CHAPTER TWO - MATERIALS AND METHOD	33
2.1 Motivation and Objectives	33
2.2 Synthesis Plan	34
2.3 Experimental	36
2.3.1 Materials	36
2.3.2 Instrumentation	36
2.3.3 Synthesis procedures and Spectroscopic Information	37
2.3.3.1 Synthesis of 9-methyl-3-nitro-9 <i>H</i> -carbazole (127)	37
2.3.3.2 Synthesis of 9-methyl-9 <i>H</i> -carbazol-3-amine (128).....	38
2.3.3.3 Synthesis of 9-methyl-9 <i>H</i> -carbazole-3-carbaldehyde (129)	38
2.3.3.4 General Procedure for the Synthesis of Schiff bases (130-141).....	39
2.3.3.5 General Procedure for the Synthesis of β -lactams (142-153)	39
CHAPTER THREE - EXPERIMENTAL RESULTS	42
3.1 Spectroscopic Spectra	42
3.1.1 IR Spectra	42
3.1.2 NMR Spectra	48
CHAPTER FOUR - DISCUSSION AND RESULTS	53
4.1 Synthesis of the Compounds	53
4.1.1 Synthesis of the Amino Carbazole (128).....	53
4.1.2 Synthesis of the Aldehyde Carbazole (129)	54
4.1.3 Synthesis of the Schiff bases (130-141) and β -lactams (142-153)	54

CHAPTER FIVE - CONCLUSIONS.....	62
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5.1 Conclusions	62
-----------------------	----

REFERENCES.....	63
------------------------	-----------



LIST OF FIGURES

	Page
Figure 1.1 Carbazole	2
Figure 1.2 Carbazole derivatives against tumors cells.....	2
Figure 1.3 Carbazole derivatives in current use or in stage of clinical development	3
Figure 1.4 Carbazole derivatives with cytotoxic activity.....	3
Figure 1.5 Dimeric carbazole compounds	4
Figure 1.6 Carbazole compounds with anti-inflammatory activities.....	5
Figure 1.7 Carbazole compounds with anti-inflammatory and anti-pyretic activities.....	5
Figure 1.8 Carbazole antagonists of the neuropeptide Y-5.....	6
Figure 1.9 Carbazole compounds against metabolic disorders	6
Figure 1.10 Carbazole compounds with antiviral activities.....	7
Figure 1.11 Carbazole thio-tetrazole derivatives	8
Figure 1.12 Carbazole compounds with antimalarial activity	8
Figure 1.13 Carbazole compounds with antitubercular activity	9
Figure 1.14 Carbazole compounds with antitubercular and antiparasitic activities.....	9
Figure 1.15 Carbazole pyrrole derivatives with antitubercular activity.....	10
Figure 1.16 Carbazole 1,2,3-triazole derivatives with antitubercular activity	10
Figure 1.17 Carbazole quinolone derivative	11
Figure 1.18 β -Lactam ring	12
Figure 1.19 Examples of commercial β -lactam compounds.....	13
Figure 1.20 4-Heteryldithio β -lactam derivative.....	14
Figure 1.21 β -Lactam derivatives inhibitors of tumor cells.....	15
Figure 1.22 Bromoquinazolinone β -lactam derivatives.....	16
Figure 1.23 Benzimidazole β -lactam derivatives.....	16
Figure 1.24 4-amino-5-naptho-furan-1,2,4- triazole β -lactam derivatives	17
Figure 1.25 Isonicotinic acid hydrazide β -lactam derivatives	17
Figure 1.26 Ezetimibe β -lactam and derivatives with antihyperlipdemic activity	18
Figure 1.27 Isonocotinyl hydrazone β -lactam derivatives	19

Figure 1.28 β -Lactam derivatives with anticonvulsant activity	19
Figure 1.29 5-Ethyl pyridine-2-ethanol β -lactam derivatives	20
Figure 1.30 1-Butyl-3-substituted-4-(2-aryl-1 <i>H</i> -indol-3-yl) β -lactam derivative.....	20
Figure 1.31 Benzimidazolyl thioacetamida β -lactam derivatives	21
Figure 1.32 8-Hydroxyquinoline β -lactam derivatives	21
Figure 1.33 Tetrahydrocarbazol β -lactam derivatives	22
Figure 1.34 Carbazole and thiadiazol β -lactam derivatives	22
Figure 1.35 Retrosynthesis of β -lactams 142-144	23
Figure 1.36 Di-nitration and reduction of carbazole (1)	24
Figure 1.37 Di-nitration and reduction of carbazole derivative 106	25
Figure 1.38 Mono-nitration of carbazole (1).....	25
Figure 1.39 Reduction of carbazole derivative 110	25
Figure 1.40 Mono-nitration and reduction of carbazole (1).....	26
Figure 1.41 Retrosynthesis of β -lactams 148-153	26
Figure 1.42 Formylation of carbazole derivative 126 by Kantevari's method	27
Figure 1.43 Formylation of carbazole derivative 126 by Buu-Hoë-Hoán's method	27
Figure 1.44 Formylation of carbazole derivative 113.....	28
Figure 1.45 Formylation of carbazole derivative 115.....	28
Figure 1.46 Formylation of carbazole derivative 117.....	29
Figure 1.47 Formylation of carbazole derivative 119.....	29
Figure 1.48 Synthesis of imines by condensation of aldehydes and amines	30
Figure 1.49 Synthesis of the Schiff base carbazole derivative 123.....	30
Figure 1.50 Synthesis of the Schiff base carbazole derivative 125.....	30
Figure 1.51 Synthetic approaches to β -lactams	31
Figure 1.52 Synthesis of lactams by Staudinger's ketene-imine reaction	32
Figure 1.53 General scheme for the synthesis of β -lactams by Güner et al.....	32
Figure 2.1 Design of the antibacterial β -lactams	33
Figure 2.2 Carbazole aldehyde and amine to be synthesized	34
Figure 2.3 Carbazole compounds to be synthesized	34
Figure 2.4 Synthesis Plan Conditions	35
Figure 2.5 Carbazole compound 127	37

Figure 2.6 Carbazole compound 128	38
Figure 2.7 Carbazole compound 129	38
Figure 2.8 Carbazole β -lactams synthesized	40
Figure 3.1 IR Spectra of compound 142	42
Figure 3.2 IR Spectra of compound 143	43
Figure 3.3 IR Spectra of compound 144	43
Figure 3.4 IR Spectra of compound 145	44
Figure 3.5 IR Spectra of compound 146	44
Figure 3.6 IR Spectra of compound 147	45
Figure 3.7 IR Spectra of compound 148	45
Figure 3.8 IR Spectra of compound 149	46
Figure 3.9 IR Spectra of compound 150	46
Figure 3.10 IR Spectra of compound 151	47
Figure 3.11 IR Spectra of compound 152	47
Figure 3.12 IR Spectra of compound 153	48
Figure 3.13 ^1H -Spectra of compound 142 in $\text{DMSO}-d_6$ 400 MHz	49
Figure 3.14 ^1H -Spectra of compound 147 in $\text{DMSO}-d_6$ 400 MHz	50
Figure 3.15 ^1H -Spectra of compound 148 in CDCl_3 400 MHz	51
Figure 3.16 ^1H -Spectra of compound 149 in CDCl_3 400 MHz	52
Figure 4.1 Synthesis of 9-methyl-3-nitro-9 <i>H</i> -carbazole (127)	53
Figure 4.2 Synthesis of 9-methyl-9 <i>H</i> -carbazol-3-amine (128)	54
Figure 4.3 Synthesis of 9-methyl-9 <i>H</i> -carbazole-3-carbaldehyde (129)	54
Figure 4.4 Synthesis of the Schiff Bases (130-141) precursors for β -lactams	55
Figure 4.5 Synthesis of β -lactams (142-153)	56
Figure 4.6 Carbazole compound 142	57
Figure 4.7 Carbazole compound 143	58
Figure 4.8 Carbazole compounds 144-146	58
Figure 4.9 Carbazole compound 147	59
Figure 4.10 Carbazole compound 148	60
Figure 4.11 Carbazole compound 149	60
Figure 4.12 Carbazole compounds 150-153	61

LIST OF TABLES

	Page
Table 2.1 Carbazole β -lactams synthesized by number (No.) and name.	40
Table 2.2 Carbazole β -lactams synthesized, functional group (R), chemical formula, molecular weight, yield and melting point.....	41
Table 4.1 Number and functional groups (R) of the Schiff Bases synthesized	55
Table 4.2 Number and functional groups (R) of the β -lactams synthesized.....	56



CHAPTER ONE

INTRODUCTION

1.1 Overview of the Carbazole Compounds

Heterocycles are cyclic compounds containing two or more, different kinds of atoms in the ring, they are present in many drugs, vitamins, natural products, biologically active compounds, etc. and have found applications as fluorescent sensors, brightening agents, plastics, semiconductors, photovoltaic cells, light harvesting systems, optical data carriers, chiral auxiliaries, organocatalysts, etc. (Buckingham et al., 2010; Eftekhari-Sis et al., 2013).

Among the big variety of heterocyclic compounds are found the alkaloids, which are Nitrogen-containing compounds generally produced by almost every variety of organisms including humans (Clayden et al., 2001; Roberts & Wink, 2013).

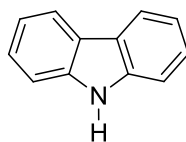
Over the past years many structurally diverse alkaloids have been isolated, synthesized and studied due to their biological and pharmacological activities. Carbazole alkaloids in particular have attracted the attention of researchers in different fields of science due to their structural features (aromaticity, high π -conjugation, and tricyclic indole moiety), ease of functionalization, biological and pharmacological activities, electronic and charge-transport properties, etc. (Fattorusso & Taglialatela-Scafati, 2008). The present chapter describes and summarizes some applications of the carbazole compounds.

1.2 Biological and Pharmacological Activities of Carbazoles

1.2.1 *Anti-tumor and Anticancer Agents*

Since carbazole (**1**) (Figure 1.1) was isolated first from coal tar in by Graeber and Glaser, (1872) several of its derivatives have been reported to have antiviral,

antibacterial, anti-tumor, anticancer activities etc. Carbazole system is present in many antitumor drugs such olivacine (**2**) (Figure 1.2) first isolated from plants (*Aspidosperma olivaceum* Müll. Arg) by Schmutz and Hunziker, (1958).



1

Figure 1.1 Carbazole

The discovering of **2** has stemmed the development and improve of more potent carbazole derivatives against tumors cells. Ellipticine (**3**) and its analog elliptinium (**4**) known as celiptium® (Figure 1.2) were found to be active against tumors and leukemia, so that in 1977 elliptinium was established in cancer chemotherapy, (Cordell, 2008; Goodwin et al., 1959; Juret et al., 1978; Kansal & Potier, 1986; Wagner & Wolff, 1977).

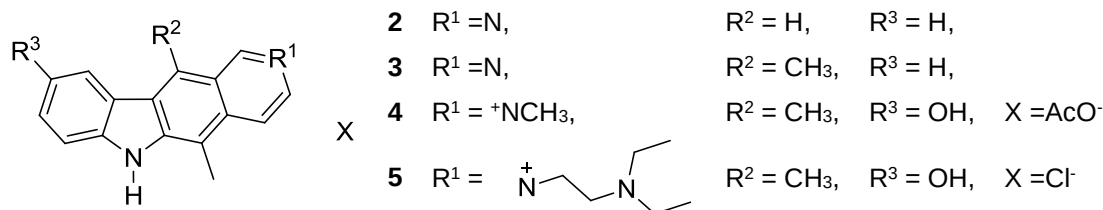


Figure 1.2 Carbazole derivatives against tumors cells

A large number of olivacine derivatives with antitumor activities are in current clinical use, or in stage of clinical development, such is the case of derivatives datelliptium (**5**), S30972-1 (**6**), S-16020 (**7**) and S-16020-2 (**8**) (Figure 1.3), all are in advanced stages of clinical trials (Auclair et al., 1978; Auclair et al., 2007; Le Mée et al., 1998; Malonne et al., 2000).

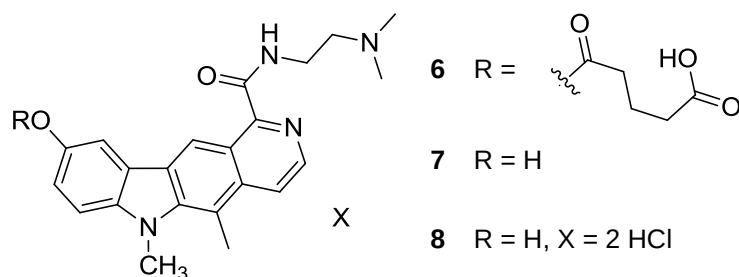


Figure 1.3 Carbazole derivatives in current use or in stage of clinical development

Besides the ring-fused carbazoles mentioned above, the Pyrayafoline D also known as isomahanine (**9**) (Figure 1.4) has screened cytotoxic activity against human leukemia cells, benzo[*a*]carbazoles **10** and **11** (Figure 1.4) exhibited cytotoxic activity against leukemia, renal tumor, colon cancer and malignant melanoma tumor cells (Pindur & Lemster, 1997), and Koenoline (**12**) (Figure 1.4) was screened as cytotoxic compound in the National Cancer Institute (NCI) in vitro anticancer drug discovery (NCS-654286) (Fiebig et al., 1985; Ito et al., 2006; Knölker & Reddy, 2002; Liger et al., 2007).

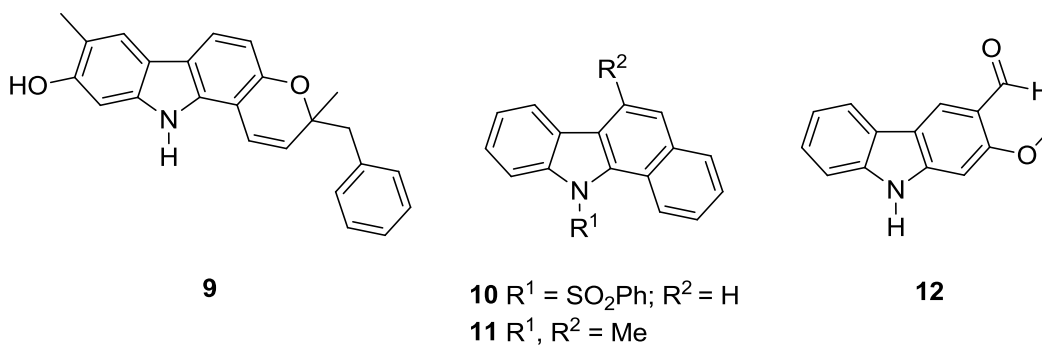
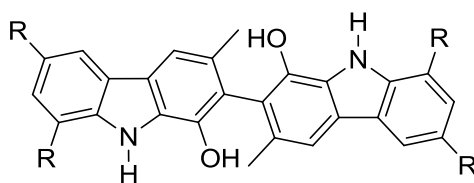


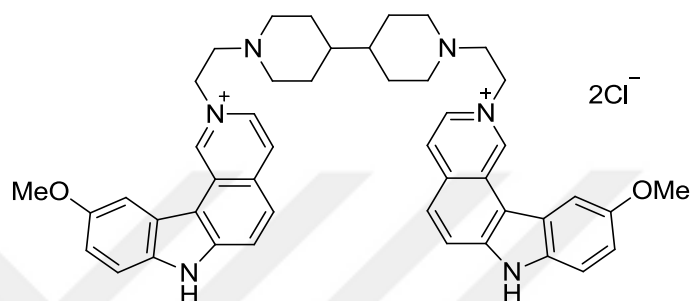
Figure 1.4 Carbazole derivatives with cytotoxic activity

Dimeric carbazole compounds such Clausemine-A (**13**) and bis(*O* demethylmurrayafoline-A (**14**) (Figure 1.5), have displayed cytotoxicity against cancer cells as well antimalarial activity and ditercalinium® (NSC 335 153) (**15**) (Figure 1.5) is clinically used as Deoxyribonucleic acid (DNA) intercalator in the treatment of cancer (Bringmann et al., 1995; Bringmann et al., 1998).



13 R = OMe

14 R = H



15

Figure 1.5 Dimeric carbazole compounds

1.2.2 Cardiovascular, Analgesic/Anti-inflammatory and Anti-pyretic Agents

Moreover their anti-tumor and anticancer activities, carbazole compounds are used by pharmaceuticals for the treatment of cardiovascular diseases and as anti-inflammatory medications. Carazolol® also called Suacron® (BM 51.052) (**16**) (Figure 1.6) in veterinary is a medicine administrated to pigs in order to relieve the stress and prevent frenzy during mating, mastitis and metritis while in humans is used for the treatment of angina pectoris and tachycardias (Innis et al., 1979; Kay et al., 2016). Other cardiovascular insufficiencies like hypertension and heart failure are treated with the carbazole vasodilating β -adrenergic blocking agent known as Carvedilol, Coreg™® or GSK (**17**) (Figure 1.6) (Feuerstein et al., 1997).

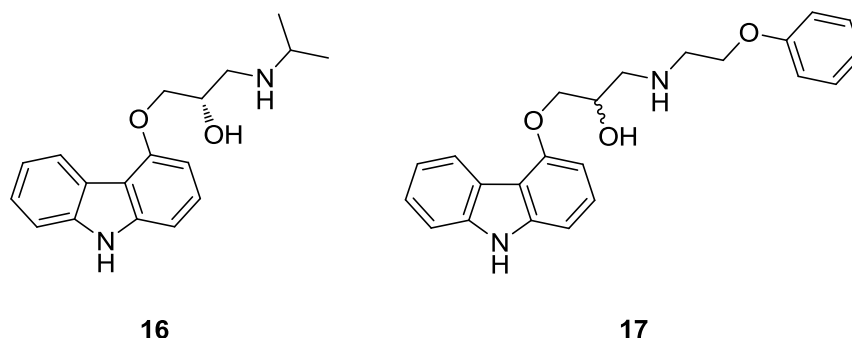


Figure 1.6 Carbazole compounds with anti-inflammatory activities

As analgesic drugs, carbazole derivative Carprofen (**18**) (Figure 1.7) has been used commercially as a substitute for non-steroidal anti-inflammatory drugs under the commercial names of Imadyl® or Rimadyl® for dogs, cows and horses. It is worth mentioning that Carprofen's effect in cellular tests resulted comparable to hydrocortisone and higher than ibuprofen (Masaki et al., 1977). Another example of the therapeutic properties of carbazole compounds is the *N*-alkyl amino carbazole, Rimcazole® (BW234U) (**19**) (Figure 1.7) which was found to be a sigma receptor antagonist capable to induce hypothermia and act as neuroleptic, antipsychotic agent (Bejanian et al., 1991; Ferris et al., 1986; Gilmore et al., 2004).

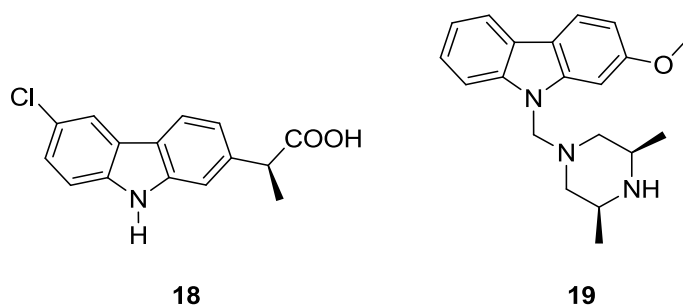


Figure 1.7 Carbazole compounds with anti-inflammatory and anti-pyretic activities

1.2.3 Antioxidant, Metabolic Disorders and Lowering Agents

From a metabolic point of view, carbazole compounds have been studied to understand biological processes and have led the synthesis of antioxidant,

antihyperuricemic, agents etc. In this context, carbazole anilide compounds **20** and **21** (Figure 1.8) have been probed as antagonists of the neuropeptide Y-5 responsible to promote the sense of hunger. Although the derivative NPY5RA-972 (**21**) did not block the neuropeptide Y-5 nor reduced feeding in rats, it helped to understand the role of the neuropeptide Y-5 for the treatment of obesity (Block et al., 2002).

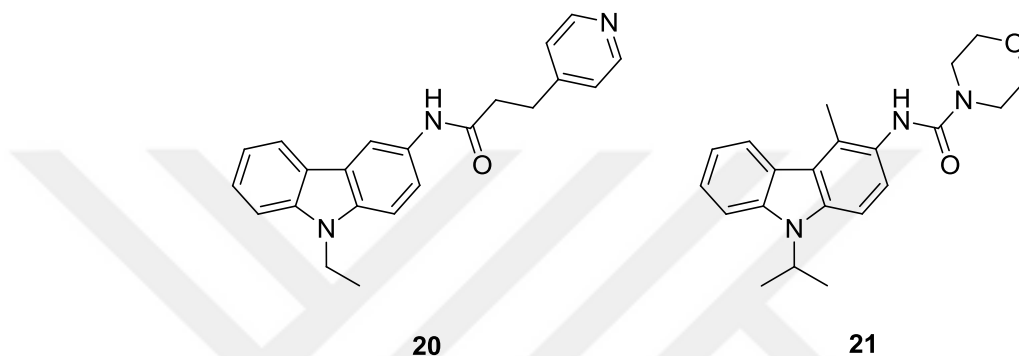


Figure 1.8 Carbazole antagonists of the neuropeptide Y-5

Carbazole compounds are non-purine alternatives to the medication used to prevent gout and hyperuricemia metabolic disorders. The compound bearing a cyclopropyl ring **22** (Figure 1.9) was found to be the most potent inhibitor of the enzyme Xanthine Oxidase (XO) associated with these disorders (Bandgar et al., 2012). Carazostatin (**23**) (Figure 1.9) has shown antioxidant activity against lipid peroxidation induced by free radicals, studies in liposomal membranes showed that carazostatin has even stronger activity than α -tocopherol (Iwatsuki et al., 1992).

