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REACTIONS OF AMINOGUANIDINE DERIVATIVES WITH ACETYLENEDICARBOXYLATE DERIVATIVES.

(M. Sc. Thesis)

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KAYSERİ

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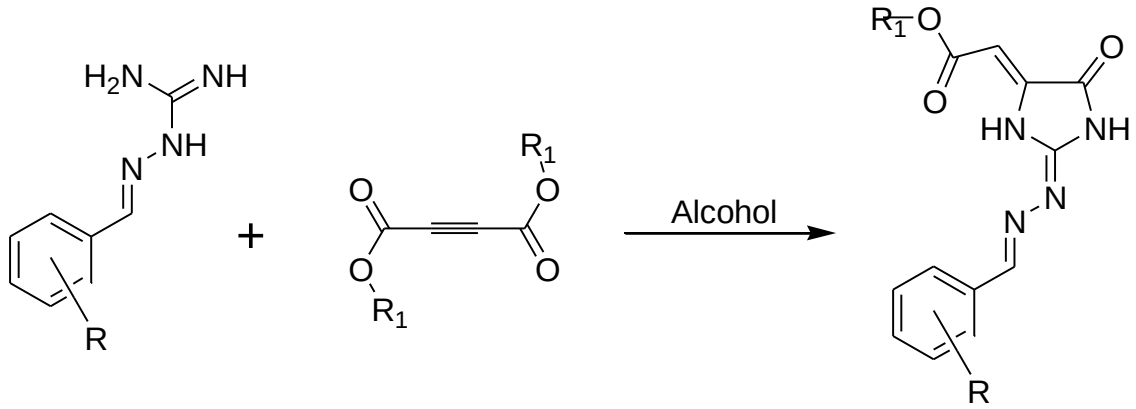
ABSTRACT

Aminoguanidine, also known as pimagedin, is a drug under investigation for the treatment diabetic nephropathy. Because of this feature, synthesis of aminoguanidin derivatives as a prospective drug for diabetic nephropathy is gained more importance.

In this study, some aminoguanidine derivatives have been synthesized by an environmentally friendly method. Then, aminoguanidine derivatives have been reacted to dimethyl acetylenedicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEAD) in order to synthesize new imidazolidine derivatives which are considered as biologically active molecules. And, structures of molecules are determined by using ^{1}H-NMR, ^{13}C-MNR, IR Spectroscopy, and elemental analysis.



Key Words: Aminoguanidine, Dimethyl acetylenedicarboxylate (DMAD), Diethyl acetylenedicarboxylate (DEAD), Imidazolidine

AMİNOGUANİDİN TÜREVLERİYLE ASETİLENDİKARBOKSİLAT TÜREVLERİNİN REAKSİYONLARI

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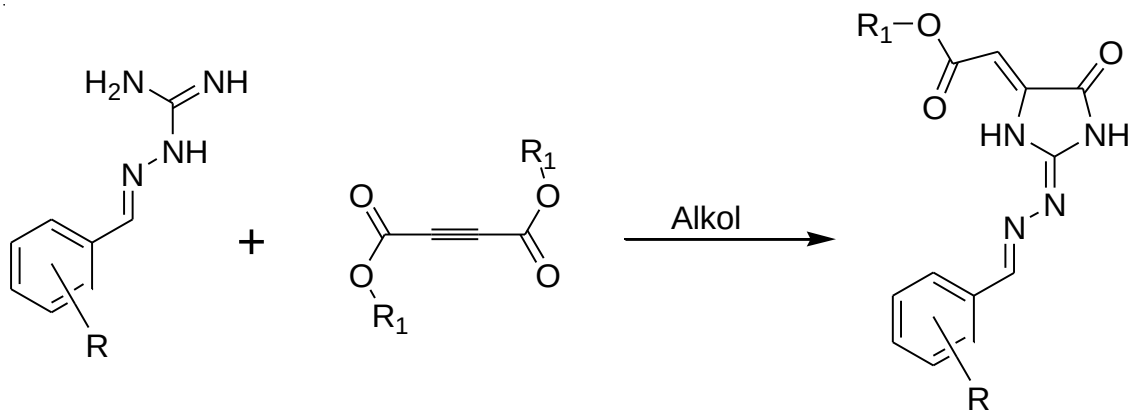
Erciyes Üniversitesi, Fen Bilimleri Enstitüsü
Yüksek Lisans Tezi, Ağustos2016
Tez Danışmanı: Prof. Dr. Zülbiye KÖKBUDAK

ÖZET

Pimagedin olarak da bilinen aminoguanidin diyabetik nefropati tedavisi için araştırma altında olan bir ilaçtır. Bu özelliğinden dolayı muhtemel diyabetik nefropati ilacı olabilecek aminoguanidin türevleri sentezlemek daha önem kazanmıştır.

Bu çalışmada bazı aminoguanidin türevleri çevre dostu bir yöntemle sentezlenmiştir. Sentezlenen türevler dimetilasetilendikarboksilat (DMAD) ve dietil asetilendikarboksilat (DEAD) ile reaksiyona sokularak yeni, biyolojik olarak aktif bir molekül olduğu düşünülen imidazolidin türevleri sentezlenmiştir. Ve moleküllerin yapıları ^{1}H-NMR, ^{13}C-NMR, IR spektroskopisi ve elementel analiz kullanılarak belirlenmiştir.



Anahtar Kelimeler: Aminoguanidin, Dimetil asetilendikarboksilat (DMAD), Dietil asetilendikarboksilat (DEAD), İmidazolidin

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INTRODUCTION

Aminoguanidine, one of guanidine derivatives, is known as pimagedin, a drug used in diabetic diseases, but it has common properties with hydrazines, so it is often called as a hydrazine derivative. Aminoguanidine, which has crystalline structure, is soluble in water and alcohol but not soluble in ether. It has strongly basic characteristics. Four different nucleophilic centers in aminoguanidine make it favourable in organic reaction. It has similarities with L-Arginine aminoacid, which is important on synthesis of nitric oxide (NO) by catalytic effect of nitric oxide syntase [1, 2]

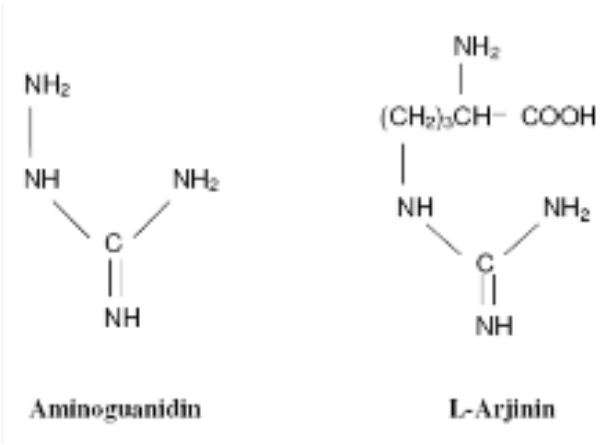


Figure 1. Chemical structures of amino guanidine and L-Arginine[1]