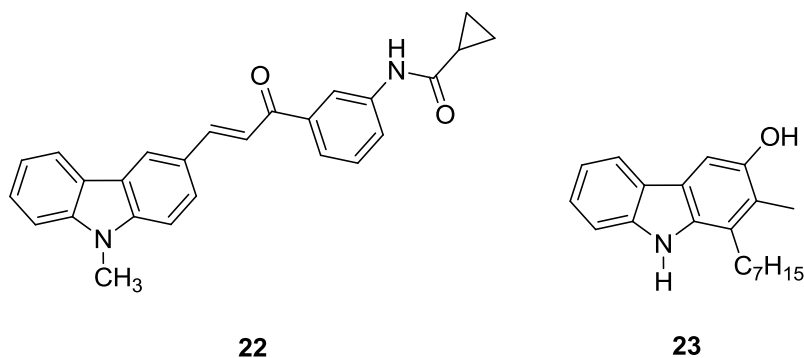


Figure 1.9 Carbazole compounds against metabolic disorders

1.2.4 Antiviral Agents

Carbazole compounds have been evaluated as antiviral compounds in virus such Human Immunodeficiency Virus (HIV) and herpes. Tubingensis A and B (**24**, **25**) (Figure 1.10) displayed activity against herpes virus type 1 (TePaske et al., 1989). *O*-Methylmukonal also known as Glycosinine (**26**) (Figure 1.10) exhibited strong anti-HIV-1 activity with a potential therapeutic index (PTI) of 56.7 (Kongkathip et al., 2005). Furthermore, siamenol (**27**) (Figure 1.10) showed moderate anti-HIV activity with potential as an HIV medication (Meragelman et al., 2000).

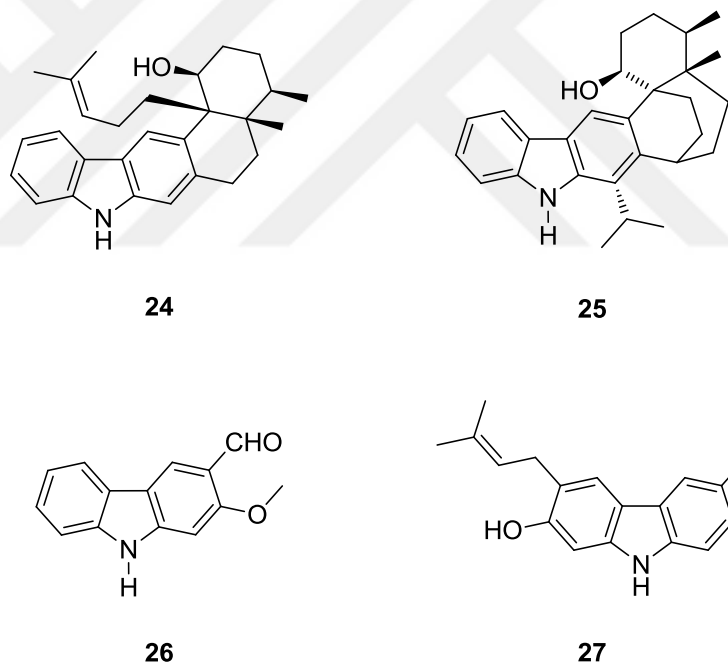


Figure 1.10 Carbazole compounds with antiviral activities

1.2.5 Antibacterial and Antifungal Agents

Increasingly important is the search for compounds with antibiotic properties due to the drug resistance generated by microorganisms. Therefore the carbazole compounds have gained interest in the discovering of new drugs because of their various

bioactivities, structural features and level of efficacy that is comparable with commercial drugs. One example are carbazole tethered thio-tetrazole derivatives **28** and **29** (Figure 1.11), these compounds possess fungal activity against *Candida albicans*, *Candida glabrata* and antibacterial activity against *Pseudomonas aeruginosa* on a similar level as commercial drugs ketoconazole and chloramphenicol (Kaplancıklı, 2011).

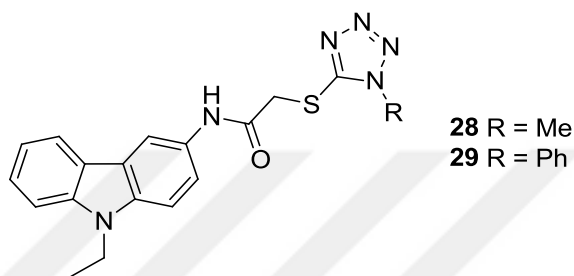


Figure 1.11 Carbazole thio-tetrazole derivatives

Remarkable is the case of commercially antimalarial compound TDR301377 (**30**) (Figure 1.12) discovered by one of the centers of the World Health Organization (WHO), compound **30** has activity against chloroquine resistant *Plasmodium Falciparum* K1 (Pf-K1) and has led the design of more antimalarial compounds based on the carbazole core **31-32**, (Figure 1.12) (Molette et al., 2013)

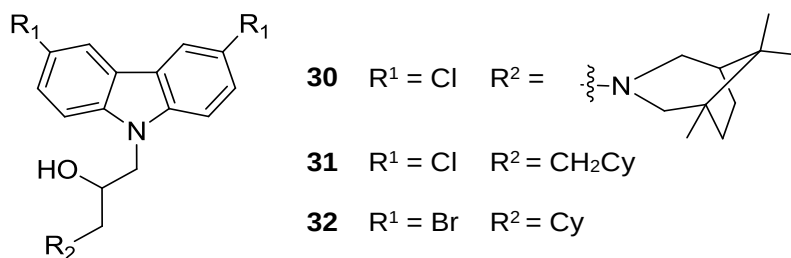


Figure 1.12 Carbazole compounds with antimalarial activity

Another example are the carbazoles with multiple activities found in *Clausena excavate*; clausine K (clauszoline-J) (**33**), 7-methoxy-mukonal (**34**), mukonal (**35**), 3-formylcarbazole (**36**) and methyl carbazole-3-carboxylate (**37**) (Figure 1.13), possess activity against *Mycobacterium tuberculosis* H₃₇Ra and most of them presents anti-

fungal activity against *Candida albicans* (Sunthitikawinsakul et al., 2003) (Choi et al., 2006).

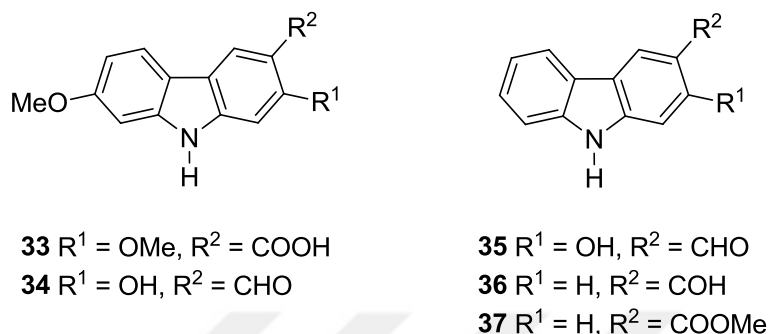


Figure 1.13 Carbazole compounds with antitubercular activity

Additionally, compounds **36** and **37** along with 3-formyl-6-methoxycarbazole (**38**), Micromeline (**39**) and Lansine (**40**) (Figure 1.14) present activity against *Mycobacterium tuberculosis* H₃₇Rv (Ma et al., 2005). Lansine (**40**) besides its anti-tubercular activities, has potency against *Leishmania Donovanii* (the parasite responsible of leishmaniasis disease transmitted through the bite of sandflies) and its derivatives **41-43** (Figure 1.14) are promising compounds with enhanced activity against the axenic amastigotes of the parasite (Pieroni et al., 2012).

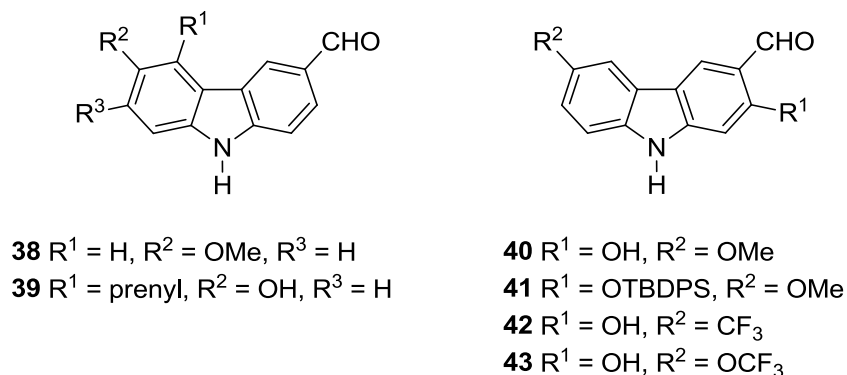


Figure 1.14 Carbazole compounds with antitubercular and antiparasitic activities

Carbazole moiety in many cases potentiate the activities of compounds, here instance the case of the hybrid derivatives of pyrrole and carbazole **44-55** (Figure 1.15) against

Mycobacterium tuberculosis H₃₇Rv. All the compounds of the series resulted active, being the fluoride substituted **45** the most active agent with lower cytotoxicity (Surineni et al., 2015).

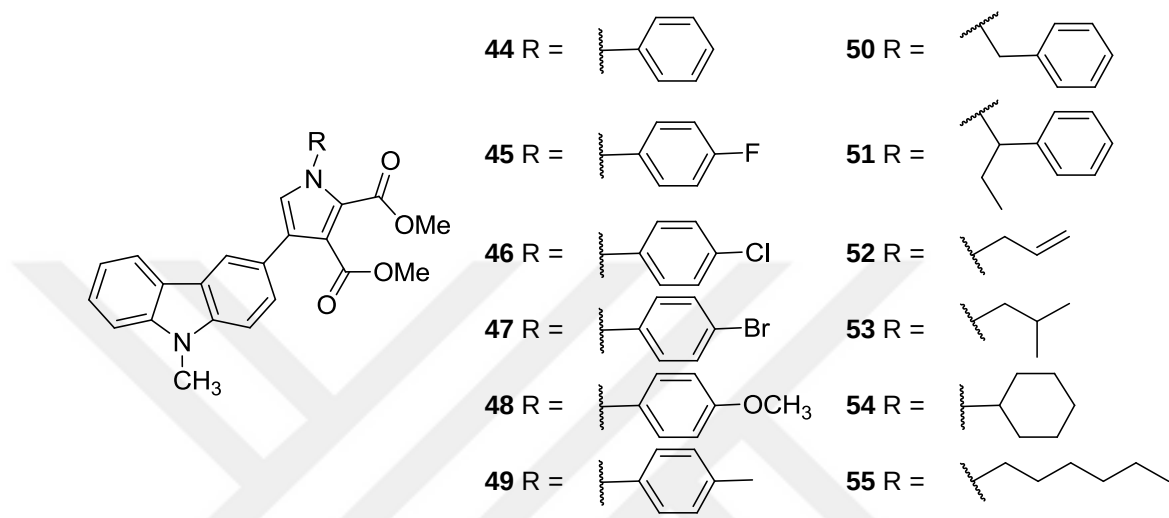


Figure 1.15 Carbazole pyrrole derivatives with antitubercular activity

The same happened to the hybrid derivatives of 1,2,3-triazole and carbazole **56** and **57** (Figure 1.16) which have exhibited even more anti-mycobacterial activity against *Mycobacterium tuberculosis* H₃₇Rv than the antitubercular medications pyrazinamide and ethambutol (Patpi et al., 2012; Surineni et al., 2015).

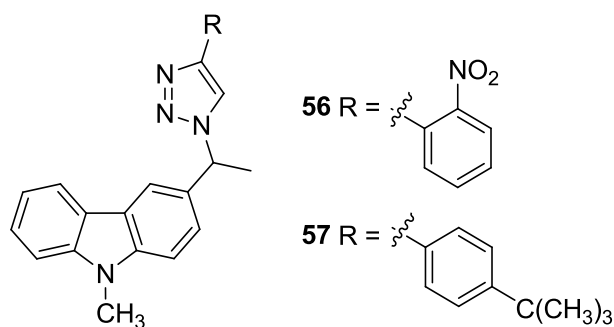
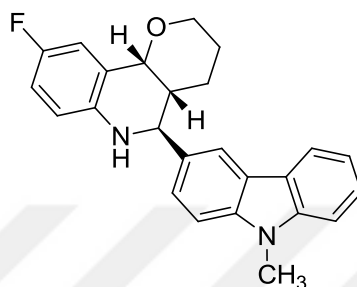


Figure 1.16 Carbazole 1,2,3-triazole derivatives with antitubercular activity

Similarly, the activity of quinolones in combination with carbazole system is raised, such is the case of **58** (Figure 1.17) which has screened anti-tubercular activity against *Mycobacterium Tuberculosis* H₃₇Rv with comparable values to ethambutol (Kantevari et al., 2011).



58

Figure 1.17 Carbazole quinolone derivative

Carbazole compounds are highly sensitive to substitution, this feature leaves the possibility of including esters, glycols, sugars, amino acids, Schiff bases or β -lactams in the structure, in order to produce compounds capable of fight against the resistance through agents developed by microorganisms (Kantevari et al., 2011; Patpi et al., 2012; Surineni et al., 2015).

Since carbazole ring's activity can be influenced by substituents, it allows an enhancement of the effect in β -lactam (2-azetidinone) rings. Carbazole skeleton attached in systems like penicillin (**59**), cephalosporin (**60**), aztreonam (**62**), etc. (Figure 1.19) would led to obtain synthons of antibacterial with diverse pharmacological activities.

1.3 Overview of β -lactam Compounds

Lactams are cyclic amide compounds of different ring sizes, among them are found the β -lactams, 2-azetidinones or 2-oxoazetidine, which are four membered cyclic compounds named as such because the nitrogen atom is bonded to the β -carbon next to the carbonyl group (Figure 1.18) (Burton et al., 2000; Singh & Sudheesh, 2014).

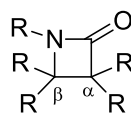


Figure 1.18 β -Lactam ring

β -Lactam compounds have a long history in medicinal chemistry since they constitute an essential part of analgesic, anti-inflammatory, anti-hyperglycemic, anticancer, antiviral and particularly antibiotic compounds (Fudalla et al., 2014).

β -Lactam compounds are well known as antibiotic agents, they comprise more than 65 % of the antibiotics in the market (Fudalla et al., 2014). According to their toxicity and margin of action they are classified as: Penicillins, cephalosporins, carbapenems, monobactams and β -lactamase inhibitors. Some famous examples of each group are: Penicillin G (**61**), cephalosporin-C (**62**), imipenem (**63**), aztreonam (**64**) and clavulonic acid (**65**) (Figure 1.19) (Banik, 2013; Saeb-Parsy et al., 1999).

In the case of **61-64** (Figure 1.19), their mode of action consists in inhibiting the enzymes responsible for the formation of the cell wall, through the reaction of acylation between the lactams and the enzymes called penicillin binding protein (PBP). Once the PBPs react with the lactam, they are no longer active and the microorganism dies (Banik, 2017; Knowles, 1985).

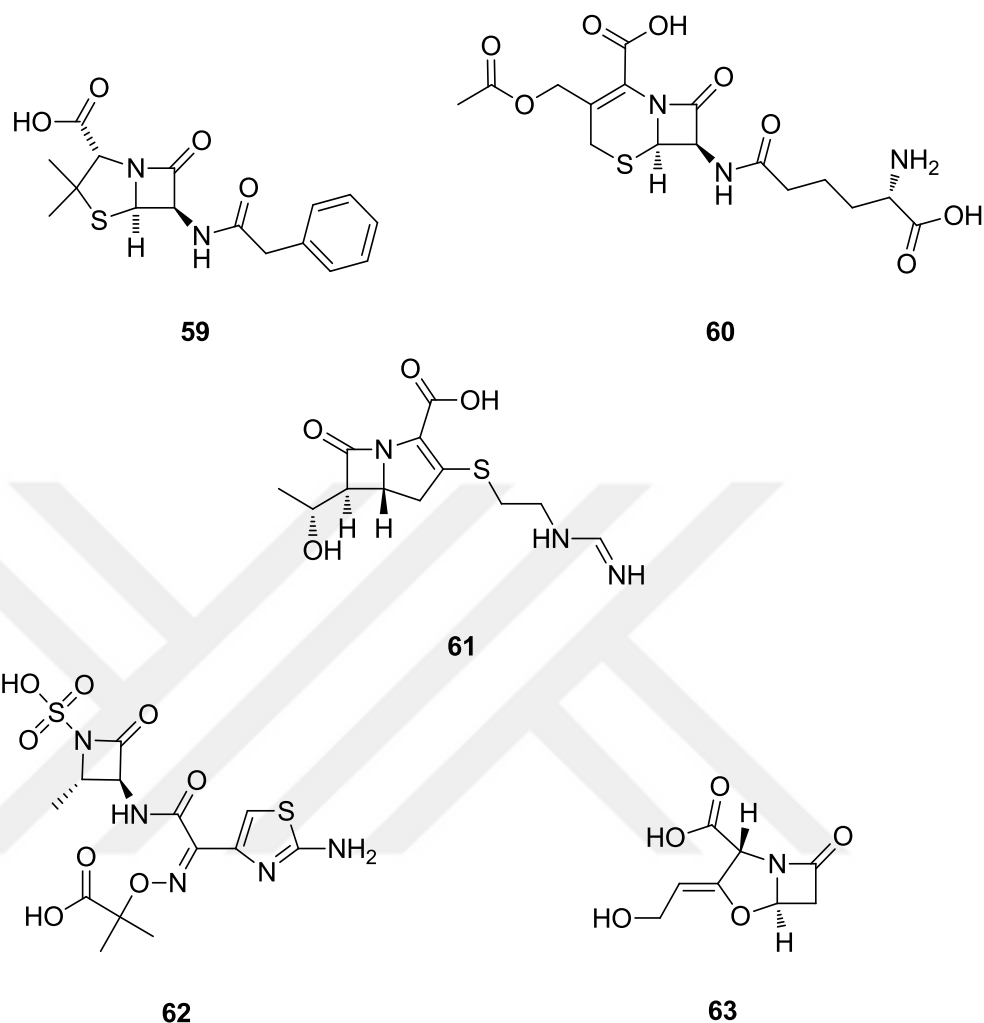


Figure 1.19 Examples of commercial β -lactam compounds

However the excessive use of β -lactam has caused in the microorganisms the development of defense mechanisms to combat the effects of the antibiotics. Defenses such as efflux pumps, enzymes β -lactamases which hydrolyze β -lactam ring and rend it useless, and alterations in the production and affinity of PBPs have driven the pharmaceutical research to the develop of new β -lactam antibiotics with a more specific antibacterial activity (Paige, 1984).

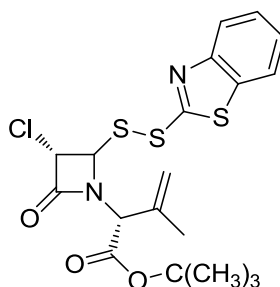
β -lactam antibiotics without fused rings such 3-chloro monocyclic β -lactams have attracted the attention of researchers, due to their powerful antimicrobial, anti-inflammatory, analgesic, anticonvulsant activities. The combination of 3-chloro

monocyclic β -lactams with other compounds, has allowed the development of novel compounds (Kong et al., 2010). The present chapter describes and summarizes some biological and pharmacological activities of the β -lactam compounds, emphasizing its antibacterial properties by which are better known.

1.4 Biological and Pharmacological Activities of β -lactam Compounds

1.4.1 Anti-tumor and Anticancer Agents

Since β -lactams are used mostly as antibacterial agents without significant toxicity, molecules incorporating lactams have been studied as anticancer agents. One example are the derivatives of 4-heteryldithio which showed antitumor activity on human fibro sarcoma, mouse hepatoma, melanoma and neuroblastoma, and fibroblasts. The compound **64** (Figure 1.20) was the most potent and also showed correlation between its cytotoxic action and the intracellular generation of nitric oxide radicals, hence this compound is promisorial (Chavan & Pai, 2007).



64

Figure 1.20 4-Heteryldithio β -lactam derivative

Compounds **65** and **66** (Figure 1.21) were identified as potent inhibitors of tumor cell growth in three cell lines, displaying anti-proliferative activity in low concentrations. The presence of polar and small groups such chloride in the lactam ring resulted favorable for the anti-proliferative activity. These compounds a means of overcoming drug resistance hepatocellular cancer cells (Veinberg et al., 1998).

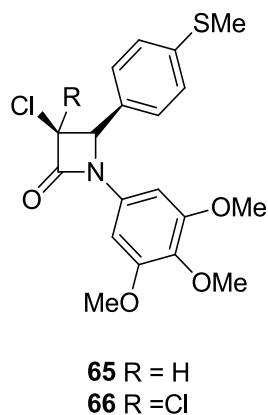


Figure 1.21 β -Lactam derivatives inhibitors of tumor cells

1.4.2 Analgesic/Anti-inflammatory and Anti-pyretic Agents

A large number of non-steroidal anti-inflammatory drugs present gastric toxicity that over long use gets into gastro-intestinal ulceration, bleeding and nephrotoxicity. Therefore, owing to their low toxicity, β -lactams compounds have been studied as potential inflammatory agents. One example are β -lactams of bromoquinazolinones **67** and **68** (Figure 1.22) which have been tested for anti-inflammatory and analgesic and ulcerogenic activities, the compound **67** with *o*-chlorophenyl substitution showed the high activities in the series, other compounds such **68** showed activity comparable to phenylbutazone, it was found that *p*-chlorophenyl substitution increase the anti-inflammatory activity (Kumar et al., 2007; Kumar & Rajput, 2009).

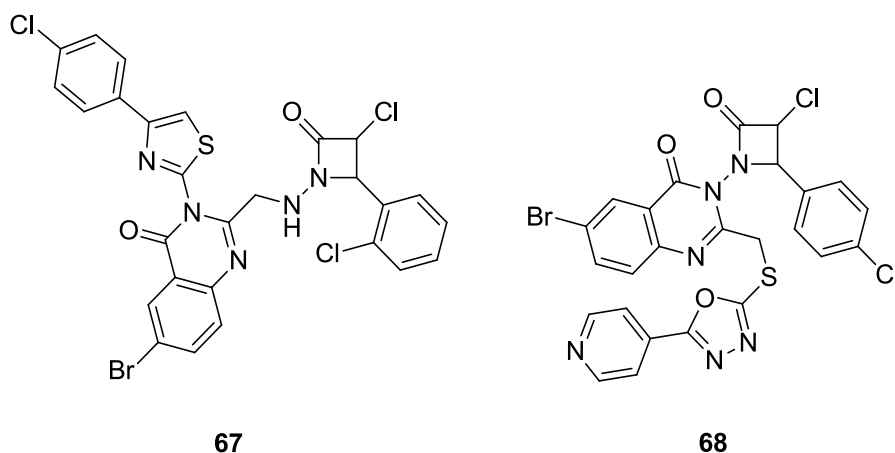


Figure 1.22 Bromoquinazolinone β -lactam derivatives

Hybrids of benzimidazole nucleus with β -lactams have been studied with the intention to increase the analgesic and anti-inflammatory effects of benzimidazole. The compounds obtained **69** and **70** (Figure 1.23) screened for analgesic and anti-inflammatory activity with a clear difference in the activities due to the substitution in the phenyl ring; the *p*-hydroxy and methoxy substituted compounds were essential for the analgesic and anti-inflammatory effect (Chhajed & Upasani, 2016).

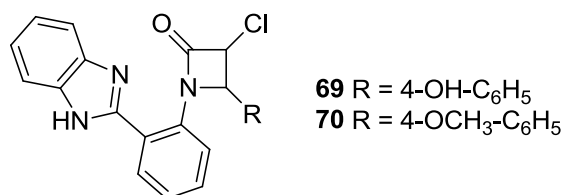


Figure 1.23 Benzimidazole β -lactam derivatives

Some other β -lactams have exhibited multiple activities as antibacterial, antifungal, anti-inflammatory, analgesic, diuretic and antipyretic activities, this is the case for the 3-mercapto-4-amino-5-naphtho-furan-1,2,4- triazoles **71-73** (Figure 1.24). It was observed that the compounds with electron withdrawing substituents (**73**) in the phenyl ring, resulted in enhancement of antibacterial activity and antifungal activity, but for the anti-inflammatory and analgesic activity, the presence of electron donating groups (**71**, **72**) were the responsible in the enhancement of the activity. The compounds also were found

to display diuretic activity and exhibited excellent antipyretic activity which may be due to combined anti-inflammatory and analgesic effects (Kumaraswamy et al., 2013).

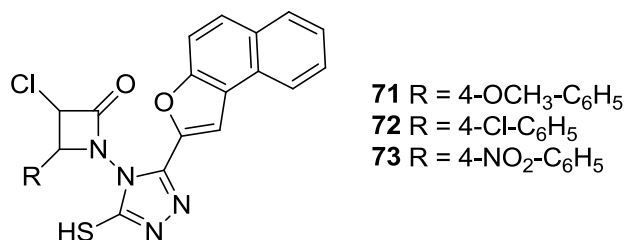


Figure 1.24 4-amino-5-naphtho-furan-1,2,4- triazole β -lactam derivatives

β -Lactams of isonicotinic acid hydrazide such **74-76** (Figure 1.25) were found to have analgesic activity and anti-inflammatory activity greater than that naproxen and protective effects of gastric mucosal lesions. In general the compounds with substituents at the positions 2, 4 and 2 of the phenyl group in the lactam showed maximum anti-inflammatory and analgesic activity (Gilani et al., 2011).

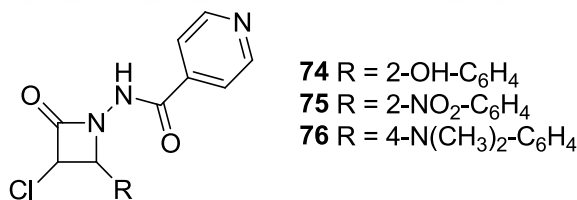


Figure 1.25 Isonicotinic acid hydrazide β -lactam derivatives

1.4.3 Antihyperlipidemic Agents

β -lactam compounds possess lipid lowering properties, the studies over these systems has fallen into the discovering of commercial drug ezetimibe (**77**) (Figure 1.26); capable of reducing low density lipoprotein-cholesterol (LDL-C) levels in blood, generated by diabetes, and has directed the efforts to obtain derivatives **78-81** (Figure 1.26). These new compounds showed antihyperlipidemic activity, it means they showed reduction in cholesterol levels, good percentage of reduction in triglyceride comparable with the lipid

lowering effects of **79**, particularly the compound **80** showed good ability to elevate the High-density lipoproteins (HDL) levels as **79** (Arya et al., 2013).

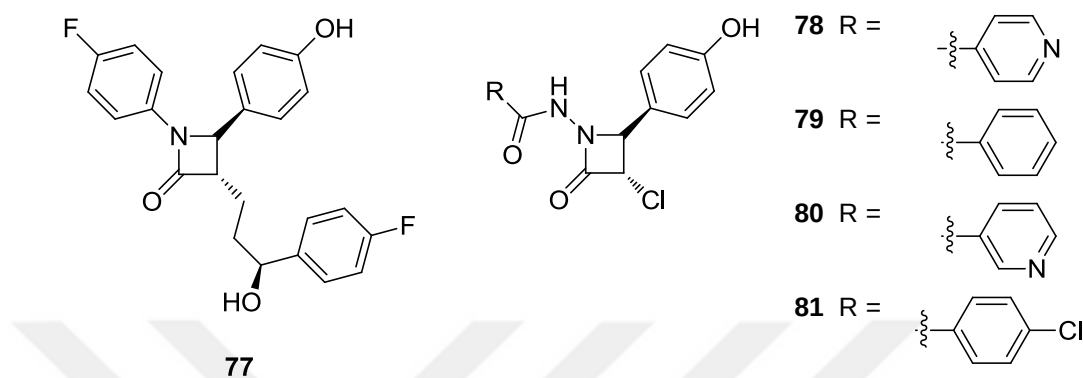


Figure 1.26 Ezetimibe β -lactam and derivatives with antihyperlipidemic activity

1.4.4 Antidepressant and Anticonvulsant Agents

Various β -lactams compounds have been studied due to their effects on the Central Nervous System (CNS), among them are for example the β -lactams of isonocotinyl hydrazone **82-84** (Figure 1.27) which possess antidepressant activity in similar levels to commercial drug Fluoxetine and in the tests of memory deficit resulted nootropic, improving the cognitive function. Is worth to mention that the activities of these compounds were higher when para nitro, halogens and dimethoxy substituents on phenyl were used (electro withdrawing substituents) (Thomas et al., 2016).

Opposite effect of the substituents in the phenyl ring was observed when same β -lactams were tested for anticonvulsant activity in the Maximal Electroshock Seizure (MES) model. The derivatives having electron withdrawing substituents resulted lesser in activity, moreover those having para substituents in the phenyl ring showed greater activities than meta and ortho compounds. The compound **84** (Figure 1.27) resulted the most active since the substitution increased the lipophilicity and interactions with the receptors (Hasan et al., 2011).

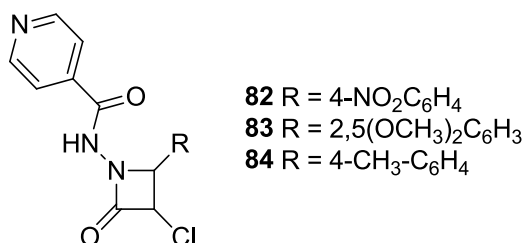


Figure 1.27 Isonicotinyl hydrazone β -lactam derivatives

Some β -lactam compounds have been found to be active candidates, as anticonvulsants agents in comparison to standard drugs. Another example are the β -lactam of quinolin-2-one **85** (Figure 1.28) which screened excellent anticonvulsant activity in MES model at 3 different time intervals, and the derivatives of *p*-amino benzoic **86-88** (Figure 1.28) which resulted also active by MES (Pawar et al., 2011; Pawar et al., 2012).

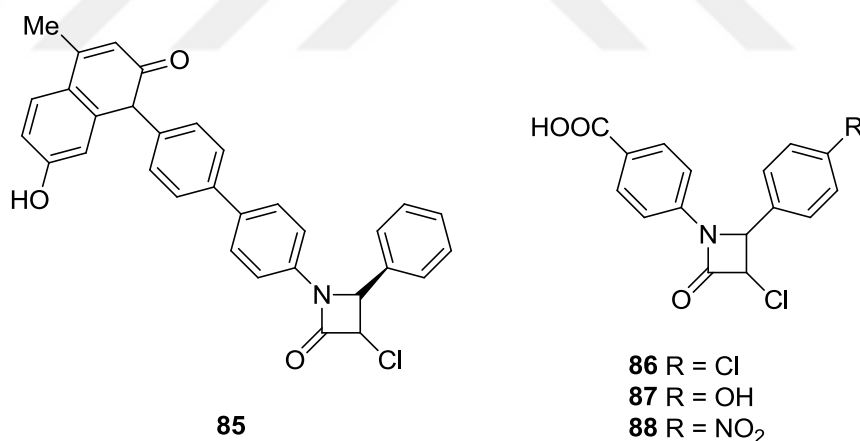


Figure 1.28 β -Lactam derivatives with anticonvulsant activity

1.4.5 Antibacterial and Antifungal Agents

A large number of compounds containing β -lactams possess powerful antibiotic properties, for that reason the studies of the structure and activity of these compounds continues to be very active.

The structure of β -lactams in general is more effective against gram-negative bacteria than gram-positive bacteria, however, it has been seen that electron withdrawing substituents attached to the nucleus lactam ring, influences the antimicrobial activity, such is the case of β -lactams of 5-ethyl pyridine-2-ethanol **89-92** (Figure 1.29). The selectivity of these compounds was affected by the substitution of chloride and bromide and by the substitution of the phenyls attached to the lactam ring, the compounds with bromide (**89**) were more active against bacteria and fungi species, however the compounds with chloride (**90**) had similar activity to the standard and greater margin of activity. The results showed that compounds having substitution 2-Cl in the aromatic rings (**91**) were active against *Escherichia coli* and *Candida albicans* but substitution at 3, 5-Cl (**92**) was excellent against all bacteria (Patel et al., 2014).

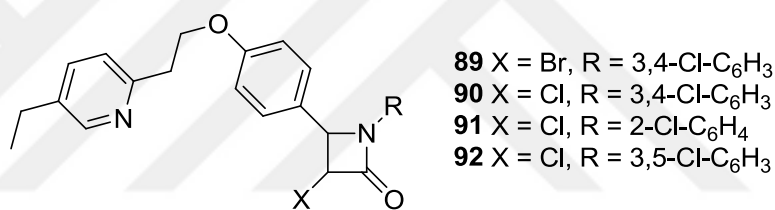


Figure 1.29 5-Ethyl pyridine-2-ethanol β -lactam derivatives

The compounds of 1-butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl)- β -lactams including chlorine moiety in the lactam ring, were reported with enhanced activity against the *Escherichia coli*, *Klebsiella pneumoniae*, and fungi *Aspergillus flavus* and *Aspergillus niger*; the most active compound was **93** (Figure 1.30) (Pathak et al., 2004).

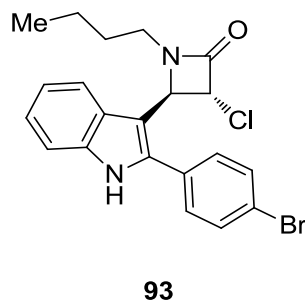


Figure 1.30 1-Butyl-3-substituted-4-(2-aryl-1*H*-indol-3-yl) β -lactam derivative

With respect about the activity and substitution in the phenyl rings attached to the lactam ring, it was observed in most of the β -lactams of benzimidazolyl thioacetamida **94-96** (Figure 1.31), that the electron-withdrawing substitution on the aromatic ring increases the activities, especially the substitution at C-4 (**94**, **95**) just excepting compound **96** which was the most potent. The compounds resulted active against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* bacteria and *Candida albicans*, *Candida krusei*, and *Aspergillus niger* fungus (Desai & Desai, 2006).

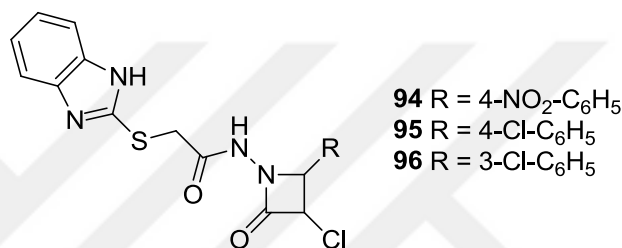


Figure 1.31 Benzimidazolyl thioacetamida β -lactam derivatives

β -lactams of 8-hydroxyquinolines **97-99** (Figure 1.32) have been profusely studied by different groups as antibacterial against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Klebsiella Pneumonia* and *Bacillus subtilis*. The results have been found significant in comparison with the standards ciprofloxacin and ampicillin but as antifungals the results were noticeable against *Candida albicans* (Maity et al., 2012; Sangu et al., 2012).

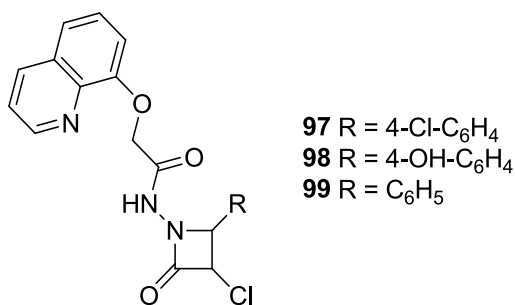


Figure 1.32 8-Hydroxyquinoline β -lactam derivatives

The hybrid of tetrahydrocarbazol ring with β -lactams has resulted in compounds **100** and **101** (Figure 1.33) with antibacterial activity against *Bacillus cereus*, *Bacillus subtilis*, *Streptococcus mutans* and *Micrococcus luteus* and antifungal activity against *Aspergillus niger*, *Candida albicans*, *Alternaria macrospora* and *Fusarium oxysporum*. The compounds with electron donating substituents like, hydroxyl, methoxy, methyl, etc. exhibited better activities than those unsubstituted phenyl and nitrophenyl (Surendiran et al., 2009).

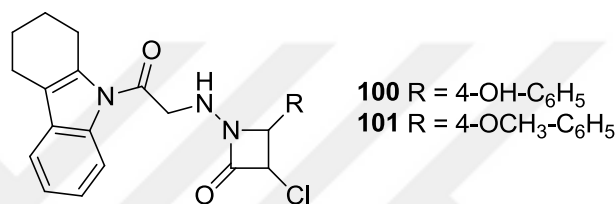


Figure 1.33 Tetrahydrocarbazol β -lactam derivatives

Hybrid compounds have given good results, one example are the hybrid compounds of carbazole, thiadiazol and β -lactams **102** and **103** (Figure 1.34) which screened activity against *Escherichia coli*, *Streptococcus aureus*, *Shigella flexneri* and *Shigella dysenteriae*, and antifungal activity against *Candida albicans*, *Crysosporium pannical*, *Aspergillus niger* and *Rhizopus oryzae*. The compound **102** resulted the most potent also in tests as anticonvulsant but as anti-inflammatory ranked second, while its analogue compound **103** resulted with same activity as the standard drug phenylbutazone (Srivastava et al., 1999).

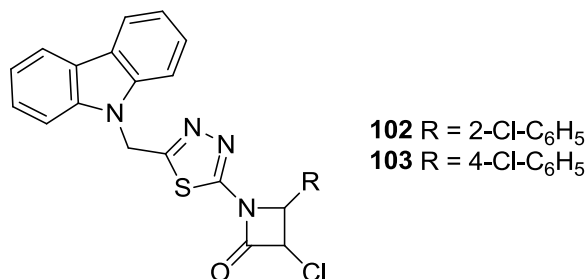


Figure 1.34 Carbazole and thiadiazol β -lactam derivatives

In this context carbazole skeleton allows an enhancement of the potent antibacterial activity in β -lactam rings and led to obtain novel synthons with diverse pharmacological activities. In the present work the synthesis and characterization of a series of novel 9-methyl-9*H*-carbazole compounds with azetidinone moieties, through functionalization, condensation and Staudinger reactions is performed. The synthesized compounds were identified by Infrared spectroscopy (IR) and Nuclear Magnetic Resonance (NMR) spectroscopy.

1.5 State of Research

1.5.1 Synthesis of the Amine Carbazole

The synthesis of the β -lactams was designed to involve three steps using low cost starting materials. These steps include the functionalization of the carbazole ring, the condensation in order to generate the precursors Schiff bases **130-135** (Figure 1.35) and finally the step to obtain the lactams **142-147** (Figure 1.35) by the Staudinger reaction.

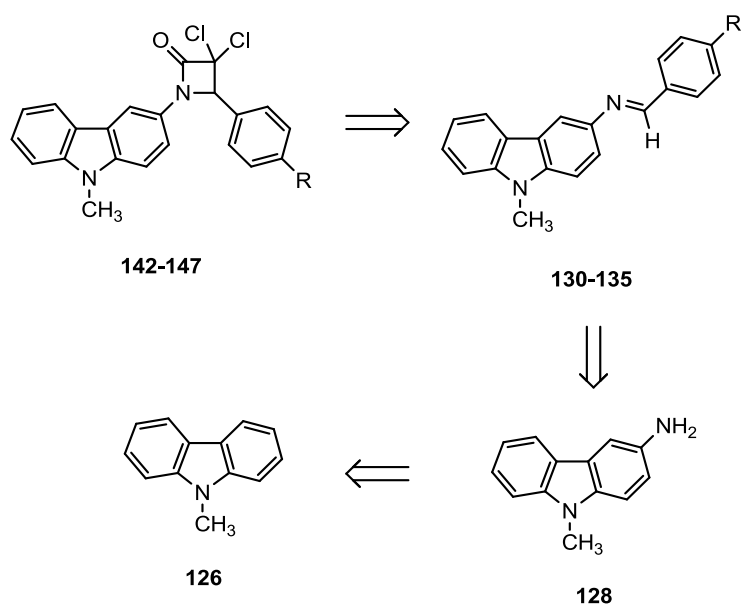


Figure 1.35 Retrosynthesis of β -lactams 142-144

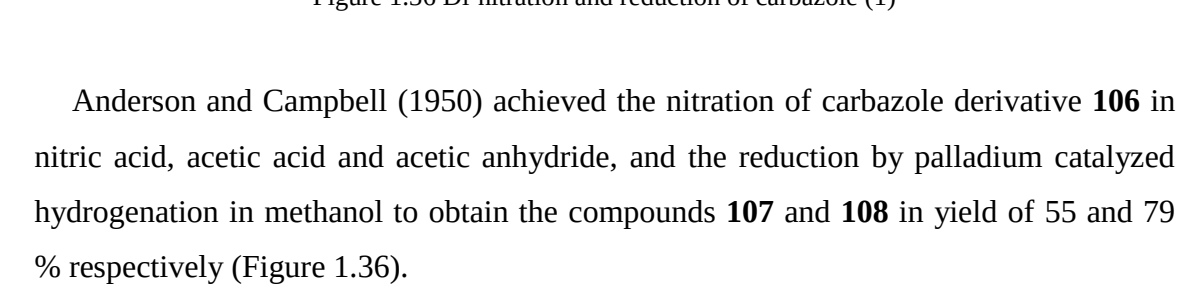
Maity's group discovered that Grotta's method is more convenient because it gives the product with higher purity and yield. They, in turn carried out the nitration of **1.36**) with $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$, acetic acid (HOAc) and acetic anhydride. Subsequently the reduction with metallic tin, acetic acid, and concentrated hydrochloric acid. To afford **104** and **105** in 85 % and 78 % of the respective products (Grigoras & Antonoiaia, 2005).