Significant biological effects of aminoguanidine have been revealed recently. The first found out effect was inhibition of diamine oxydase enzyme which catalyzes deterioration of biologically active diamines like putrescine and histamine [2, 3]. Secondly discovered biological effect of aminoguanidine is inhibition of nitric oxide synthase enzyme [4, 5]. The inhibition of advanced glycation end products (AGE's) is the most significant effect of aminoguanidine [6]. Glycation is cross-linking reaction between a sugar and an amino group of a protein [7]. The advanced glycation end products inhibit the ability of cell to work normally. They, also, increased in diabetes

and play significant role in diabetic problems [8, 9]. Furthermore, by causing important disorders on neurons, advanced glycation end products triggers development of Alzheimer disease [10, 11]

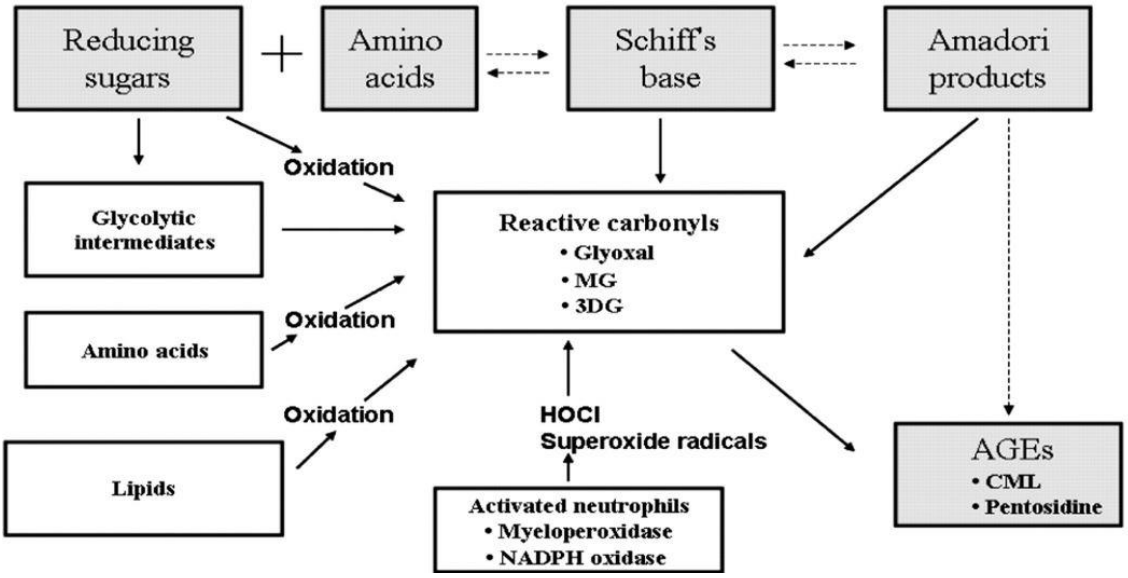


Figure 2. Bio-chemical reactions and common advanced glycation end product (AGE) compounds. DG, deoxyglucosone; MG, metyl glyoxal; CML, carboxymethyllysine; HOCl, hypocholorous acid [12]

Acetylenedicarboxylate derivatives are electron-minus acetylenic molecules having two ester groups. They are prerogative and expedient compounds which engage in easily and practically in heterocyclization. Because of having two ester group, they easily undergoes Michael addition that create a chance to synthesize heterocyclic molecules vith diverse ring sizes. By using Acetylenedicarboxylate derivatives, synthesis of some significant combined heterocyclic systems may be obtained so easily that it is very hard to synthesize by alternative paths [13].

Imidazolidine functional group plays important roles in many biological events. As primaquine derivative it plays an important role against malaria disease [14]. Imidazolidine derivatives are interesting molecules due to their existence in nature, chemical activity and numerous biological properties which are suitable for drug development. Structural changes in the imidazolidine ring bring in molecules variety of pharmacological properties, such as antibacterial, anti-inflammatory, antifungal, schistosomicides, hypoglycemic, and anti-cancer activities, among others [15].

Occasionally, imidazolidines have been obtained as derivatives of aldehydes. For example crystalline imidazolidines synthesized from a wide range of aldehydes using 1,2-bis(pmethoxybenzylamino) ethane, whereas of eight aliphatic and aromatic ketones examined, only acetone reacted with the diamine under the same conditions as those used for the aldehydes [16].

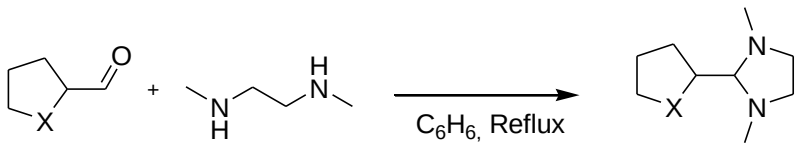


Figure 3. Synthesis of imidazolidine derivatives from aldehydes

Racemic imidazolidine-2,4-diones, generally known as hydantoins [17], are significant building blocks for enantioselective synthesis of amino acids since enantiomerically pure amino acids can be prepared from these [18].

$RCHC(O)NHC(O)NH + H_2O \rightarrow RCHC(NH_2)CO_2H + NH_3$

Hydantoin reacts with dilute hydrochloric acid to give glycine. The usefulness of this method was demonstrated on an industrial scale by Ajinomoto for the production of D-p-hydroxyphenylglycine [19]. Substituted hydantoins are also of therapeutic concern and are used, for example, for the treatment of epilepsy [20].

Hydantoin, also known as glycolylurea, is a colorless heterocyclic organic compound that generate from the reaction of glycolic acid and urea. It is an oxidized derivative of imidazolidine. Hydantoins can refer to a groups and a class of compounds with the same ring structure as the parent. For example, phenytoin groups substituted onto a hydantoin molecule [21].

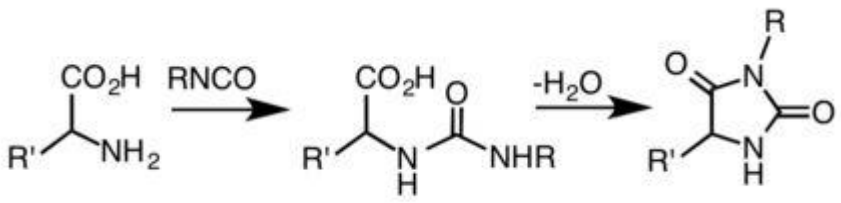


Figure 4. Synthesis of Hydontin

Hydantoin group can be shown in several pharmacologically important molecules. In therapeutic, 'hydantoins' most often refer to anti-epileptic; phenytoin and fosphenytoin which include hydantoin moieties and both used as anticonvulsants in the treatment of seizure disorders. Dantrolene, one of hydantoin derivative, is used as a muscle relaxant to treat neuroleptic malignant syndrome, malignant hyperthermia, ecstasy intoxication, spasticity [22]. Ropitoin is an example of an antiarrhythmic hydantoin [23]. As an hydantoin derivative Imiprothrin is an insecticide. Iprodione is a popular fungicide has a hydantoin group either [24].

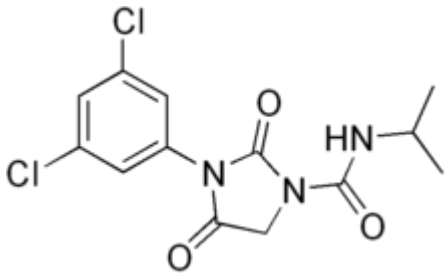


Figure 5. Structure of iprodione

We are interested in the chemistry of heterocyclic compounds containing nitrogen atoms. As a part of a research program on the synthesis of heterocyclic system including nitrogen with a view to extending the synthetic favor of dimethyl acetylendicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEAD). We have investigated the addition of them in methanol and ethanol.

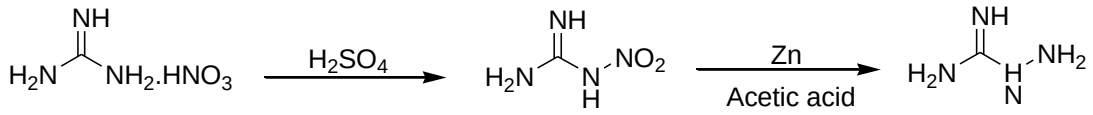
Because of the therapeutic specialty mentioned before the aim of the study was to evaluate novel potential biologically active imidazolidine derivatives.

CHAPTER 1

GENERAL INFORMATION

1.1. Synthesis of Aminoguanidine

Aminoguanidine, also known as Pimagedin, is a drug for medication of diabetic nephropathy. It is synthesized by reduction of nitro guanidine in 1892 by a pharmaceutical company, to develop a drug for kidney diseases [25]



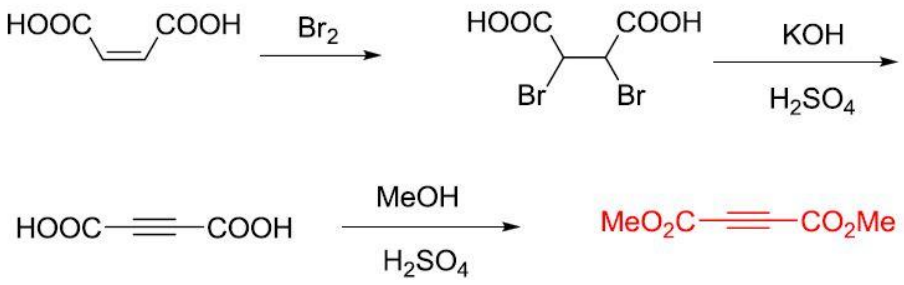
As a guanidine analog, aminoguanidine is favorable in organic reactions; however, since aminoguanidine has four asymmetric nucleophilic centers, diversity of products are quite excess, and efficiency lower than guanidine based reaction Thus it is not preferred as much as guanidine in organic synthesis. In order to overcome this problem and to increase diversity of compounds some aminoguanidine derivatives was synthesized.

1.2. Synthesis of Hetrocyclic Molecules by Using Acetylenedicarboxylate Derivatives.

Heterocyclic molecules play vital role in human body due to their biological importance and efficacy. Because of importance of heterocyclic molecules and versatility of acetylenedicarboxylate derivatives, scientists have focused their endeavor to find suitable approach to privileged compound for the synthesis a diversity of heterocyclic molecules [13]. In almost all literature, dimethyl acetylenedicarboxylate (DMAD) is used as acetylenedicarboxylate derivative. Usage of diethyl acetylenedicarboxylate (DEAD) is quite low.

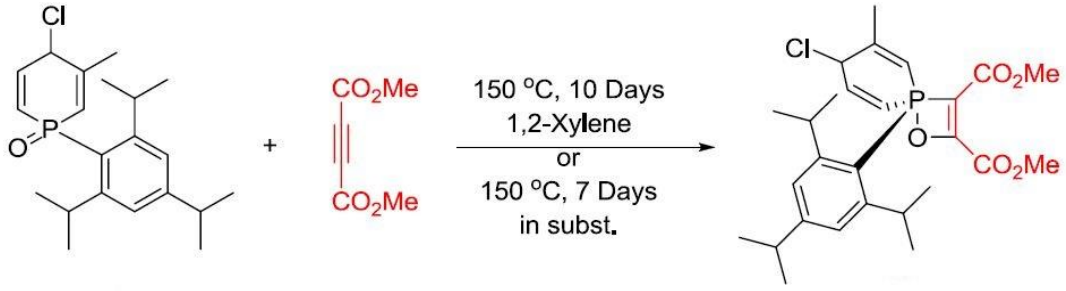
1.2.1. Synthesis of DMAD

DMAD is low-cost, commercially favourable, and easy to achieve. To synthesize DMAD, maleic acid undergoes a bromination then a dehydrohalogenation sequence to give aceltylenedicaboxylic acid first. After esterification with methanol, it obtains [26].



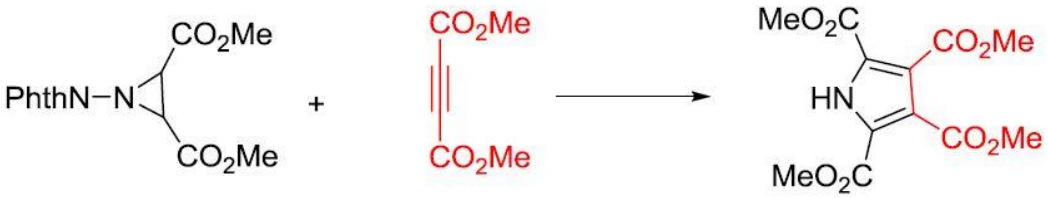
1.2.2. Synthesis of Four-Membered Rings with DMAD

Trialkyl phosphine oxide 2 reacts with DMAD to give oxaphosphetene 3 instead of the Diels–Alder cyclo adduct
[27]

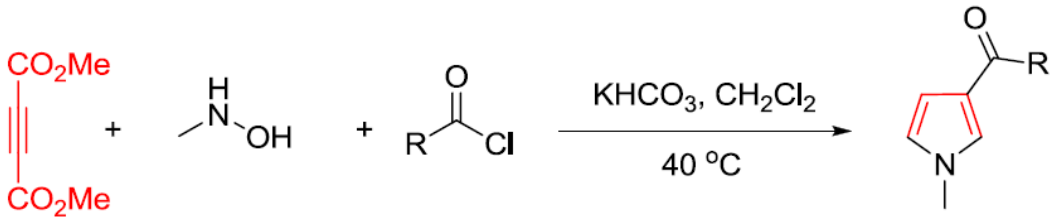


1.2.3. Synthesis of Five-Membered Rings with DMAD

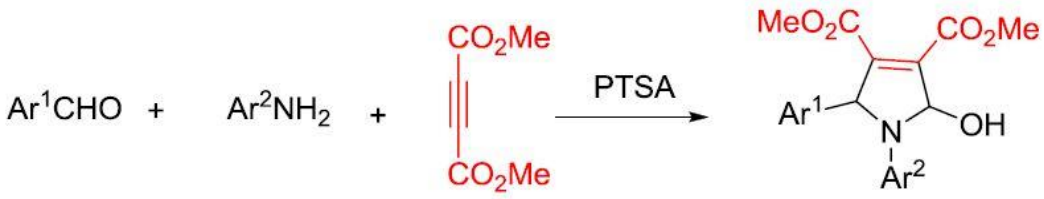
1,3-dipolar cycloaddition of formed azomethine ylide and DMAD produce a mixture of tetrasubstituted pyrroles [28].