1

 $\xrightarrow[\text{HOAc, AcO}_2\text{O, } 100\text{ }^\circ\text{C}]{\text{Cu(NO}_3)_2 \cdot 2.5\text{H}_2\text{O}}$

 $\xrightarrow[\text{reflux, 30 h.}]{\text{Sn, Conc. HCl}}$
 104

Figure 1.36 Di-nitration and reduction of carbazole (1)



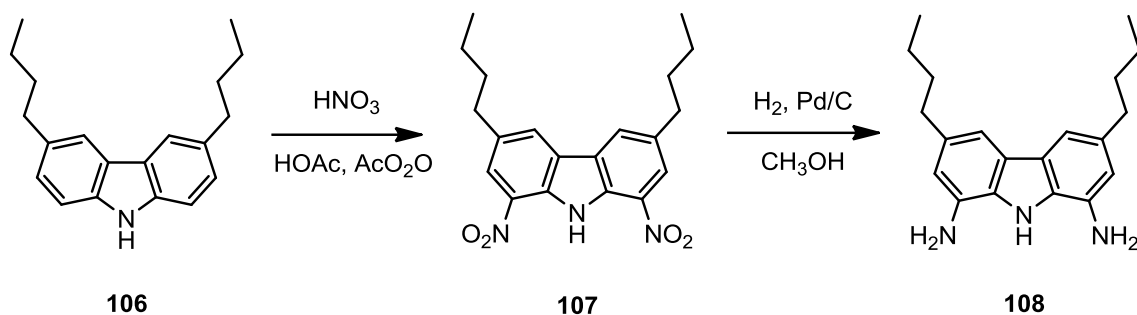


Figure 1.37 Di-nitration and reduction of carbazole derivative 106

A more practical way to avoid the di-nitro product consist in obtaining the mono nitro carbazole as Kuroki and Konishi (1954) by using nitric salts and sulfuric acid (Figure 1.38). Subsequently, the reduction can be carried out with nickel and hydrazine as Lancelot et al. (1983) and obtain the amino compound **111** in 81 % (Figure 1.39).

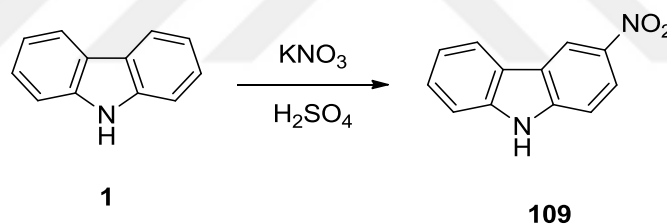


Figure 1.38 Mono-nitration of carbazole (1)

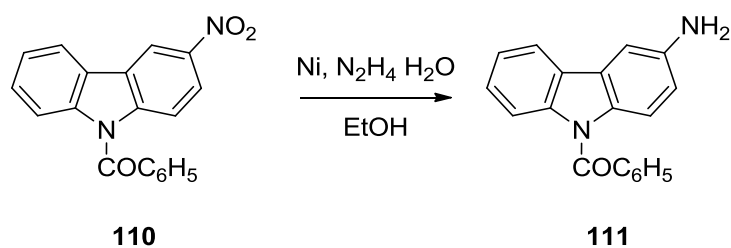


Figure 1.39 Reduction of carbazole derivative 110

The amine compound can be produced through various methods, as seen before, so the combination of reaction steps is possible. Recently into our group, the amino

compound has been obtained from carbazole **1** by using copper salts in acetic acid and acetic anhydride and nickel with hydrazine in ethanol (Figure 1.40) (Şen, 2012).

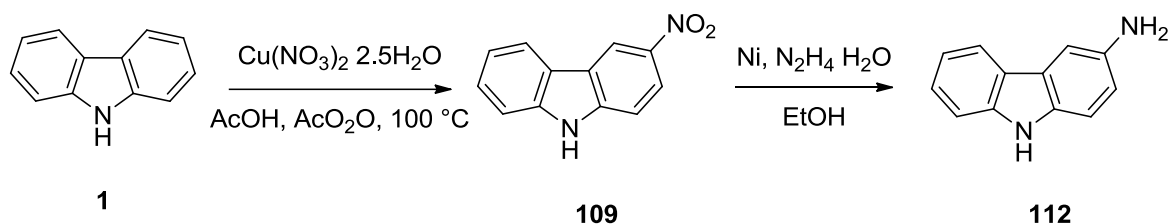


Figure 1.40 Mono-nitration and reduction of carbazole (**1**)

1.5.2 Synthesis of the Aldehyde Carbazole

The synthesis of the β -lactams involves in one step the condensation of amines with aldehydes in order to generate the precursors Schiff bases (Figure 1.41).

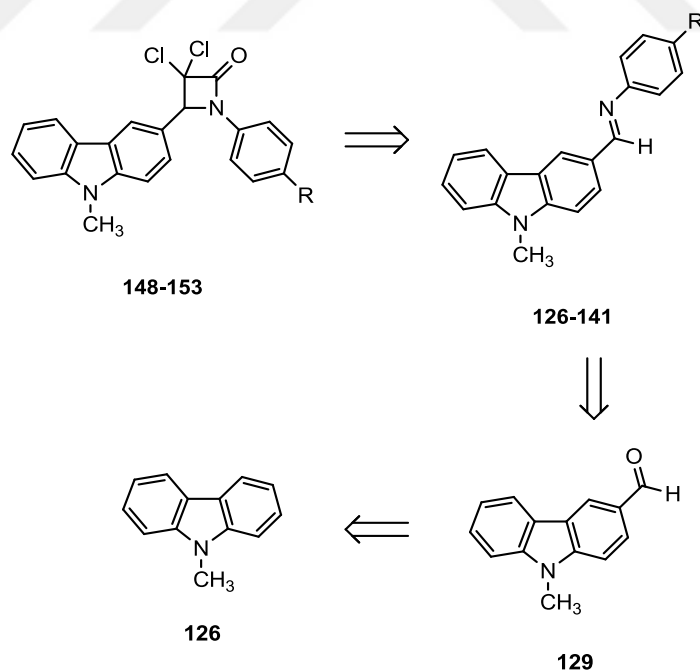


Figure 1.41 Retrosynthesis of β -lactams 148-153

The 9*H*-carbazole-3-carbaldehyde derivatives are important starting materials in the synthesis of new active compounds because their aldehyde fragment can be joined to new components by coupling. These important compounds have been prepared by Kantevari et al. (2011) in yields of 80 % by using 9-methyl-9*H*-carbazole (**126**), α, α -dichloromethyl methyl ether and SnCl₄ at room temperature (RT) in dichloromethane (DCM) (Figure 1.42).

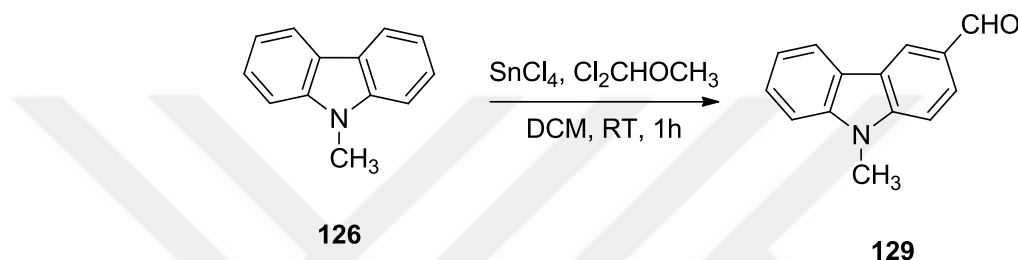


Figure 1.42 Formylation of carbazole derivative 126 by Kantevari's method

Furthermore, Buu-Hoë and Hoán (1951) performed the formylation of 9-methyl-9*H*-carbazole and 9-alkyl- and 3,9-dialkylcarbazoles through a Vilsmeier–Haack reaction by using *N*-methylformanilide (NMF) (Figure 1.43) (Dalton et al., 1967).

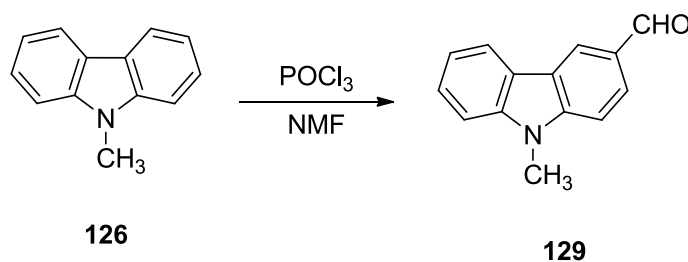


Figure 1.43 Formylation of carbazole derivative 126 by Buu-Hoë-Hoán's method

Mi et al. (2011) performed the Vilsmeier–Haack reaction of 9-(2-Ethylhexyl)-9*H*-carbazole derivative **113**, in a mixture of *N,N*-dimethylformamide (DMF) and 1,2-dichloroethane, in this way they afforded 77.3 % of the compound (Figure 1.44). The same conditions have been used by the groups of Kim et al. (2012) and Gu et al. (2016), who obtained different carbazole derivatives in low yields of 50 %.

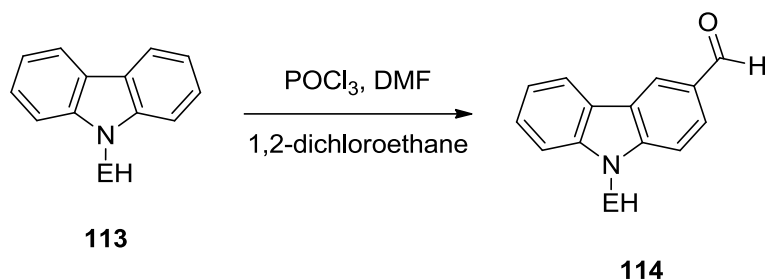


Figure 1.44 Formylation of carbazole derivative 113

Mixtures of DMF and chlorobenzene have been used by Zeng et al. (2009) who followed the method previously described by Lee et al. (2005) to synthesize the compound **116** in 81 % (Figure 1.45).

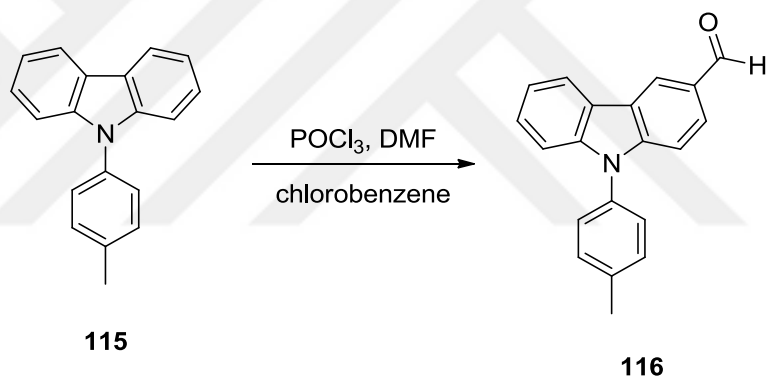


Figure 1.45 Formylation of carbazole derivative 115

In most of the cases the use of solvents is due to the solubility of the compound and the quantities are minimum, one example is the work made by Shi and collaborators. They carried out the Vilsmeier–Haack reaction with DMF, chloroform and POCl₃ to obtain the aldehyde compound **118** in 73 % (Figure 1.46) (Shi et al., 2012).

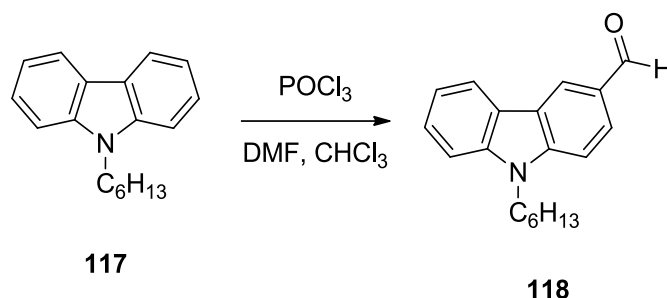


Figure 1.46 Formylation of carbazole derivative 117

The most of conditions of the Vilsmeier–Haack reaction vary slightly, but simplest one is the POCl_3/DMF complex as a catalyst, thus mono- and di-formyl compounds can be obtained. One example is the formylation of 9-ethyl-9*H*-carbazole (**119**) which yielded the compound **120** in 80 % (Figure 1.47). Is worth to mention that, this reaction has been employed into our group with encouraging results (Bandgar et al., 2012; Budreckiene et al., 2006; Díaz et al., 2002; Gündoğdu Hızlıateş, 2013).

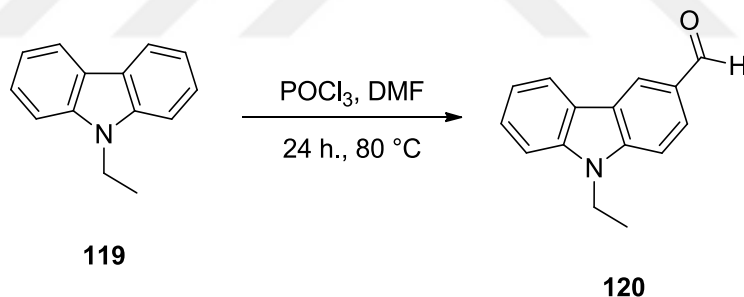


Figure 1.47 Formylation of carbazole derivative 119

1.5.3 Synthesis of the Schiff Bases

Imines also called Schiff Bases are usually produced by condensation reactions (Figure 1.48) between aldehydes or ketones with primary amines (Daintith, 2004; Smith & March, 2007).

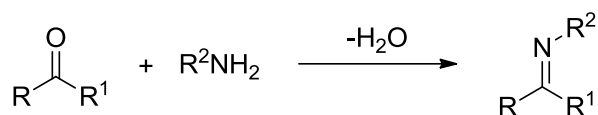


Figure 1.48 Synthesis of imines by condensation of aldehydes and amines

Among the methodologies reported to obtain carbazole compounds bearing Schiff bases are those employing catalytic amounts of para toluene sulfonic acid (TsOH) or glacial acetic acid, H₂SO₄, HCl, or pyridinium *p*-toluene sulphonate, even ZnCl₂, TiCl₄, SnCl₄, BF₃Et₂O, MgSO₄, Mg(ClO₄)₂, etc. in polar protic solvents such methanol and ethanol or solvents with high boiling point in order to facilitate elimination of water by azeotropic distillation, (Figure 1.49-50) (Deniz İş, 2009; Koyuncu, 2011; Li et al., 2016; Yılmaz, 2012).

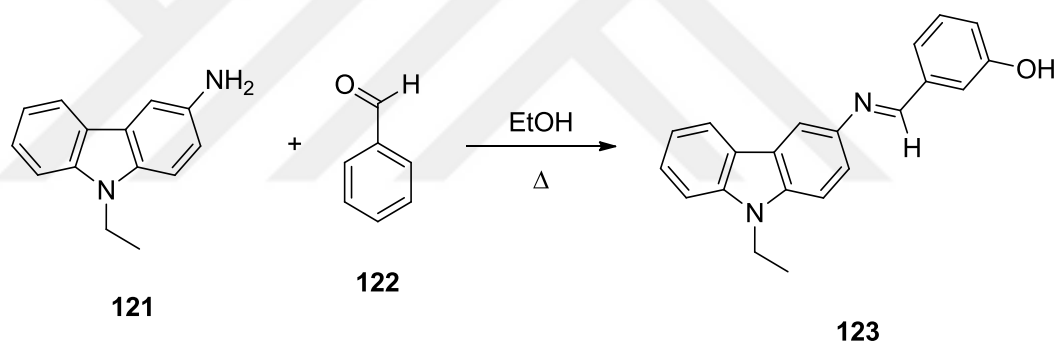


Figure 1.49 Synthesis of the Schiff base carbazole derivative 123

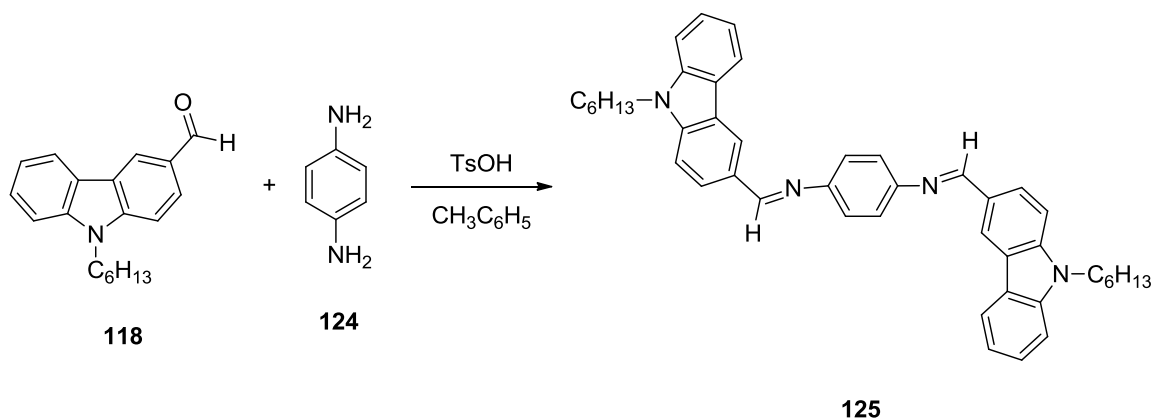


Figure 1.50 Synthesis of the Schiff base carbazole derivative 125

Imines can be prepared from alcohols and amines via oxidative process, by addition of Grignard or organolithium reagents to cyanides, from alkyl and aryl cyanides with phenols or ethers, from addition reactions of amine salts to aromatic ketones, etc. but for practical purposes in this thesis, the condensation of amines and aldehydes is treated (Qin et al., 2013).

1.5.4 Synthesis of Lactams

Many synthetic approaches have been reported to construct β -lactams, hence some of them are depicted (Figure 1.51) (Singh, 2003).

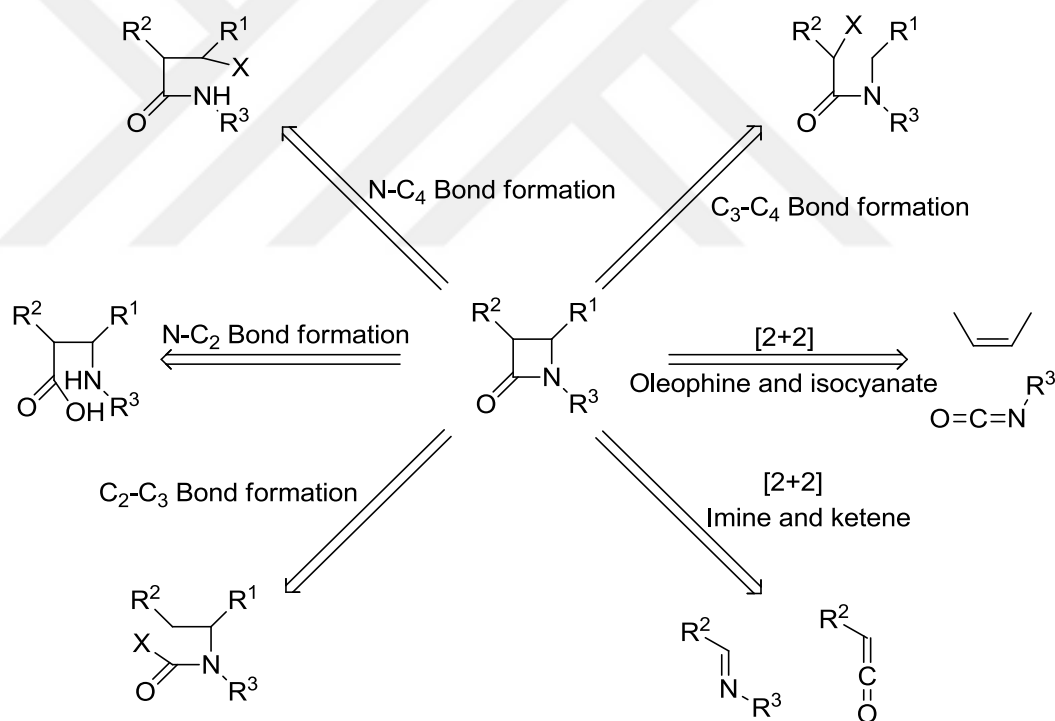


Figure 1.51 Synthetic approaches to β -lactams

The main synthetic route to obtain lactams is the Staudinger's ketene-imine reaction. The reaction involves acid chlorides or α -diazoketones in presence of triethylamine as ketene precursors. The stereochemistry of resulting β -lactams can be with *cis*, *trans* or a mixture of both (Figure 1.52) and it depends of many factors such the solvent, base,

imine substitution, order of the addition of the reagents, temperature, etc. (Banik & Becker, 2000; Xu, 2009).