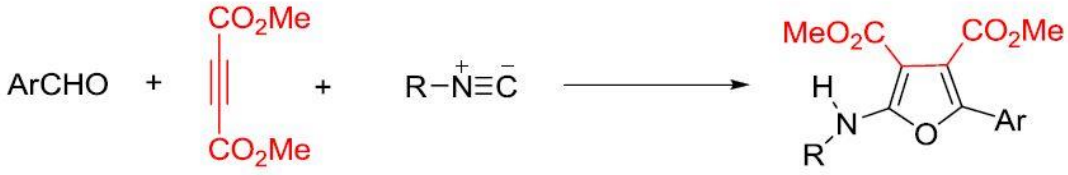
The multicomponent reaction of *N*-methyl hydroxyl amine, DMAD and acyl chlorides with $KHCO_3$ as catalyzer led to *N*-methyl-3- acyl pyrroles[29]



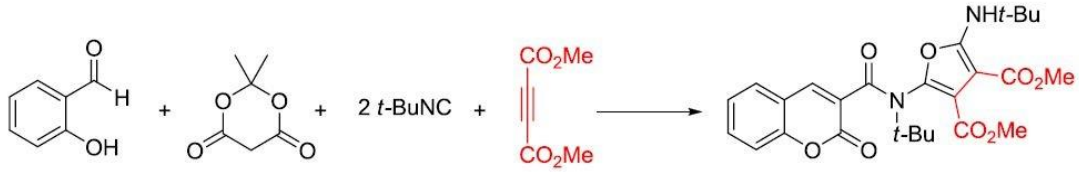
DMAD, aryl amines, Aromatic aldehydes, and in aqueous ethanol in the presence of p-toluenesulfonic acid (PTSA) gives polysubstituted 2-hydroxy hydropyrroles [30].



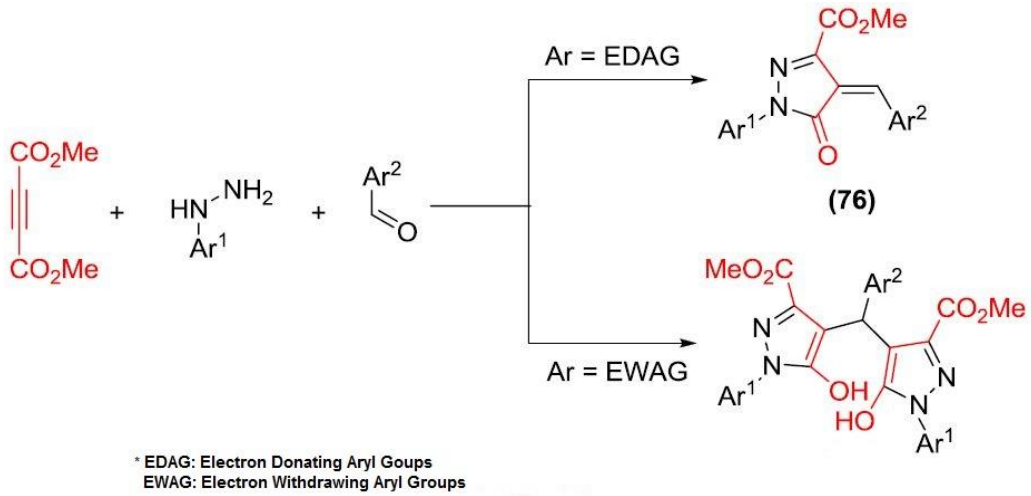
Aldehydes reacted with the molecule derived from the addition of isocyanides to DMAD to produce 2-amino furans [31].



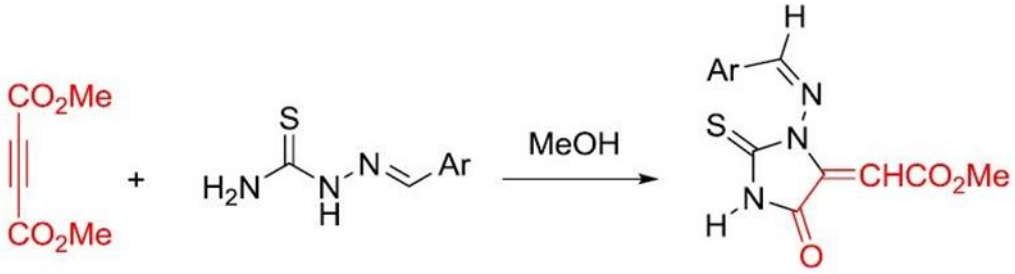
One-pot multicomponent reaction between 2-hydroxy aromatic isocyanides, aldehyde, 2,2-Dimethyl-1,3-dioxane-4,6-dione, and DMAD, gives dimethyl-2- (N-tert-butyl-2-oxo-2H-chromene-3-carboxamido)-5-(tert-butylamino) furan-3,4-dicarboxylate [32].



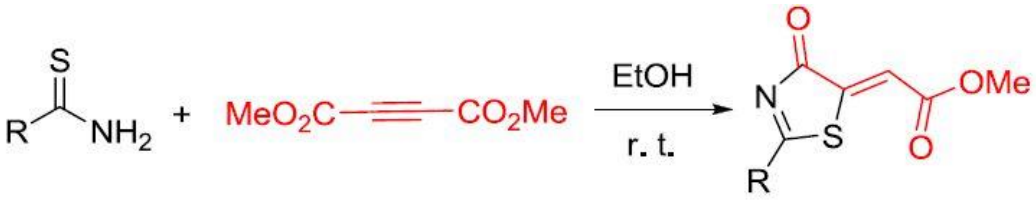
A one-pot multicomponent domino reaction between phenylhydrazine, DMAD, , and aromatic aldehydes generated arylidene pyrazolones according to aryl group two new pyrazole rings have synthesized [33].



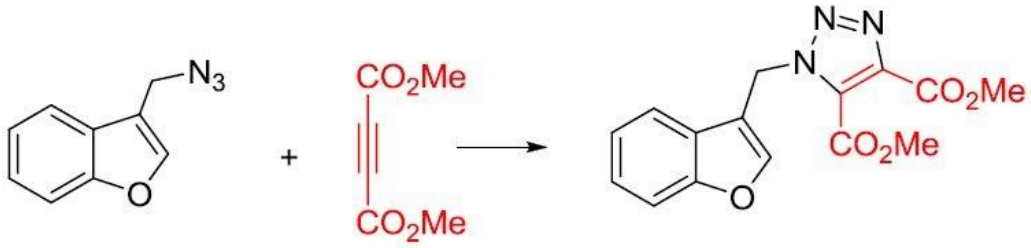
Substituted imidazoles can be obteined from thiosemicarbazone of aryl aldehydes reacting with DMAD [34].



Thioamides reacted with DMAD in ethanol at room temperature to give thiazole derivatives as a sole product [35].

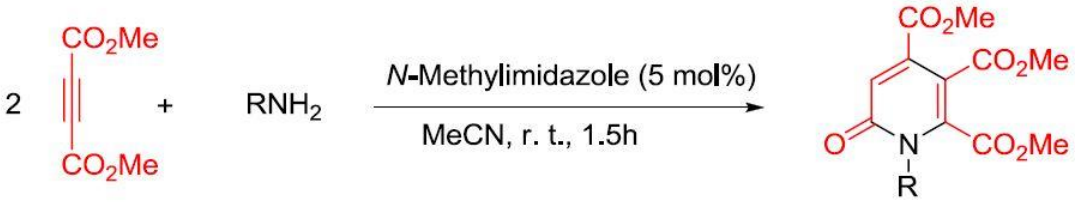


Triazoles is formed via 1,3-dipolar cycloaddition of azide with DMAD. Palladium supports the reaction [36].