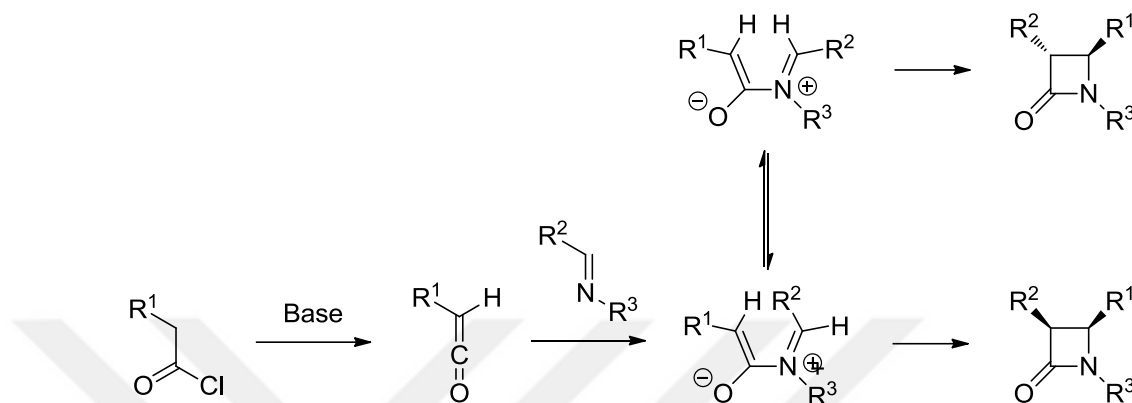


Figure 1.52 Synthesis of lactams by Staudinger's ketene-imine reaction

The reaction proceeds in three steps, in the first step the nucleophile (imino nitrogen) attacks the carbon of the ketene to form a zwitterionic intermediate, then the cyclization occurs and the azetidinones is formed. Several authors have applied the Staudinger reaction to synthesize 2-azetidinones with diverse substituents (Banik & Becker, 2000).

One example of this reaction is in the synthesis of substituted 1,4-diaryl-2-azetidinones from 4,4-benzylidene-anilines, dichloroacetyl chloride and triethylamine by Güner et al. (2005), the respective lactams were tested for antimicrobial activity, against bacteria and fungus .

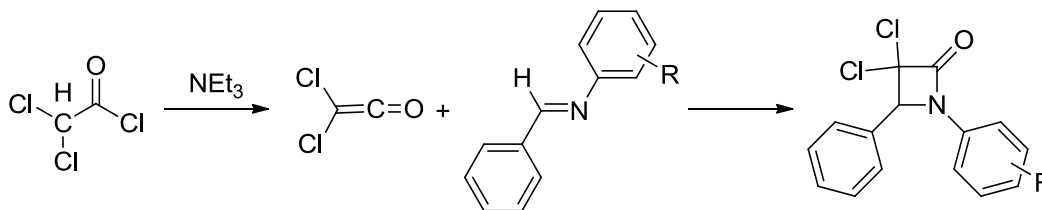


Figure 1.53 General scheme for the synthesis of β -lactams by Güner et al.

CHAPTER TWO

MATERIALS AND METHOD

2.1 Motivation and Objectives

Due to microorganisms develop resistance to antibacterial agents and cause major problems in the treatment of infections. There is a strong need for new antibacterial active compounds against resistant bacteria, here we envisaged to combine the 9-methyl-9*H*-carbazole system with substituted azetidinone moieties in order to synthesize them through condensations and ketene-imine cycloadditions. The new series of compounds may be used in the future as potential new antibacterial agents (Rao, 1998; Salih et al., 2016).

For the design of the compounds were considered two segments:

- The first segment the lactam attached to carbazole, which is the pharmacophore containing chloride units appended to provide drug like properties and serves as a mimetic group, and a substituted aromatic ring to correlate the antimicrobial activity with the substitution of the compounds.
- The second segment correspond to the carbazole, the methyl tethered to the carbazole's nitrogen is append to provide drug like properties and lipophilicity.

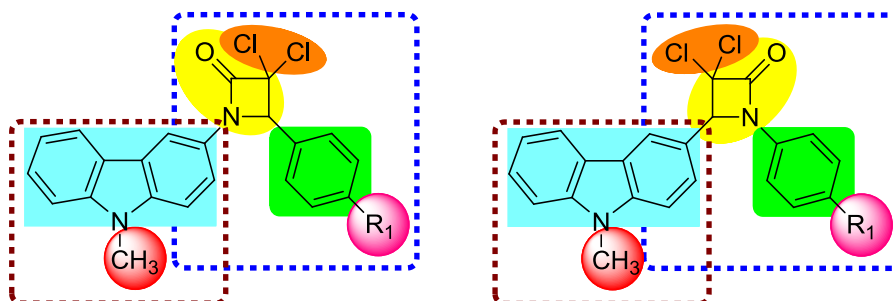


Figure 2.1 Design of the antibacterial β -lactams

Based on this purpose, the following objectives were set for:

- Synthesis of 9-methyl-9*H*-carbazol-3-amine (**128**).
- Synthesis of 9-methyl-9*H*-carbazole-3-carbaldehyde (**129**).

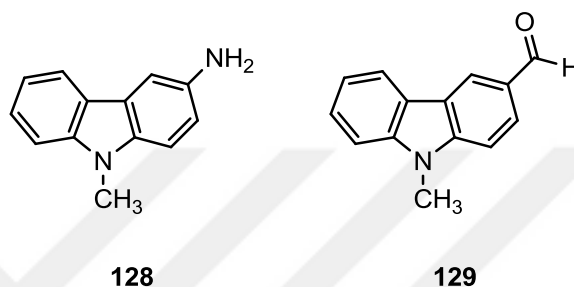


Figure 2.2 Carbazole aldehyde and amine to be synthesized

- Synthesis of various β -lactams with potential antibacterial activity (**142-153**)

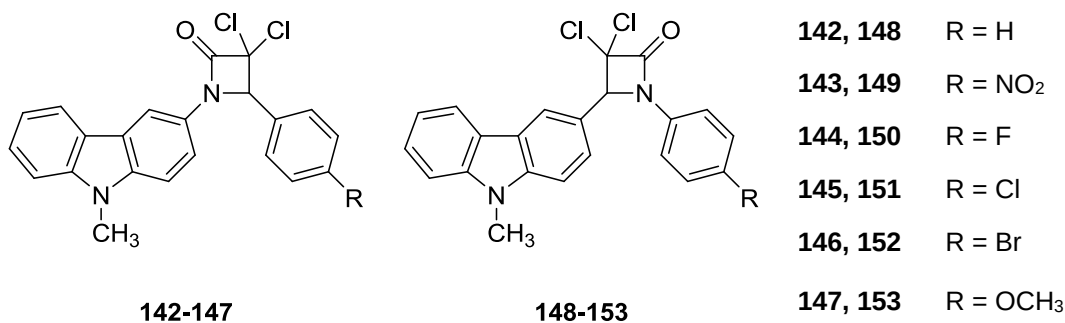


Figure 2.3 Carbazole compounds to be synthesized

2.2 Synthesis Plan

This work produced a series of carbazole compounds bearing a β -lactam moiety toward the route of synthesis outlined below.

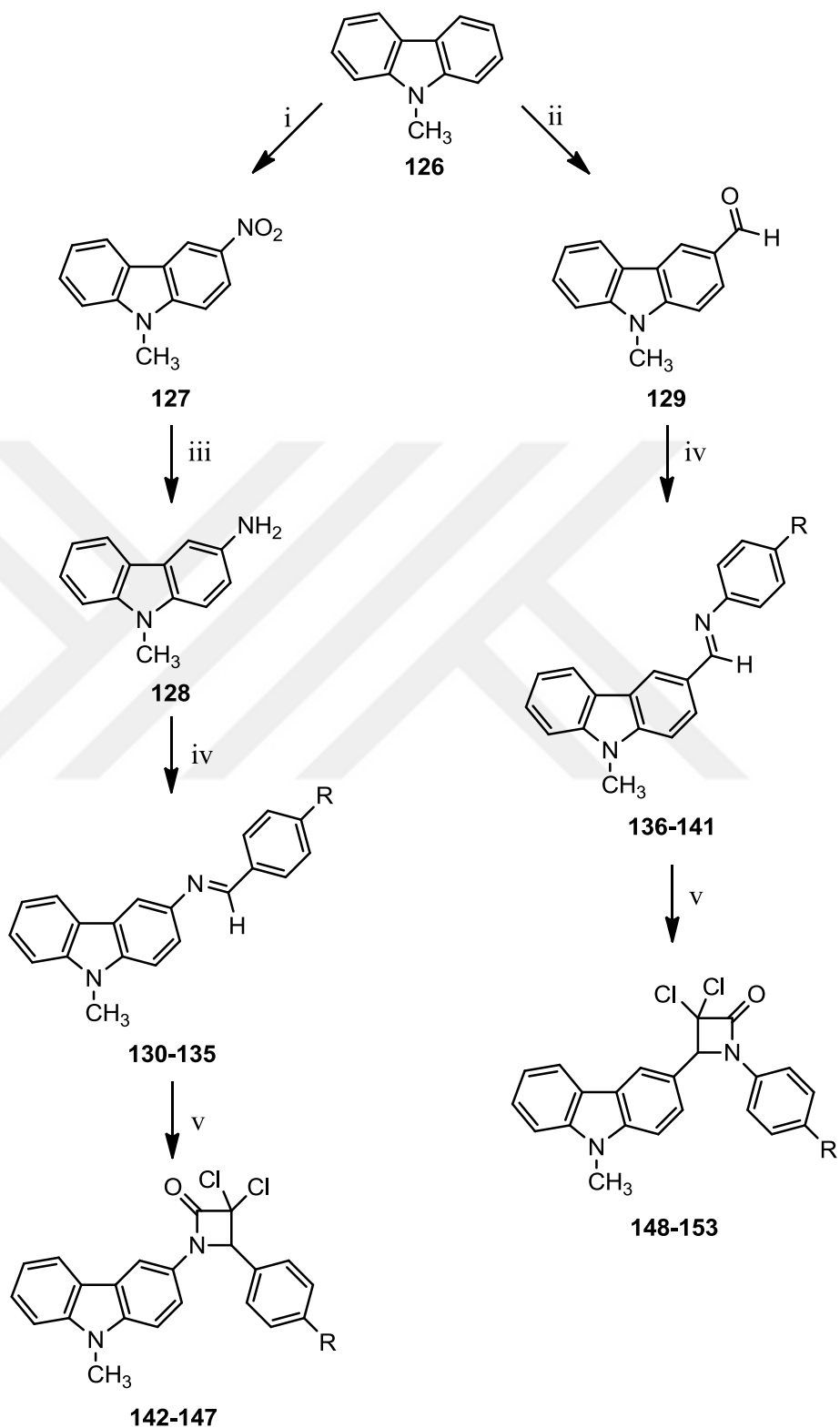


Figure 2.4 Synthesis Plan Conditions: i) Cu(NO₃)₂, HOAc, OAc₂O ii) POCl₃, DMF, iii) Pd/C, EtOH, N₂H₄ iv) TsOH, C₆H₆ v) NEt₃, 2,2-dichloroacetyl chloride, Dioxane

2.3 Experimental

2.3.1 Materials

- **Reaction conditions and reagents**

All the chemicals, reagents and solvents used for the synthesis and purification were purchased from commercial sources (Aldrich, Fluka, Merck) and were used without further purification

- **Chromatography**

All reactions courses and product mixtures were followed by TLC (Thin layer chromatography) on silica gel, aluminum sheets 60 F₂₅₄ from Merck.

All flash chromatography columns were performed using silica gel 60 (0.040-0.063 mm, 230-400 mesh) from Merck

2.3.2 Instrumentation

- **Melting points**

Melting points were determined in open glass capillary tubes on an Electrothermal IA9100 Fisher Scientific Digital Melting Point Apparatus.

- **IR Spectra**

Infrared spectra were recorded using a Perkin-Elmer Spectrum BX-II Model FTIR spectrophotometer, using samples in KBr disks. The measurements are reported on ν/cm^{-1} (wavenumber scale).

- **NMR Spectra**

^1H NMR spectra were recorded on a Varian AS-400 NMR spectrometer using Dimethyl Sulfoxide deuterated ($\text{DMSO-}d_6$) and chloroform deuterated (CDCl_3) as solvents and TMS as the internal standard. Chemical shifts δ values are expressed in ppm, referring to the internal standard.

Abbreviations of signal multiplicities: s = singlet, d = doublet, dd = doublet of a doublet, m = multiplet. The coupling constants (J) are reported in Hertz (Hz).

2.3.3 *Synthesis procedures and Spectroscopic Information*

2.3.3.1 *Synthesis of 9-methyl-3-nitro-9H-carbazole (127)*

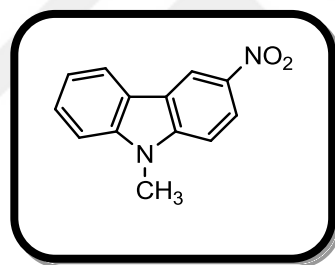


Figure 2.5 Carbazole compound 127

A solution of $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$ (6.5 g, 27 mmol) in a mixture of acetic acid (50 mL) and acetic anhydride (100 mL) was stirred at room temperature. To this solution the 9-methyl-9H-carbazole (**126**) (10.0 g, 55 mmol) was added in portions and the reaction was stirred at room temperature for an hour and then poured into 250 mL of cold water. Finally the precipitate was filtrated and washed five times with 100 mL of water.

Chemical Formula: $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_2$

Molecular Weight: 226.23 g/mol

Yield: 99 %

2.3.3.2 Synthesis of 9-methyl-9H-carbazol-3-amine (128)

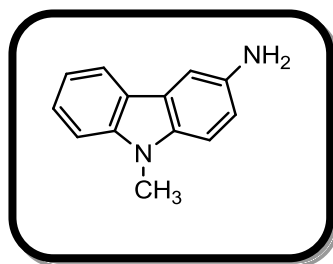


Figure 2.6 Carbazole compound 128

To a solution of 9-methyl-3-nitro-9H-carbazole (5.0 g, 22 mmol) (**127**) in 150 mL of ethanol was added 15% of Pd/C (750 mg), and the mixture was stirred for 30 min. Finally hydrazine monohydrate (10 mL, 220 mmol) was added and the reaction refluxed 4 hrs. The reaction mixture was washed with ethyl acetate and water, the residue was evaporated to dryness and recrystallized from MeOH (Şen, 2012).

Chemical Formula: C₁₃H₁₂N₂

Molecular Weight: 196.25 g/mol

Yield: 80.5 %

2.3.3.3 Synthesis of 9-methyl-9H-carbazole-3-carbaldehyde (129)

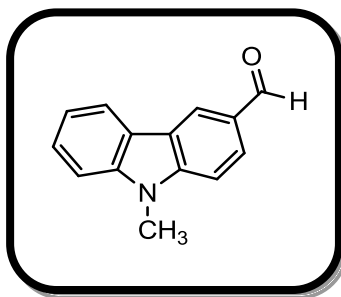


Figure 2.7 Carbazole compound 129

A solution of POCl₃ (6.5 g, 58 mmol) in dry DMF (30 mL, 388 mmol) was stirred and cooled at -0 °C. After 1 hr. a solution of the 9-methyl-9H-carbazole (**126**) (10 g, 48

mmol) in DMF (25 mL, 323 mmol) was added drop by drop and the reaction refluxed 24 hrs. The reaction was then quenched by addition of crushed ice, neutralized with NaOH and extracted with CHCl₃ (3 x 10 mL). The organic phase was washed 2 times with 100 mL of water and was dried over sodium sulphate. Finally the crude product was purified by column chromatography on silica gel using hexane and ethyl acetate mixture (1:3) as eluent (Gündoğdu Hızlıateş, 2013).

Chemical Formula: C₁₄H₁₁NO

Molecular Weight: 209.24 g/mol

Yield: 69 %

2.3.3.4 General Procedure for the Synthesis of Schiff bases (130-141)

The respective amino or aldehyde 9-methyl-carbazole derivatives (2.0 g) were dissolved in 50 mL of benzene under mild heating. Then a solution of equimolar quantities of the aromatic aldehyde (in the case of 9-methyl-9H-carbazol-3-amine) (**128**) or aromatic amine (in the case of 9-methyl-9H-carbazole-3-carbaldehyde) (**129**) in 100 mL was added and stirred with a catalytic quantity of *p*-toluene sulfonic acid. The reaction mixture was refluxed for 8 hrs. and the resultant was washed, filtered and dried.

2.3.3.5 General Procedure for the Synthesis of β -lactams (142-153)

A solution of the respective Schiff's bases and 2 equivalents of triethylamine in 1, 4-dioxane (50 mL) was stirred for 15 min., then a mixture of 2 equivalents of chloroacetyl chloride was added drop wise at 0-5 °C to the solution and the mixture was refluxed overnight. The precipitated amine hydrochloride salts were filtered and the mixture was washed with a solution 5% HCl and 3 times with water and dried over sodium sulfate. The crude obtained was purified by column chromatography on silica gel using hexane and ethyl acetate mixture (1:3) as eluent, and the products were crystallized from hexane/ether.

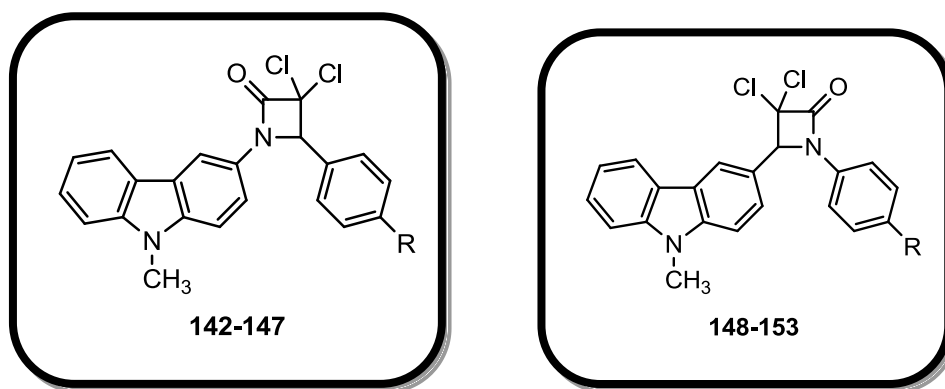


Figure 2.8 Carbazole β -lactams synthesized

The numbers, names, functional groups, chemical formula, molecular weight, yields and melting point of the compounds are shown in Tables 2.1-2.

Table 2.1 Carbazole β -lactams synthesized by number (No.) and name.

No.	Name of the compounds
142	3,3-dichloro-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)-4-phenylazetidin-2-one
143	3,3-dichloro-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)-4-(4-nitrophenyl)azetidin-2-one
144	3,3-dichloro-4-(4-fluorophenyl)-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
145	3,3-dichloro-4-(4-chlorophenyl)-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
146	4-(4-bromophenyl)-3,3-dichloro-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
147	3,3-dichloro-4-(4-methoxyphenyl)-1-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
148	3,3-dichloro-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)-1-phenylazetidin-2-one
149	3,3-dichloro-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)-1-(4-nitrophenyl)azetidin-2-one
150	3,3-dichloro-1-(4-fluorophenyl)-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
151	3,3-dichloro-1-(4-chlorophenyl)-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
152	1-(4-bromophenyl)-3,3-dichloro-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one
153	3,3-dichloro-1-(4-methoxyphenyl)-4-(9-methyl-9 <i>H</i> -carbazol-3-yl)azetidin-2-one

Table 2.2 Carbazole β -lactams synthesized, functional group (R), chemical formula, molecular weight, yield and melting point

No.	R	Chemical Formula:	Molecular Weight (g/mol):	Yield (%)	Melting Point (° C)
142	H	C ₂₂ H ₁₆ Cl ₂ N ₂ O	395.28	11.4	175
143	NO ₂	C ₂₂ H ₁₅ Cl ₂ N ₃ O ₃	440.28	25.9	170
144	F	C ₂₂ H ₁₅ Cl ₂ FN ₂ O	413.27	14.3	195
145	Cl	C ₂₂ H ₁₅ Cl ₃ N ₂ O	429.73	19.7	167
146	Br	C ₂₂ H ₁₅ BrCl ₂ N ₂ O	474.18	24.6	168
147	OCH ₃	C ₂₃ H ₁₈ Cl ₂ N ₂ O ₂	425.31	17.3	216
148	H	C ₂₂ H ₁₆ Cl ₂ N ₂ O	395.28	44.9	219
149	NO ₂	C ₂₂ H ₁₅ Cl ₂ N ₃ O ₃	440.28	63.7	132
150	F	C ₂₂ H ₁₅ Cl ₂ FN ₂ O	413.27	20.6	118
151	Cl	C ₂₂ H ₁₅ Cl ₃ N ₂ O	429.73	47.7	91
152	Br	C ₂₂ H ₁₅ BrCl ₂ N ₂ O	474.18	30.8	189
153	OCH ₃	C ₂₂ H ₁₆ Cl ₂ N ₂ O	395.28	31.7	112

CHAPTER THREE

EXPERIMENTAL RESULTS

3.1 Spectroscopic Spectra

3.1.1 IR Spectra

IR (KBr, ν/cm^{-1}): 3052, (Ar-H stretch), 2934 (CH stretch), 1772 (C=O stretch), 1600, 1474 (Ar C-C stretch), 1322, 1234 (C-Cl stretch), 1156 (C-H wag) (Figure 3.1).

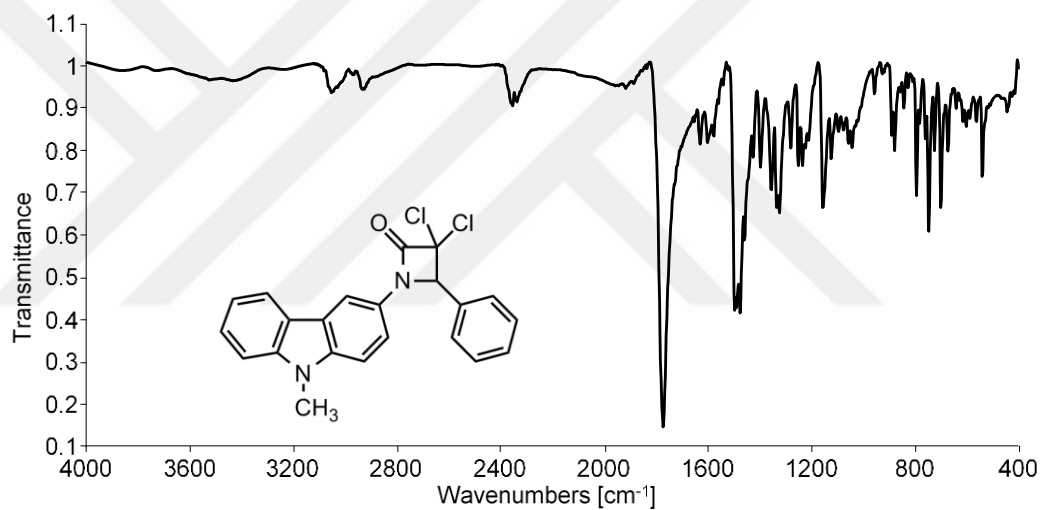


Figure 3.1 IR Spectra of compound 142

IR (KBr, ν/cm^{-1}): 3050, (Ar-H stretch), 2930 (CH stretch), 1774 (C=O stretch), 1664, 1602 1492 (Ar C-C stretch), 1518 (N-O asym. stretch), 1348, 1250 (C-Cl stretch) (Figure 3.2).

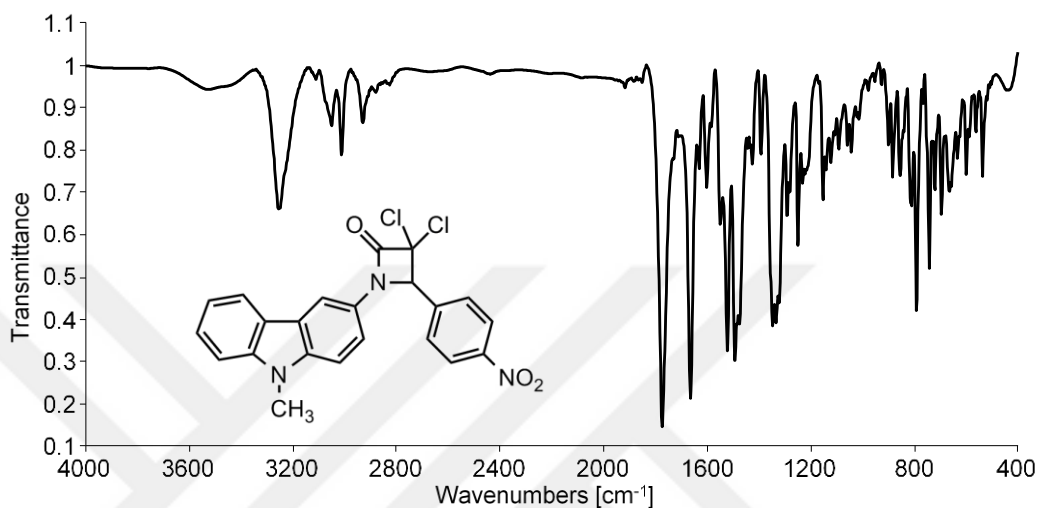


Figure 3.2 IR Spectra of compound 143

IR (KBr, ν/cm^{-1}): 3054, (Ar-H stretch), 2942 (CH stretch), 1770 (C=O stretch), 1606 1490 (Ar C-C stretch), 1322(C-Cl stretch), 1250 (C-F stretch), 1236 (C-Cl stretch), 1156 (C-H wag), 844 (C-F stretch) (Figure 3.3).

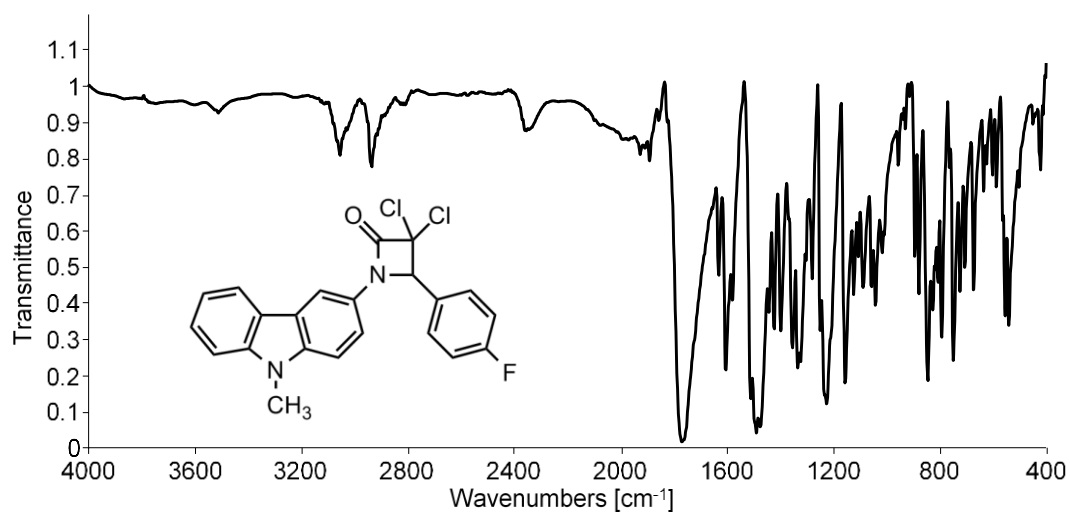


Figure 3.3 IR Spectra of compound 144

IR (KBr, ν/cm^{-1}): 3046, (Ar-H stretch), 2936 (CH stretch), 1764 (C=O stretch), 1596, 1492 (Ar C-C stretch), 1319, 1250 (C-Cl stretch), 1156 (C-H wag), 1090, 896 (C-Cl stretch) (Figure 3.4).

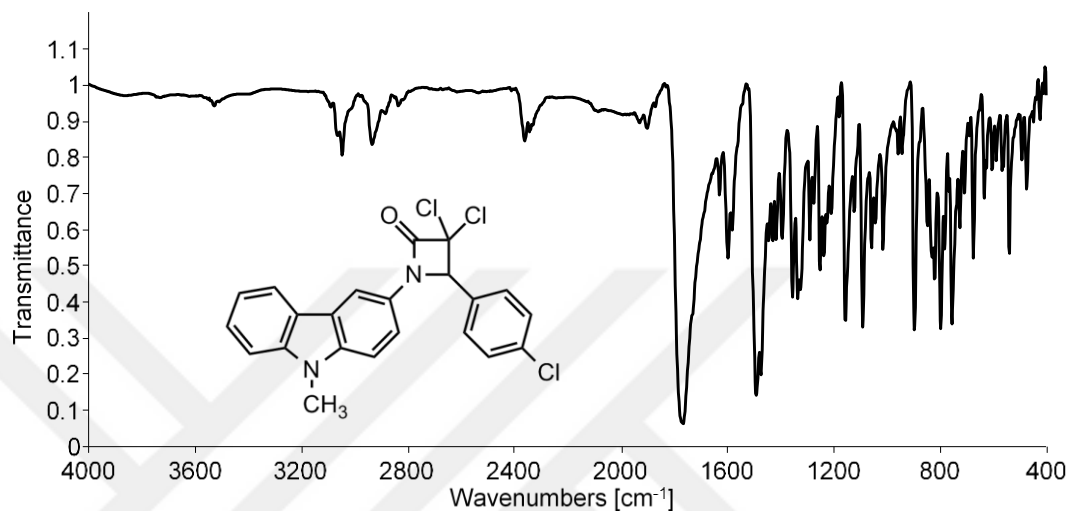


Figure 3.4 IR Spectra of compound 145

IR (KBr, ν/cm^{-1}): 3046, (Ar-H stretch), 2930 (CH stretch), 1766 (C=O stretch), 1664, 1592, 1488 (Ar C-C stretch), 1320, 1250 (C-Cl stretch), 1010 (C-Br stretch) (Figure 3.5).

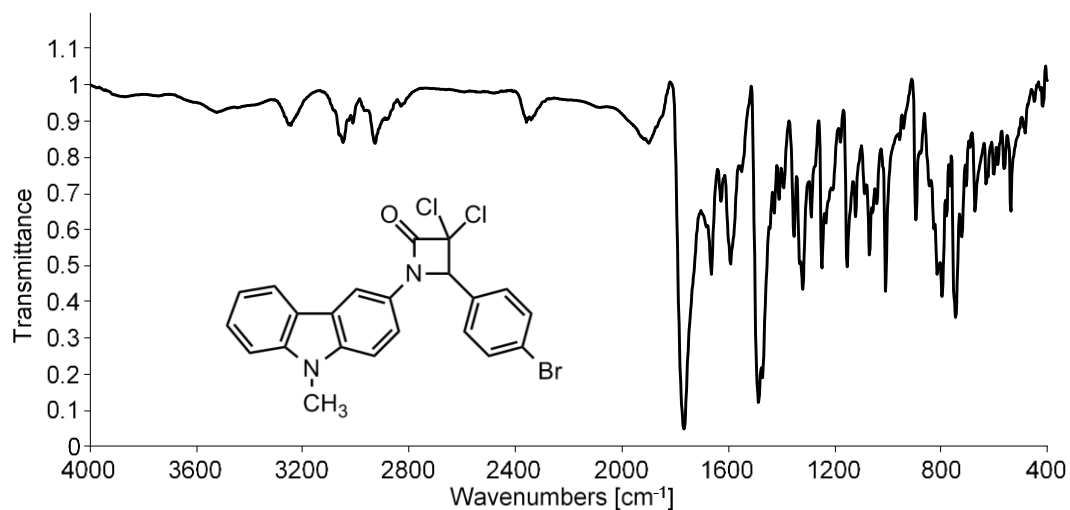


Figure 3.5 IR Spectra of compound 146

IR (KBr, ν/cm^{-1}): 3010, (Ar-H stretch), 2930 (CH stretch), 1764 (C=O stretch), 1662, 1150, 1496 (Ar C-C stretch), 1322, 1248 (C-Cl stretch), 1150 (C-H wag) (Figure 3.6).

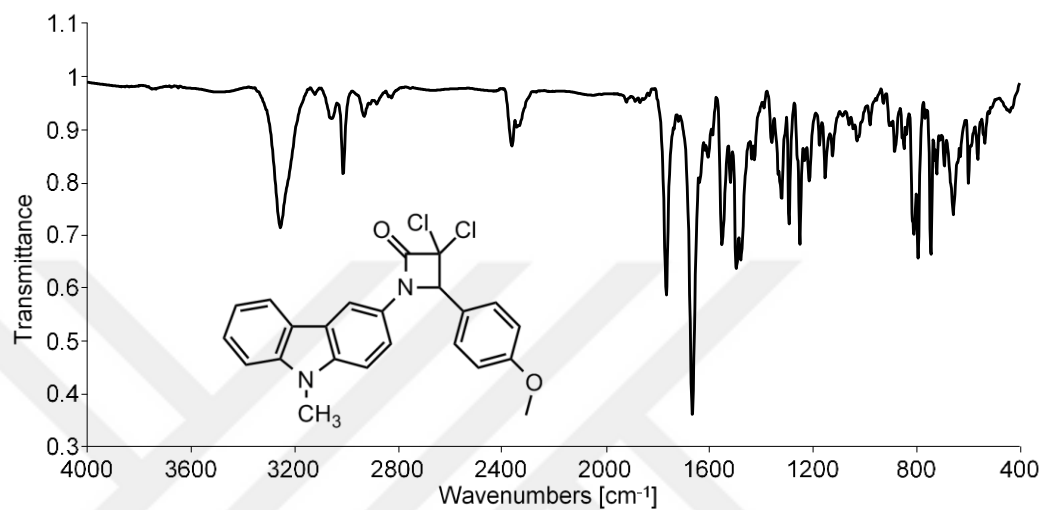


Figure 3.6 IR Spectra of compound 147

IR (KBr, ν/cm^{-1}): 3048, (Ar-H stretch), 2934 (CH stretch), 1772 (C=O stretch), 1598 (Ar C-C stretch), 1496, 1386 (Ar C-C stretch), 1338, 1250 (C-Cl stretch), 1150 (C-H wag) (Figure 3.7).

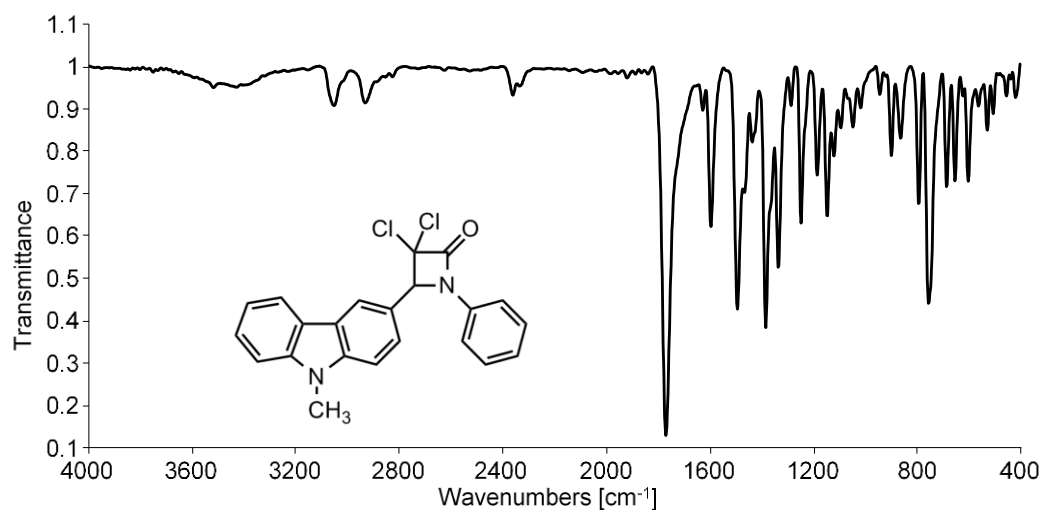


Figure 3.7 IR Spectra of compound 148

IR (KBr, ν/cm^{-1}): 3050, (Ar-H stretch), 2930 (CH stretch), 1784 (C=O stretch), 1594 (Ar C-C stretch), 1518 (N-O asym. stretch), 1496, 1373 (Ar C-C stretch), 1338, 1248 (C-Cl stretch), 1140 (C-H wag) (Figure 3.8).

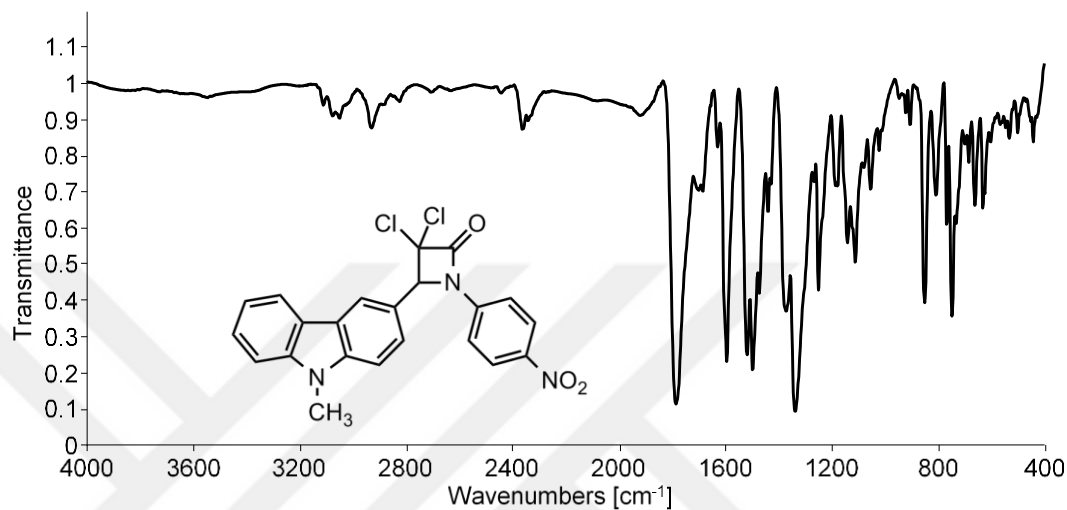


Figure 3.8 IR Spectra of compound 149

IR (KBr, ν/cm^{-1}): 3052, (Ar-H stretch), 2932 (CH stretch), 1778 (C=O stretch), 1600 (Ar C-C stretch), 1508, 1386 (Ar C-C stretch), 1332, 1248 (C-Cl stretch), 1227 (C-F stretch), 1154 (C-H wag), 834 (C-F stretch) (Figure 3.9).

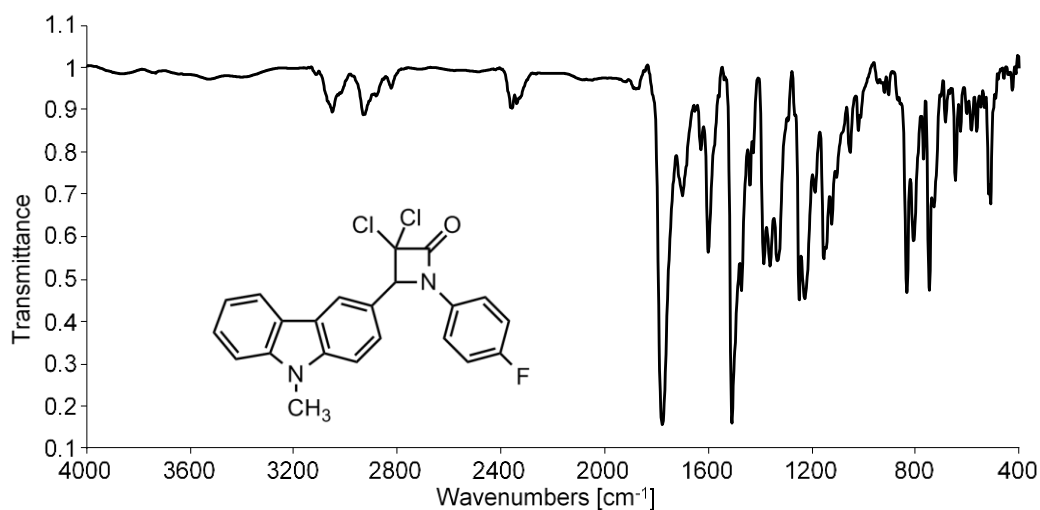


Figure 3.9 IR Spectra of compound 150

IR (KBr, ν/cm^{-1}): 3046, (Ar-H stretch), 2924 (CH stretch), 1778 (C=O stretch), 1596 (Ar C-C stretch), 1490, 1378 (Ar C-C stretch), 1328, 1248 (C-Cl stretch), 1148 (C-H wag), 1092, 826 (C-Cl stretch) (Figure 3.10).