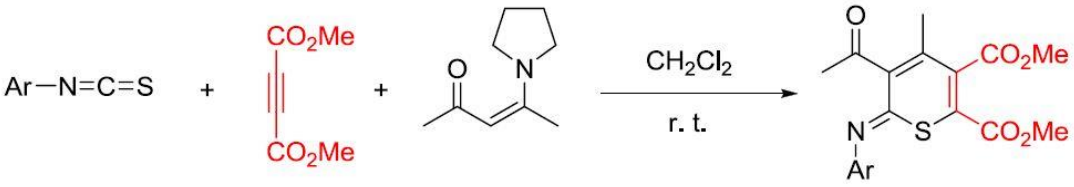


1.2.4. Synthesis of Six-Membered Rings with DMAD

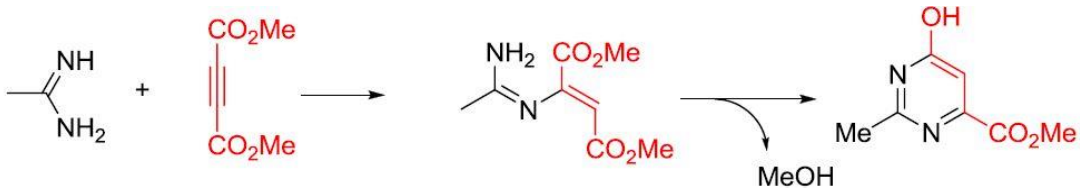
N-Methylimidazole is used as a catalyzer in the tandem reaction between primary amines and DMAD to produce functionalized 2-pyridones [37].



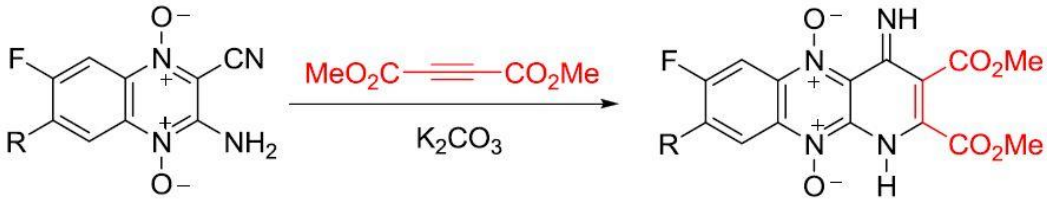
A one-pot reaction of arylthiocyanates, DMAD, and enaminones in dichloromethane at room temperature gave 6H-6-iminothio pyran-2,3-dicarboxylate [38].



Reaction of acetamide with DMAD gives a linear product via a Michael addition. Methyl 4-hydroxyl-2-methyl pyrimidine-6-carboxylate was obtained via the elimination of methanol by heating the compound [39].



DMAD react with 2-Amino-3-cyano-6-fluoro-7-substituted quinoxaline-N-oxides to yield pyrido[2,3-b]quinoxaline-N-oxides [40].



CHAPTER 2

MATERIAL AND PROCEDURES

2.1. Materials and Equipments

All commercial reagents and solvents were purchased from Merck, Sigma-Aldrich and Fluka, and used in chemical grade without further purification. Melting point was determined using Electrothermal 9200 melting point apparatus. IR spectra were recorded on Shimadzu 8400 spectrophotometer. ^{1}H NMR and ^{13}C-NMR spectra were recorded at a Bruker Avance 400 MHz^{-1} spectrometer. For elemental analysis Leco CHNSO-932 elemental analyzer was used.

2.2. Procedures and Methods

The most important parameters, which determinate states of affairs of a chemical reaction, are temperature, reaction time, concentration, solvent, catalyzer, and, structures and activity of reagents. In this study, these parameters have been taken into account to achieve optimal reaction conditions. All reaction has been occurred by stirring at room temperature and controlled by TLC chromatography. Products have been purified by Column chromatography and recrystallization.

Structural analysis of compounds has determined by using IR spectrophotometer, NMR analysis, and elemental analysis.

CHAPTER 3

RESULTS AND DISCUSSION

3.1. Synthesis of Aminoguandine Derivatives

When searching literature, it is clear that there are many ways to synthesize aminoguanidine derivatives (guanylhydrazones) [41, 42]. In this study, an environmentally friendly method used to synthesize guanylhydrazones.

3.1.1 General Procedure

In a 250 ml flask 0,1 mol aminoguanidine nitrate and 0,1 mol sodium hydroxide get mixed and then 100 mL distilled water was added and stirred for 10 minutes. After 10 minutes, 0,1 mol aromatic aldehyde added and the mixture was stirred for 10 hours at room temperature. After 10 hours the reaction was stopped and the flask was incubated in cold for 10 hours. Then solid was filtered and recrystallized in distilled water.

Table 3.1. Yields and melting points of aminoguanidine derivatives

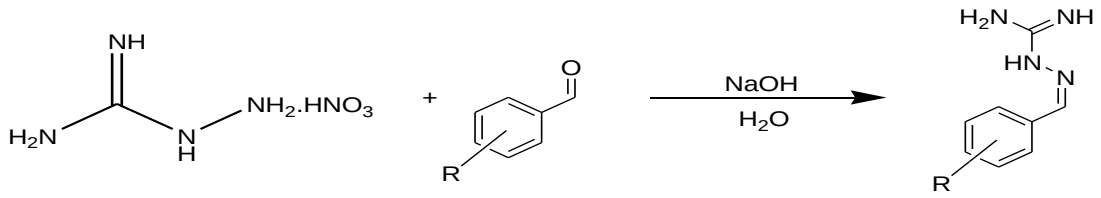


Table 3.1.Yields and melting points of aminoguanidine derivatives

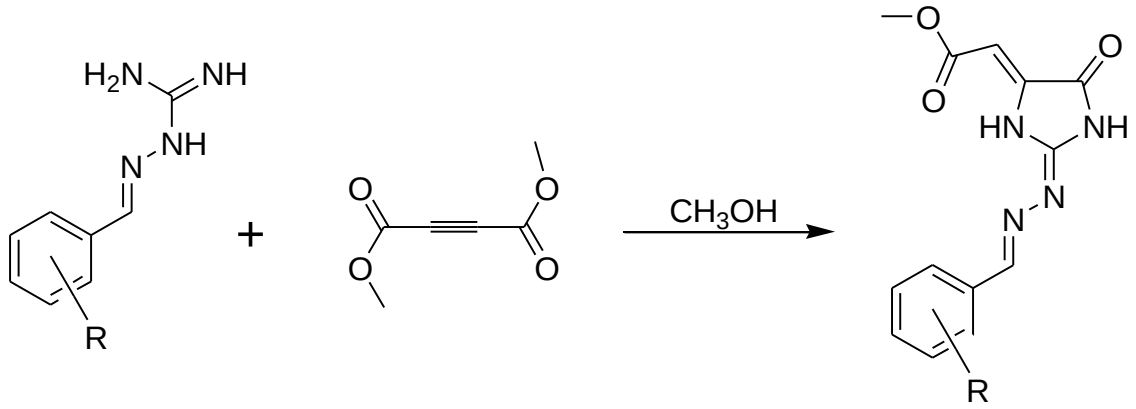
R	Yield (%)	Melting Point (^{0}C)
-	79	180-182
p-CH_3-	84	214-216
p-CH_3O-	81	191-193
p-C_2H_5O-	72	163-165
o-Cl-	82	142-143
2,4-di-Cl-	79	211-212
p- $(CH_3)_2$ CH-	59	139-140
p-NO_2-	62	207-208
2,4-di-CH_3O-	74	181-183
p-CF_3-	77	112-113