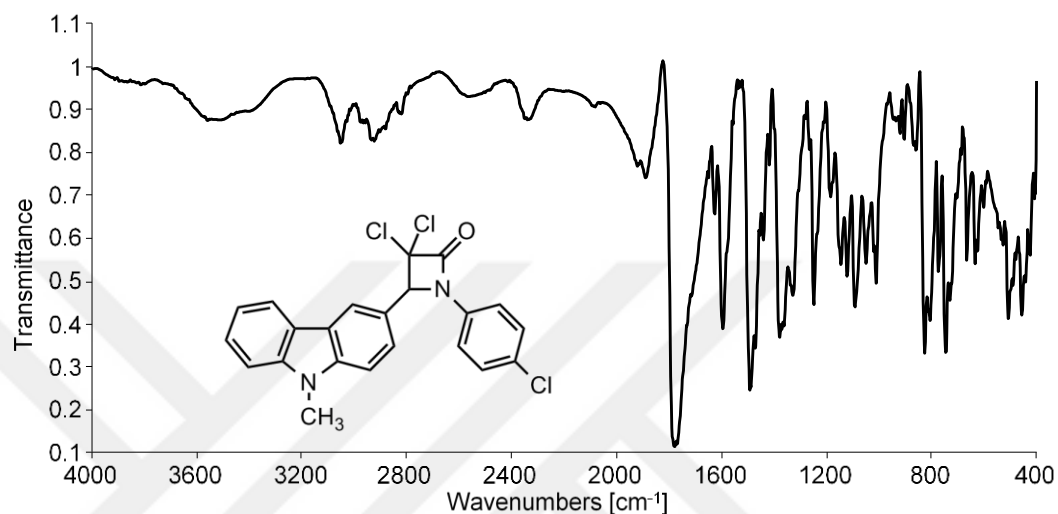


Figure 3.10 IR Spectra of compound 151

IR (KBr, ν/cm^{-1}): 3054, (Ar-H stretch), 2932 (CH stretch), 1778 (C=O stretch), 1596 (Ar C-C stretch), 1490, 1382 (Ar C-C stretch), 1338, 1246 (C-Cl stretch), 1142 (C-H wag), 804 (C-Br stretch) (Figure 3.11).

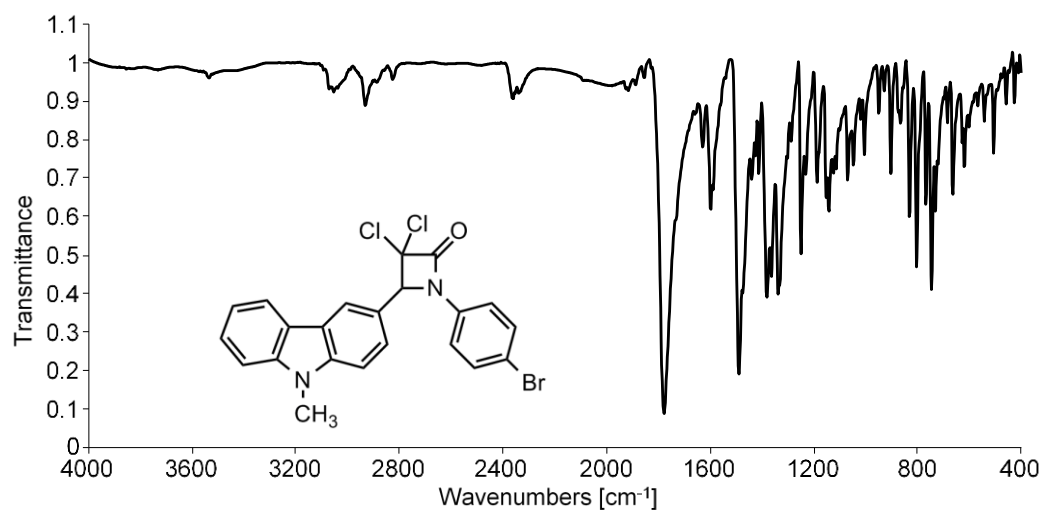


Figure 3.11 IR Spectra of compound 152

IR (KBr, ν/cm^{-1}): 3050, (Ar-H stretch), 2930 (CH stretch), 1770 (C=O stretch), 1596 (Ar C-C stretch), 1512, (Ar C-C stretch), 1324, 1250 (C-Cl stretch), 1148 (C-H wag), 1122 (C-O stretch) (Figure 3.12).

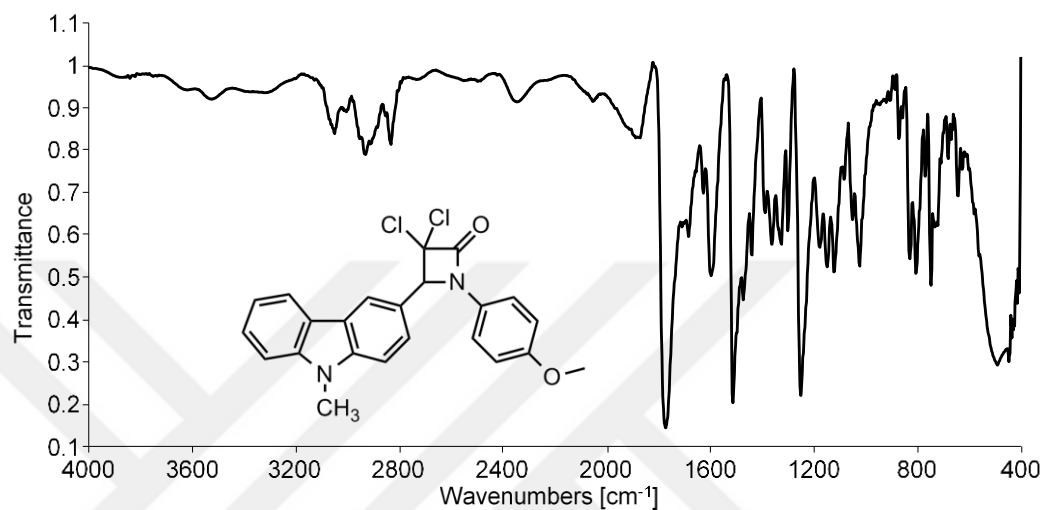


Figure 3.12 IR Spectra of compound 153

3.1.2 NMR Spectra

Below are shown the ^1H NMR spectra.

¹H NMR (400 MHz, DMSO-*d*₆, δ in ppm): 3.85 (s, 3H, NCH₃), 6.25 (s, 1H, CH), 7.20 (dd, *J* = 7.6, 7.2 Hz, 1H, ArH), 7.43 (m, 7H, ArH), 7.61 (m, 2H, ArH), 8.05 (d, *J* = 7.2, 1H, ArH) 8.18 (s, 1H, ArH) (Figure 3.13).

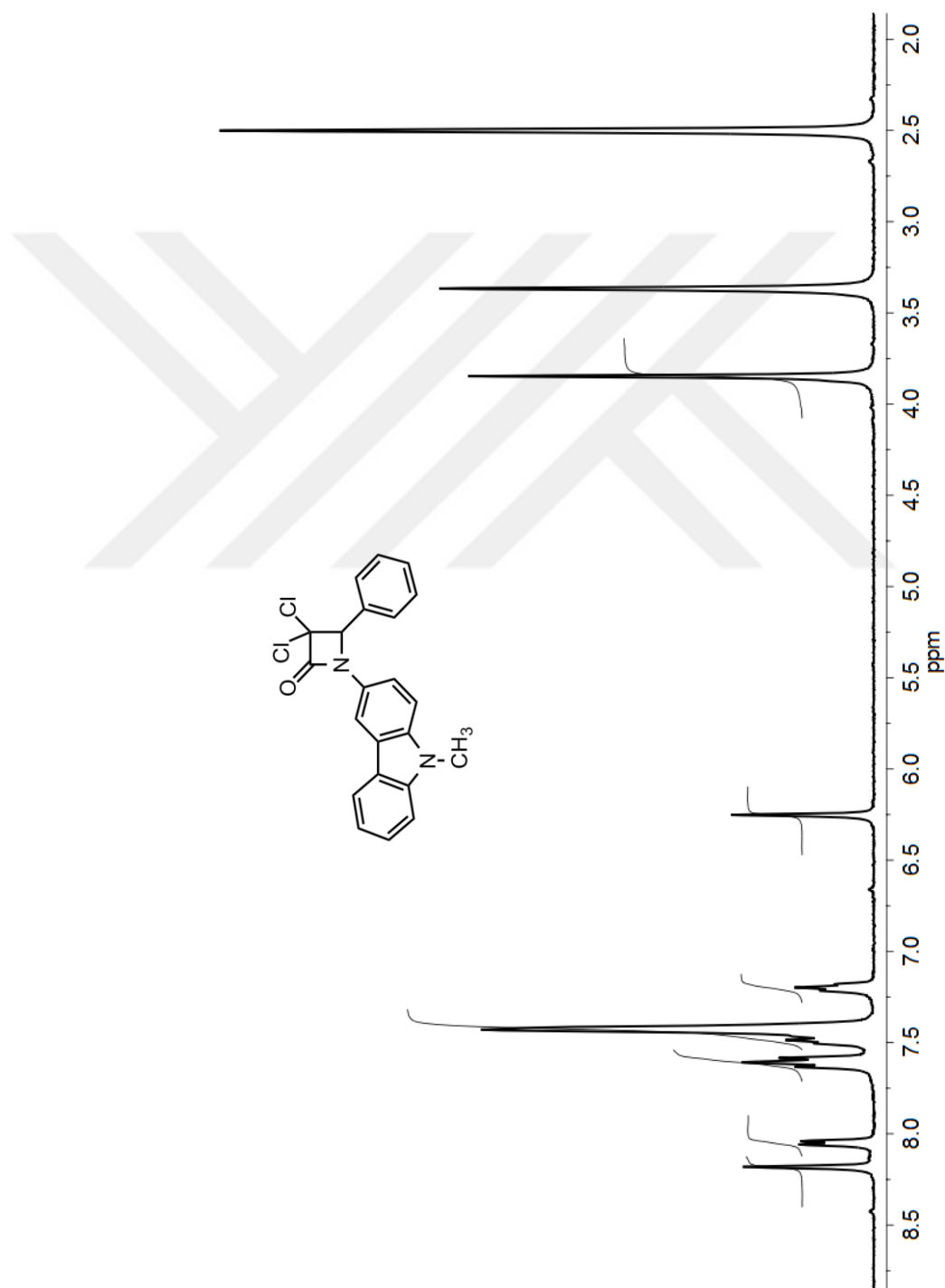


Figure 3.13 ¹H-Spectra of compound 142 in DMSO-*d*₆ 400 MHz

^1H NMR (400 MHz, DMSO- d_6 , δ in ppm): 3.87 (s, 3H, NCH₃), 3.87 (s, 3H, OCH₃), 6.65 (s, 1H, CH), 7.21 (m, 2H, ArH), 7.48 (m, 2H, ArH), 7.60 (m, 5H, ArH), 8.12 (d, J = 7.6, 1H, ArH), 8.42 (s, 1H, ArH) (Figure 3.14).

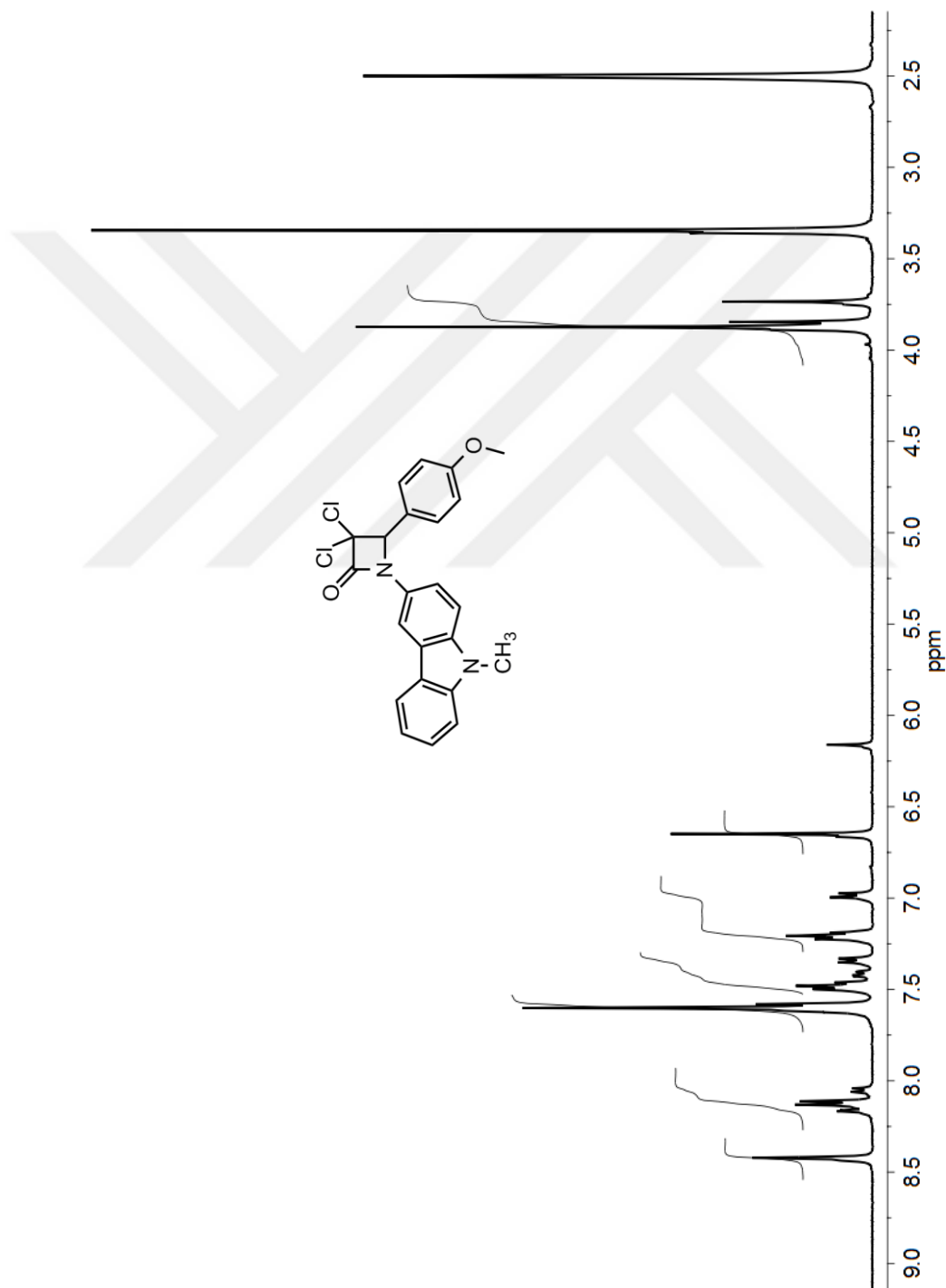


Figure 3.14 ^1H -Spectra of compound 147 in DMSO- d_6 400 MHz

^1H NMR (400 MHz, CDCl_3 , δ in ppm): 3.82 (s, 3H, NCH_3), 5.69 (s, 1H, CH), 7.10 (t, 1H, $J = 8.2$, 1 Hz, ArH), 7.24 (m, 3H, ArH), 7.38 (m, 5H, ArH), 7.49 (ddd, 1H, $J = 8.3, 6.9, 1.3$ Hz, ArH), 8.05 (s, 1H, ArH), 8.06 (d, $J = 2.8$ Hz 1H, ArH) (Figure 3.15).

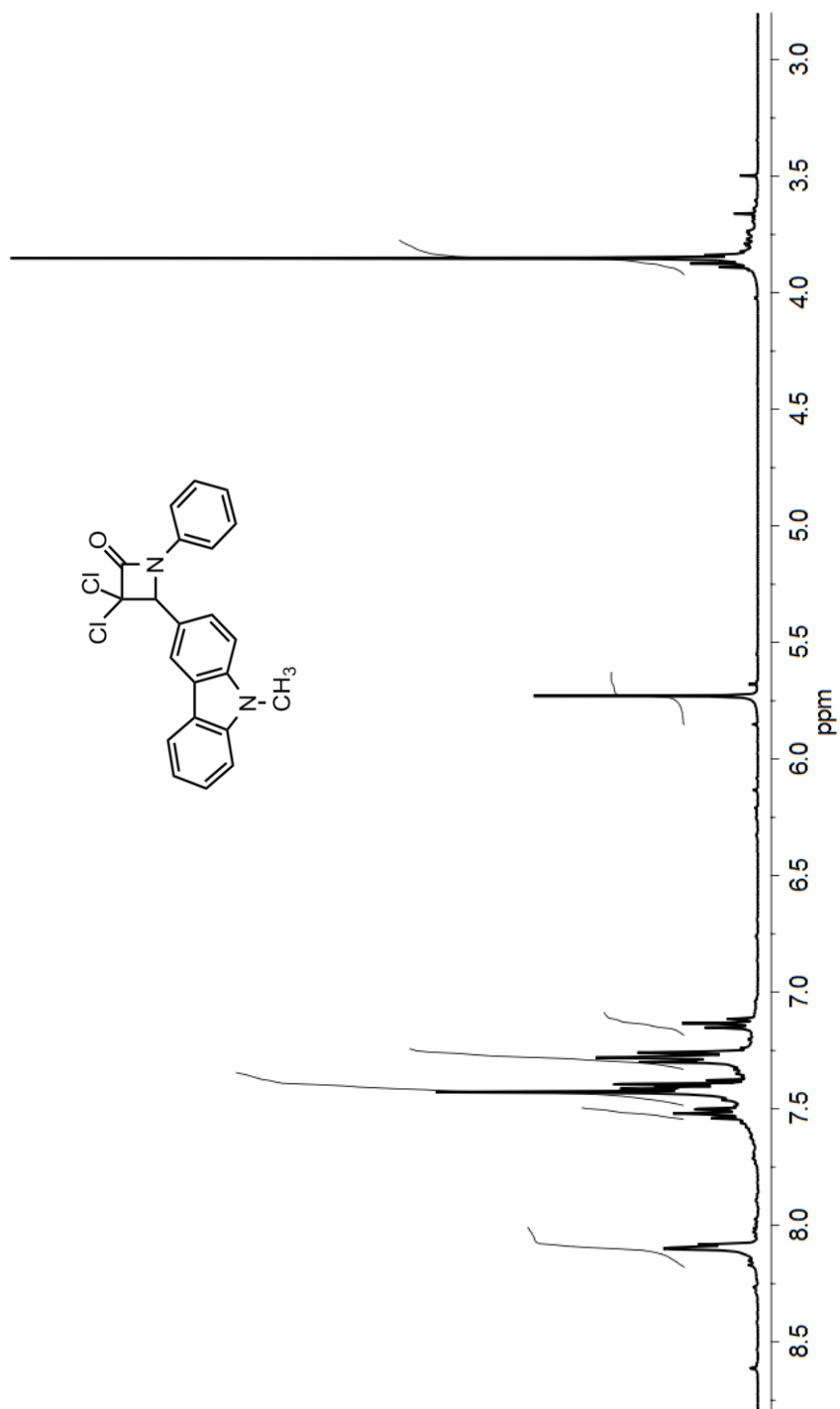


Figure 3.15 ^1H -Spectra of compound 148 in CDCl_3 400 MHz

^1H NMR (400 MHz, CDCl_3 , δ in ppm): 3.88 (s, 3H, NCH_3), 5.77 (s, 1H, CH), 7.28 (m, 1H, ArH), 7.49 (m, 6H, ArH), 8.07 (d, 2H, ArH), 8.13 (m, 1H, ArH) 8.15 (m, 1H, ArH) (Figure 3.16).

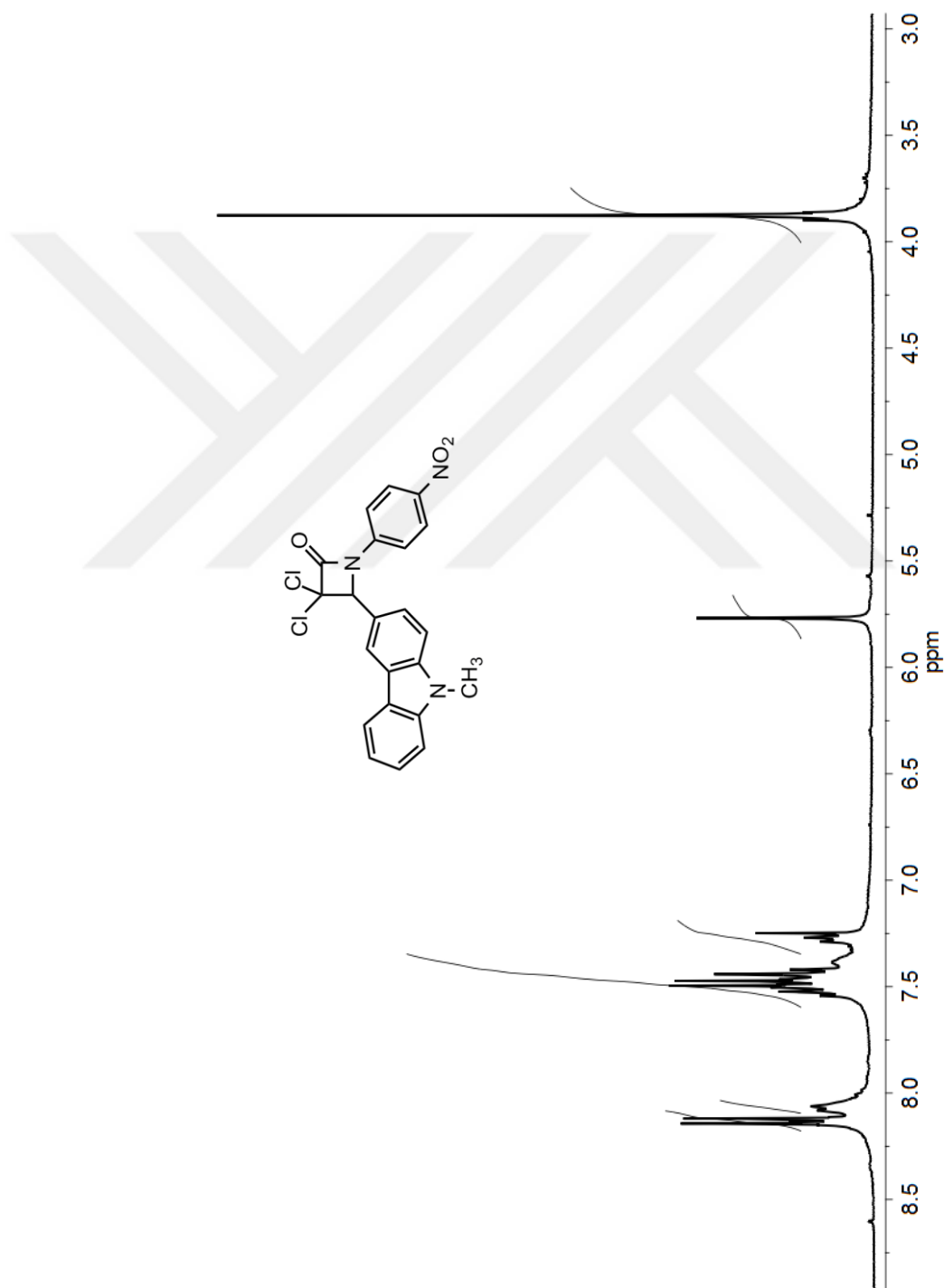


Figure 3.16 ^1H -Spectra of compound 149 in CDCl_3 400 MHz

CHAPTER FOUR

DISCUSSION AND RESULTS

4.1 Synthesis of the Compounds

4.1.1 Synthesis of the Amino Carbazole (128)

The synthesis of the carbazole- β -lactam compounds involves Schiff bases and in turn it involves the amine and aldehyde carbazole derivatives whose preparation begins with the 9-methyl-9*H*-carbazol-3-amine (**128**) and the 9-methyl-9*H*-carbazole-3-carbaldehyde (**129**).