3.2. Synthesis of Imidazolidine Derivatives

3.2.1. Reaction with dimethyl acetylenedicarboxylate (DMAD)

3.2.1.1. General Procedure

Equimolar freshly prepared aminoguanidine derivatives and DMAD were and added in a 100 mL reaction flask and stirred for 10-60 minutes in methanol at room temperature. Then, precipitated solid was filtered and purified by recrystallization,



3.2.1.2. Methyl {2-[(4-methylbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A1)

Beige solid; yield 64%; melting point: 178–179 °C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.07 (s, 1H, NH), 8.60 (s, 1H, NH), 8.14 (s, 1H, HC=N), 7.78 (d, J = 7.8 Hz, 2H, Ar), 7.30 (d, J = 7.7 Hz, 2H, Ar), 5.77 (s, 1H, HC=C), 3.50 (s, 3H, OCH_3), 2.37 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.14, 168.07, 165.04, 162.34, 142.19, 137.03, 130.42, 129.73, 129.05, 96.37, 52.18, 21.63. IR (cm^{-1}) 3425-3390 N-H stretch, 2995-2941 =C-H, 1728-1691 C=O stretch, 1627-1548 C=N stretch. Calculated elemental analysis for $C_{14}H_{14}N_4O_3$: C, 58.74; N,19.58; H, 4.93. Found: C, 58.41; N, 19.23; H,4.69.

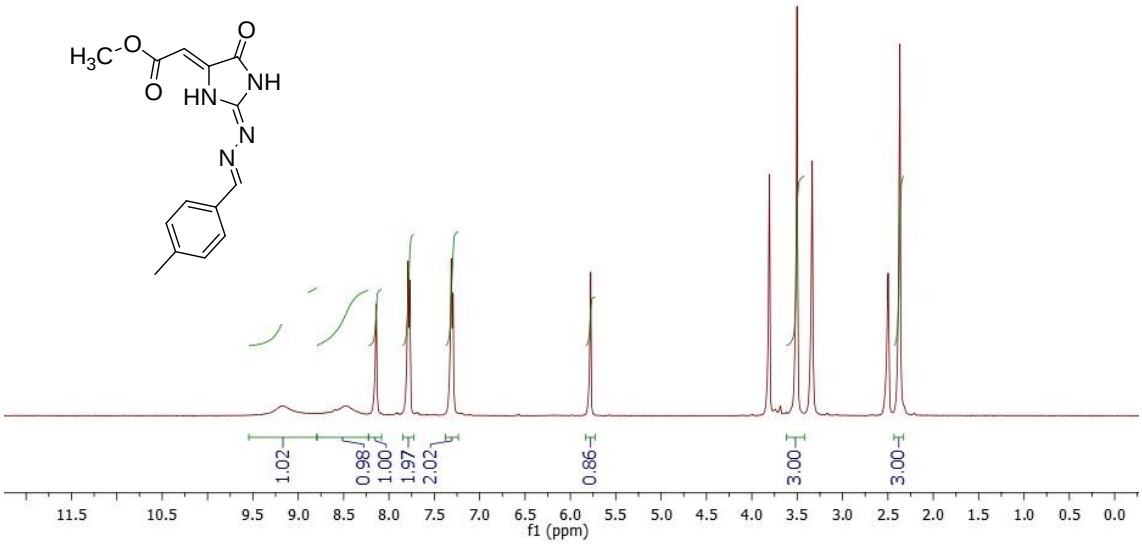


Figure 3.1.: ^{1}H-NMR spectrum of A1

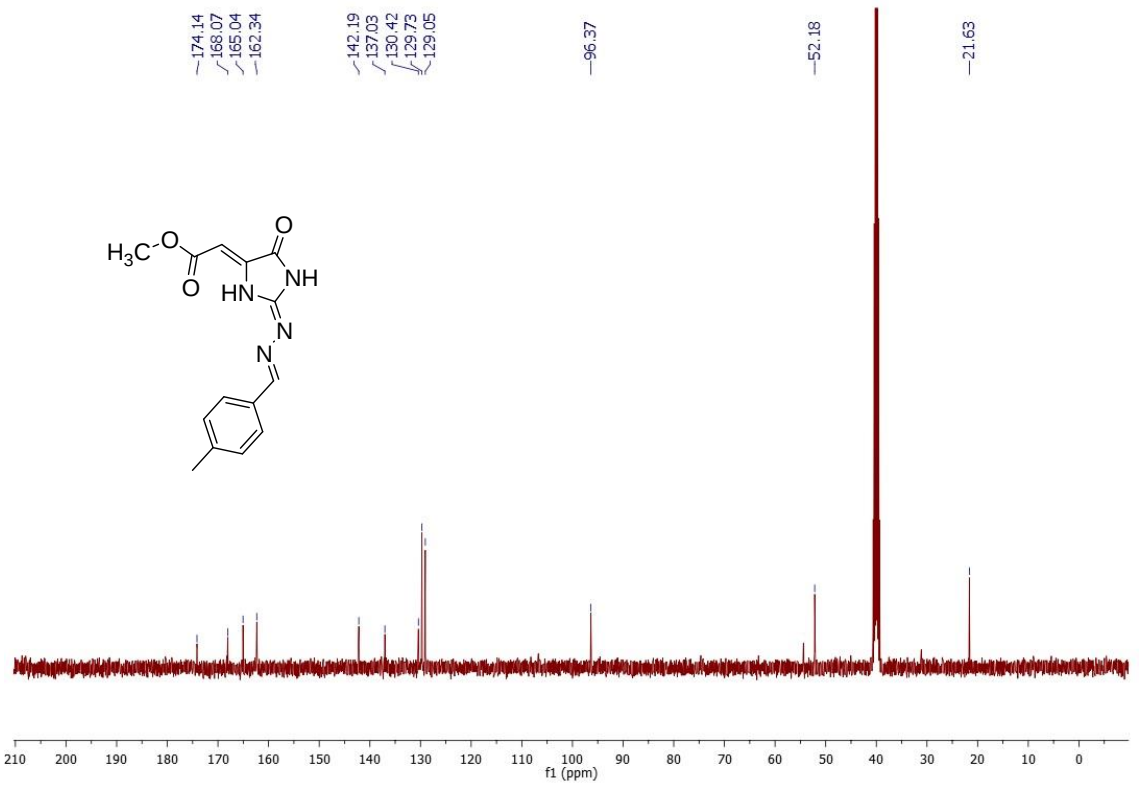


Figure 3.2. ^{13}C-NMR spectrum of A1

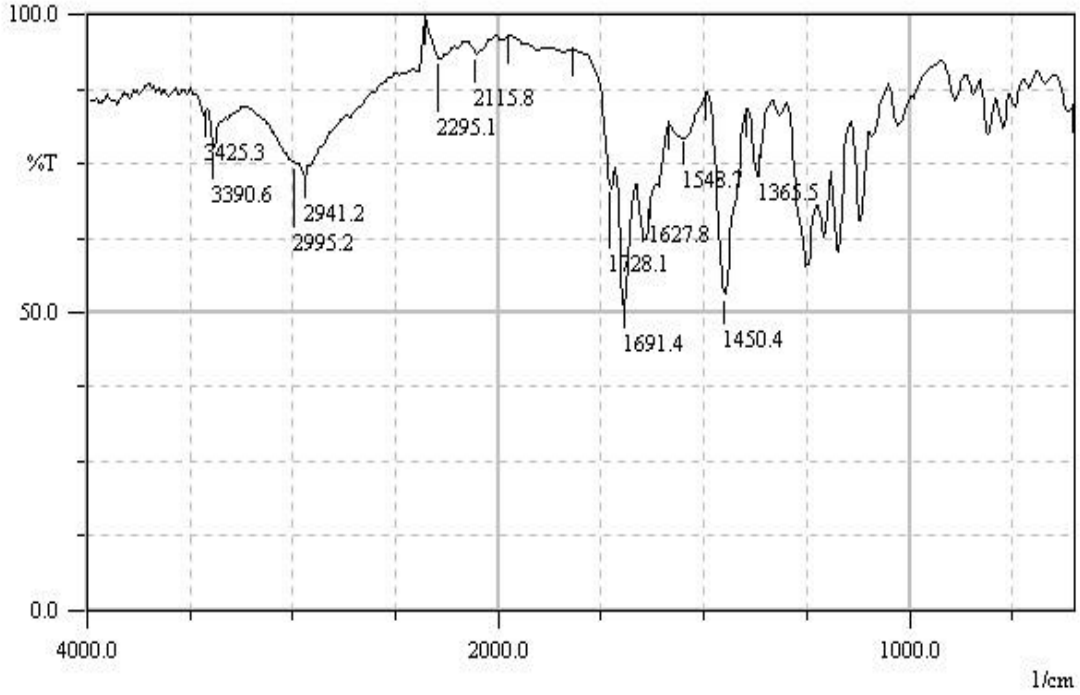


Figure 3.3. FT-IR spectrum of A1

3.2.1.3. Methyl {2-[(4-ethoxylbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A2)

Beige solid; yield 77%; melting point: 181-182 ^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 8.57 (s, 2H, 2NH), 8.17 (s, 1H, HC=N), 7.82 (d, J = 8.7 Hz, 2H, Ar), 7.03 (d, J = 8.7 Hz, 2H, Ar), 5.74 (s, 1H,), 4.10 (q, J = 6.9 Hz, 2H, OCH_2), 3.48 (s, 3H, OCH_3), 1.35 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.15, 168.03, 165.07, 163.05, 161.88, 137.33, 130.95, 125.45, 115.04, 96.07, 63.87, 52.14, 14.97. IR (cm^{-1}) 3438 N-H stretch, 2974-2929 =C-H stretch, 1737-1693 C=O stretch, 1641-1596 C=N stretch. Calculated elemental analysis for $C_{15}H_{16}N_4O_4$: C, 58. 74; N, 19.57; H, 4.93. Found: C, 58.52; N, 19.37; H, 4.81