The preparation of the 9-methyl-9*H*-carbazol-3-amine (**128**) was made easier from 9-methyl-3-nitro-9*H*-carbazole (**127**) which was obtained following the standardized methods established into our working group. The nitration of the carbazole was made by using $\text{Cu}(\text{NO}_3)_2 \cdot 2.5\text{H}_2\text{O}$ in acid acetic acid and acetic anhydride. The temperature was controlled and limited amounts of the cooper salt were used to avoid the di-nitration, so in this way the compound was obtained as a pale yellow powder in high yields of 99 % (Figure 4.1). The presence of the nitro compound was verified by comparison with the reference in TLC.

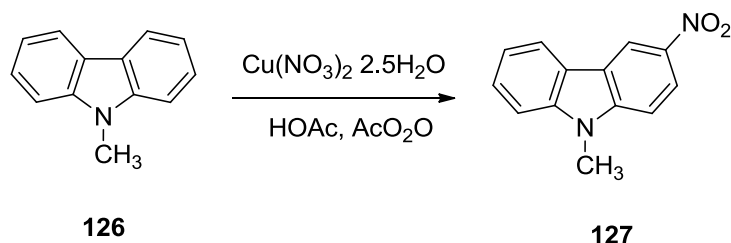


Figure 4.1 Synthesis of 9-methyl-3-nitro-9*H*-carbazole (**127**)

Subsequently, the resultant nitro compound **1** was subject to reduction with Pd/C and hydrazine monohydrate in ethanol (Figure 4.2). In this step of synthesis the compound was obtained as a beige powder in 80.5 % and stored away from light and moisture, and

as same as the nitro compound, the presence of the compound was verified with the reference.

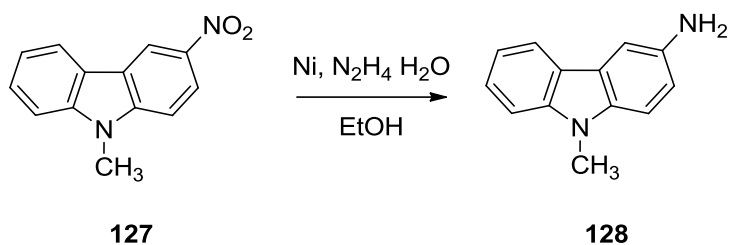


Figure 4.2 Synthesis of 9-methyl-9H-carbazol-3-amine (128)

4.1.2 Synthesis of the Aldehyde Carbazole (129)

The preparation of the 9-methyl-9H-carbazole-3-carbaldehyde (**129**) was carried out through a Vilsmeier–Haack reaction of 9-methyl-9H-carbazole (**126**) with POCl₃ and DMF (Figure 4.3), by following the protocol of Díaz and collaborators (2002). After work up and purification by column chromatography, the formylated compound **129** was obtained in 69 % of yield as a yellow powder. The structure of the aldehyde compound was confirmed by comparison with the reference in TLC and by Infrared spectroscopy.

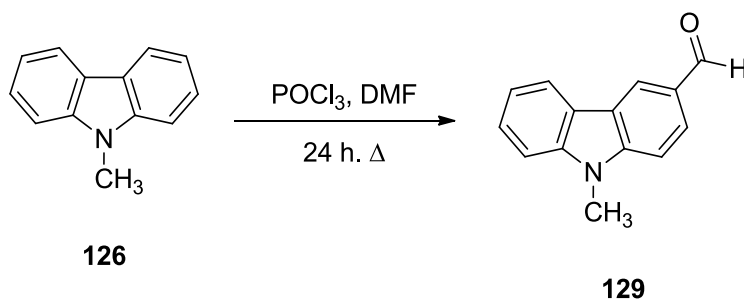


Figure 4.3 Synthesis of 9-methyl-9H-carbazole-3-carbaldehyde (129)

4.1.3 Synthesis of the Schiff bases (130-141) and β-lactams (142-153)

Once obtained the amino and aldehyde carbazole compounds (**128** and **129**), the reactions of condensation with substituted aromatic aldehydes and substituted aromatic

amines were performed in benzene with catalytic amounts of TsOH and using a Dean-Stark trap in order to facilitate elimination of water by azeotropic distillation (Figure 4.4).

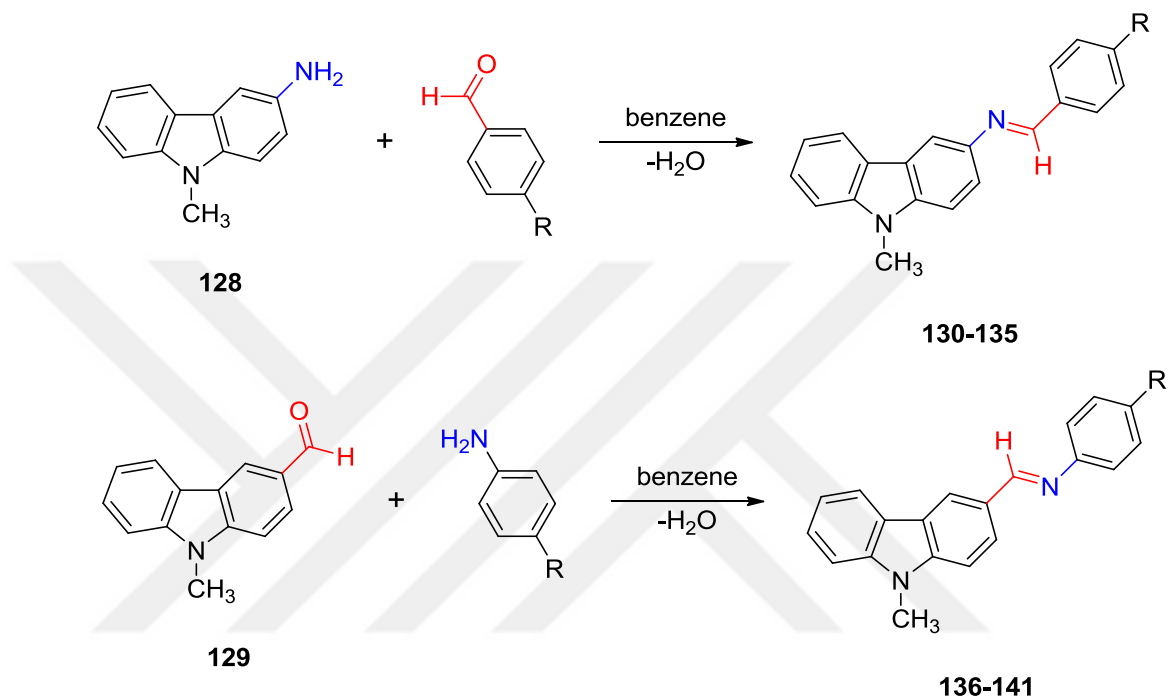


Figure 4.4 Synthesis of the Schiff Bases (130-141) precursors for β -lactams

Table 4.1 Number and functional groups (R) of the Schiff Bases synthesized

No.	R	No.	R
130	H	136	H
131	NO ₂	137	NO ₂
132	F	138	F
133	Cl	139	Cl
134	Br	140	Br
135	OCH ₃	141	OCH ₃

The precipitates in the middle of the reaction and comparison of the Retardation factor (R_f), color characteristics and fluorescence under UV light in TLC indicated the

presence of imines. The resulted Schiff bases underwent cyclocondensation reaction with chloroacetyl chloride and triethyl amine yielding the title compounds.

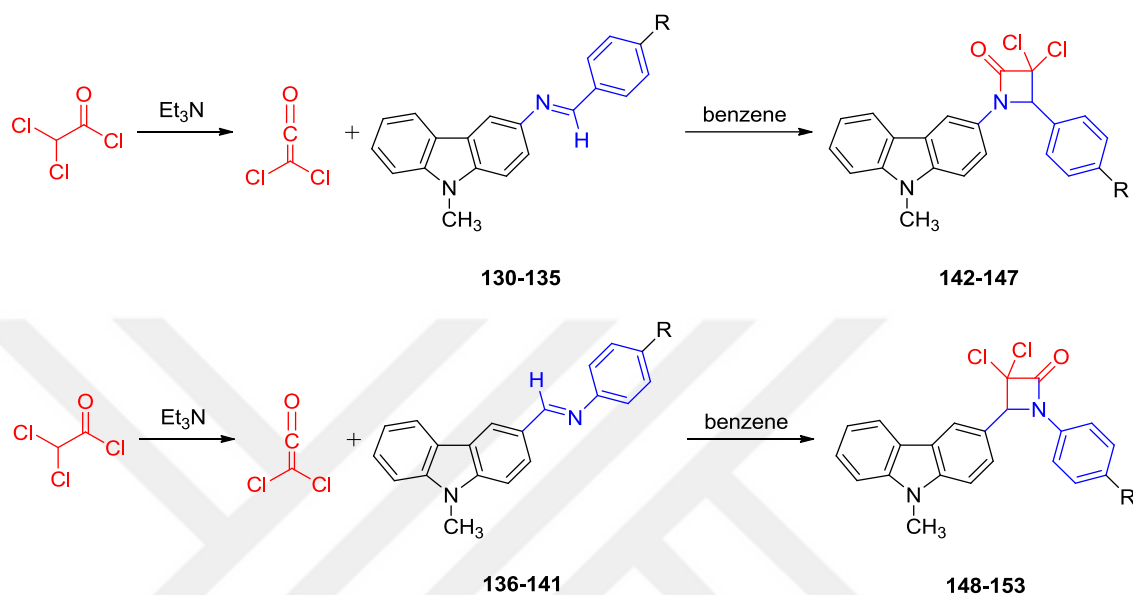


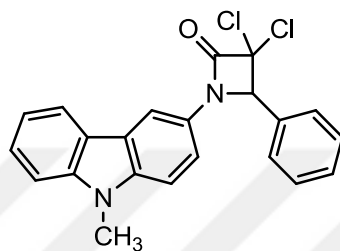
Figure 4.5 Synthesis of β -lactams (142-153)

Table 4.2 Number and functional groups (R) of the β -lactams synthesized

No.	R	No.	R
142	H	148	H
143	NO ₂	149	NO ₂
144	F	150	F
145	Cl	151	Cl
146	Br	152	Br
147	OCH ₃	153	OCH ₃

The compounds were purified by column chromatography, and the purity of the compounds was checked by TLC. The final synthesized compounds were confirmed by IR and NMR spectroscopy.

In this way, the β -lactam compound **142** was obtained in the form of yellow powder (0.46 g, yield of 11.4%) and confirmed by IR spectrum which shows disappearance of the imine's azometine group and the presence of the band corresponding to stretching vibrations of a carbonyl bond in a lactam ring at 1772 cm^{-1} , and at 1322 and 1234 cm^{-1} bands corresponding to the stretching of the carbon-chloride bond.

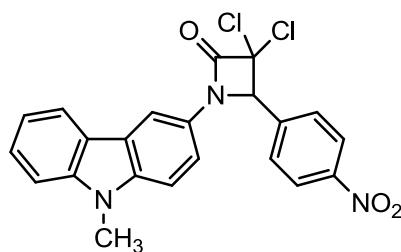


142

Figure 4.6 Carbazole compound 142

Moreover, the presence of the compound was supported by the ^1H NMR spectra which shows integration for 16 protons. The spectra shows a single signal at 3.85 ppm which integrates for 3H and was assigned to the methyl, at 6.25 ppm was observed a single signal which integrates for 1 H and was assigned to the only proton into the lactam ring.

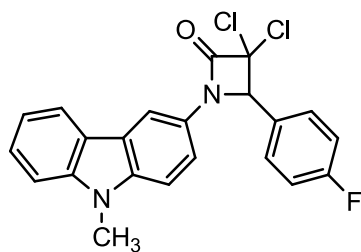
In the same way, the lactam compound **143** with substituent nitro was obtained as an orange powder (1.16 g, yield of 25.9 %). The IR spectra exhibited the presence of stretching vibrations corresponding a carbonyl bond in a lactam at 1774 cm^{-1} , at 1518 cm^{-1} a band characteristic of the nitro group which corresponds to the asymmetric stretching of the nitrogen-oxygen bond and at 1348 and 1250 cm^{-1} bands corresponding to the stretching of the carbon-chloride bond.



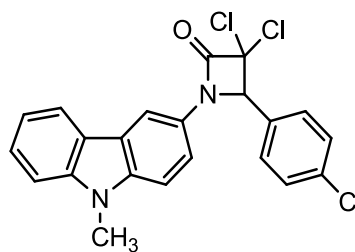
143

Figure 4.7 Carbazole compound 143

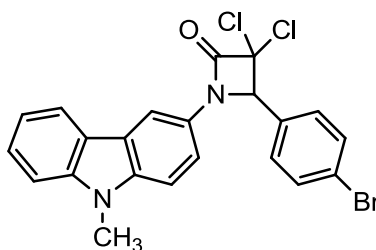
The formation of the compounds **144-146** was confirmed by IR spectroscopy which shows the band of the carbonyl stretching in the lactam ring, for each compound at 1770, 1764 and 1766 cm^{-1} . In every compound was observed the appearance of characteristic signals of the substituents in the phenyl ring, therefore respecting the compound **144** was observed at 1250 and 844 cm^{-1} the stretching band for the C-F bond, in the **145**'s spectra were observed two plus bands at 1090 and 896 for the C-Cl bond, for **146** was observed the band for the C-Br bond at 1010 cm^{-1} . The yields afforded were 14.3 % (0.6), 19.7 % (0.7) and 24.6 % (1.19) respectively.



144



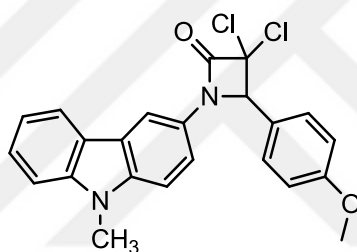
145



146

Figure 4.8 Carbazole compounds 144-146

The compound **147** was confirmed in the IR spectra by the characteristic band of the lactam carbonyl band at 1764 cm^{-1} and at 1338 and 1250 cm^{-1} by the bands corresponding to the stretching of the carbon-chloride bond in the lactam ring. Furthermore **147** was confirmed by the ^1H NMR spectra which shows integration for 18 protons. The spectra shows an accidental equivalence at 3.87 ppm since it integrates for 6 H and corresponds to the methyl attached to the carbazole ring and the methyl in the methoxy-phenyl ring, at 6.65 ppm was observed a single signal which integrates for 1 H and was assigned to the proton in the lactam ring. The yield of the product was found to be (0.75 g) 17.3%.

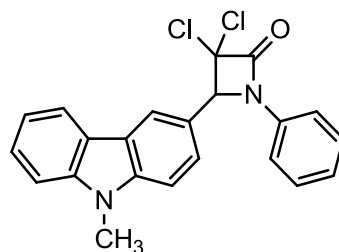


147

Figure 4.9 Carbazole compound 147

Following the same procedures, the β -lactam compound **148** was obtained in 44.9 % (1.7 g). The structure of the compound was confirmed by IR and NMR spectroscopy. The presence of the β -lactam ring was proved by the band at 1772 cm^{-1} whose frequency is higher than azetidine or free carbonyl bond frequencies due to the electron-withdrawing effect of the ring strain and neighboring chloride groups whose frequencies were observed at 1338 , 1250 cm^{-1} (C-Cl stretch).

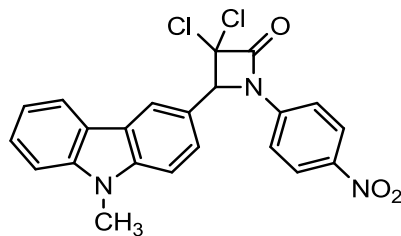
In the ^1H NMR spectra, two singlet signals were observed at 3.82 ppm and 5.69 ppm , each one integrates for 3 H and 1 H and correspond to the methyl protons and proton in the lactam ring, respectively, at 7.38 ppm was observed a multiple signal attributed to the phenyl ring.



148

Figure 4.10 Carbazole compound 148

With respect to the compound **149**, obtained in yield of 63.7 % (2.01 g), the presence of the β -lactam was probed by IR and NMR spectroscopies. The infrared spectra exhibited a strong band at 1784 cm^{-1} corresponding to the carbonyl bond in the lactam, at 1518 cm^{-1} was seen a band corresponding to the asymmetric stretching of nitrogen-oxygen bond in the nitro group and at 1338 and 1248 cm^{-1} the bands corresponding to the stretching of the carbon-chloride bond. In the ^1H NMR spectra, the integration for 15 protons was observed, as well single signals at 3.82 ppm and 5.69 ppm which integrates for 3 H and 1 H and were assigned to the methyl group and the proton into the lactam ring.

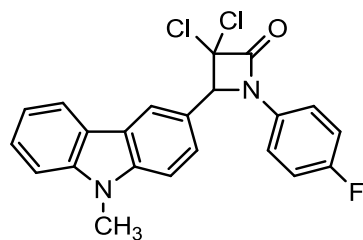


149

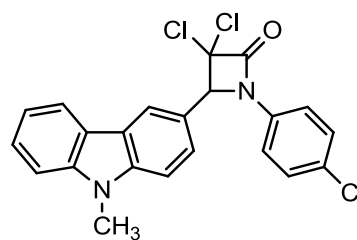
Figure 4.11 Carbazole compound 149

The structures of the compounds **150-153** were proved by IR, the frequency of the carbonyl group in the β -lactam ring ($1785\text{--}1808\text{ cm}^{-1}$) was observed for each compound at 1778, 1778, 1778 and 1770. And the characteristic frequencies of the substituents in the phenyl ring were observed for compound **150** at 834 cm^{-1} (C-F stretch), for the compound **151** at $1092, 826\text{ cm}^{-1}$ (C-Cl stretch), for **152** at 804 cm^{-1} (C-Br stretch) and for the

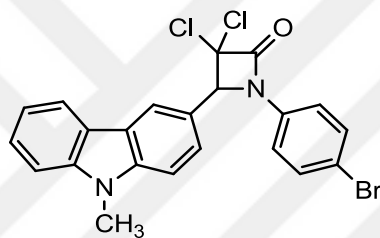
compound **153** at 1122 (C-O stretch) cm^{-1} . The yields of the products were found to be 20.6 % (0.81 g), 47.7 % (1.96 g), 30.8 % (1.23 g) and 31.7 % (1.29 g) respectively.



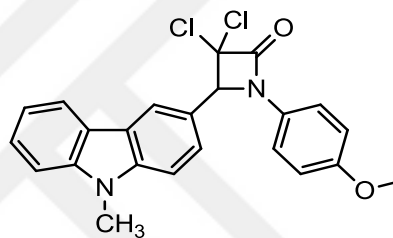
150



151



152



153

Figure 4.12 Carbazole compounds 150-153

CHAPTER FIVE

CONCLUSIONS

5.1 Conclusions

- A new series of carbazole compounds bearing β -lactam rings was successfully synthesized using reactions of nitration, formylation, condensation and cycloaddition. All compounds were synthesized from readily available reactants and reagents.
- The formation of the compounds was verified by IR and NMR spectroscopies.
- When the yields of the compounds are compared is observed that substituents electron withdrawing substituents generate β -lactams in higher amounts.
- Finally, we believe that these compounds present an interesting profile for further experimental investigations especially in the area of antimicrobial research.

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