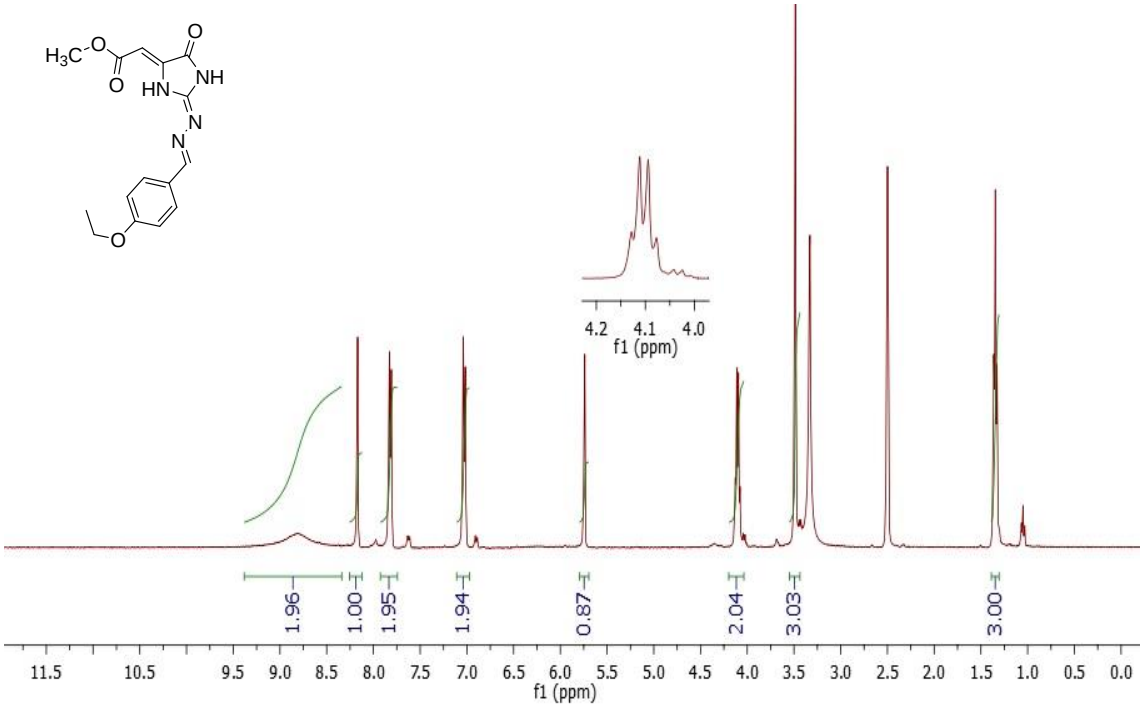


Figure 3.4. [1]H-NMR spectrum of A2

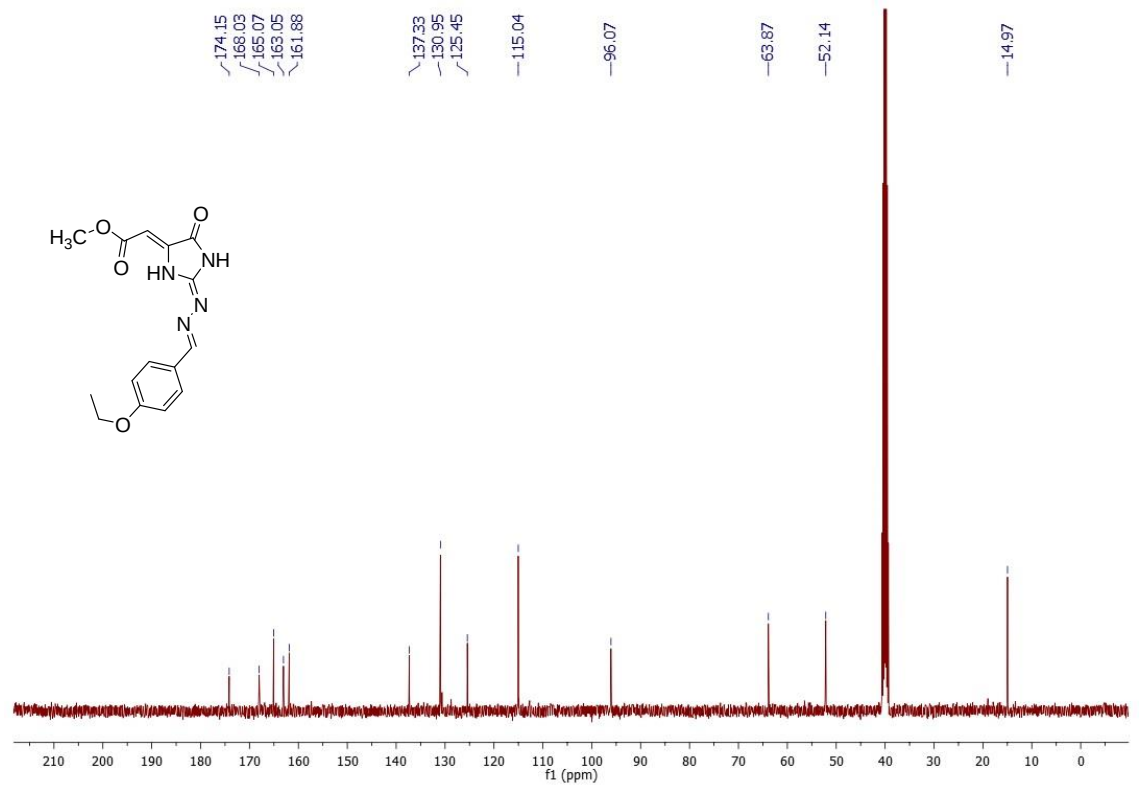


Figure 3.5. [13]C-NMR spectrum A2

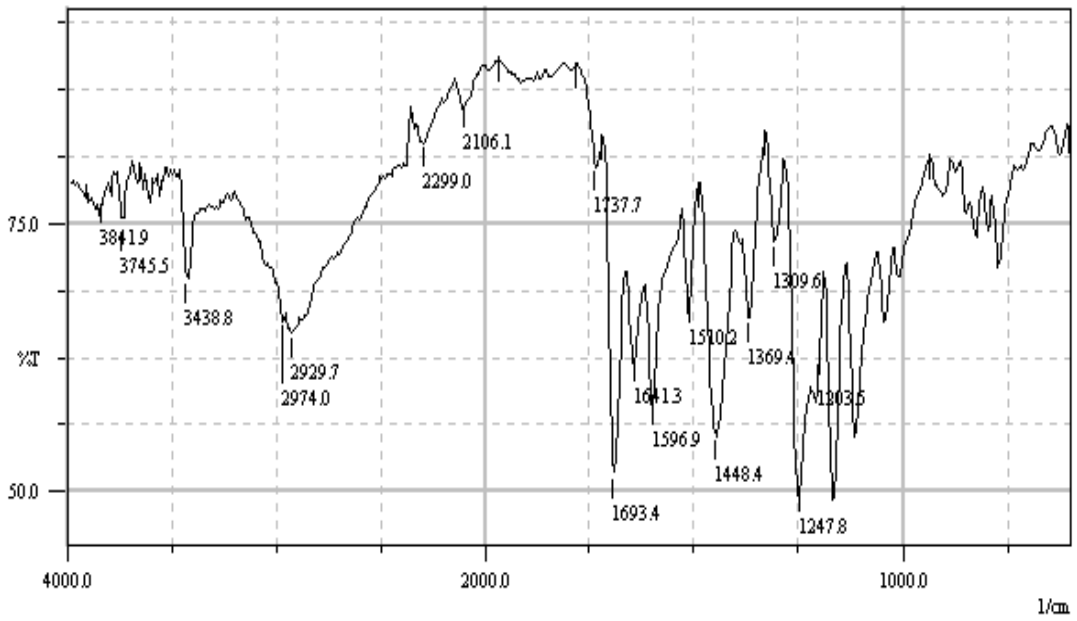


Figure 3.6. FT-IR spectrum of A2

3.2.1.4. Methyl {2-[(2,4-dimethoxylbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A3)

Yellow solid; yield 85%; melting point: 224-225^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 8.65 (s, 2H, 2NH), 8.12 (s, 1H, HC=N), 8.08 (d, J = 9.0 Hz, 1H, Ar), 6.65 (s, 2H, Ar), 5.76 (s, 1H, HC=C), 3.84 (d, J: 6,7 6H, 2OCH$_3$), 3.83, 3.53 (s, 3H, CH$_3$OC=O)$^-$. ^{13}C-NMR (100 MHz, DMSO) δ 174.20, 168.23, 164.94, 164.42, 160.71, 156.13, 136.74, 128.73, 113.58, 107.14, 98.42, 95.86, 56.34, 56.06, 52.13. IR (cm^{-1}) 3350 N-H stretch, 3947 =C-H stretch, 1703-1676 C=O stretch, 1631-1606 C=N stretch. Calculated elemental analysis for $C_{15}H_{16}N_4O_5$: C, 52.21; N, 16.86; H, 4. 85. Found: C, 52.15; N, 16.77;H, 4.76

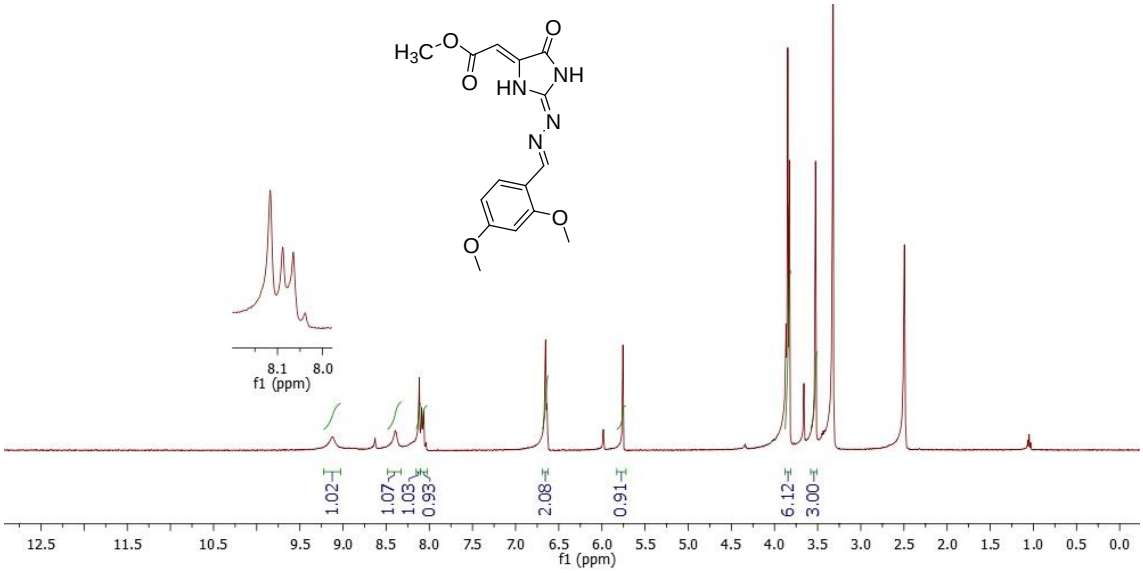


Figure 3.7. ^{1}H-NMR spectrum of A3

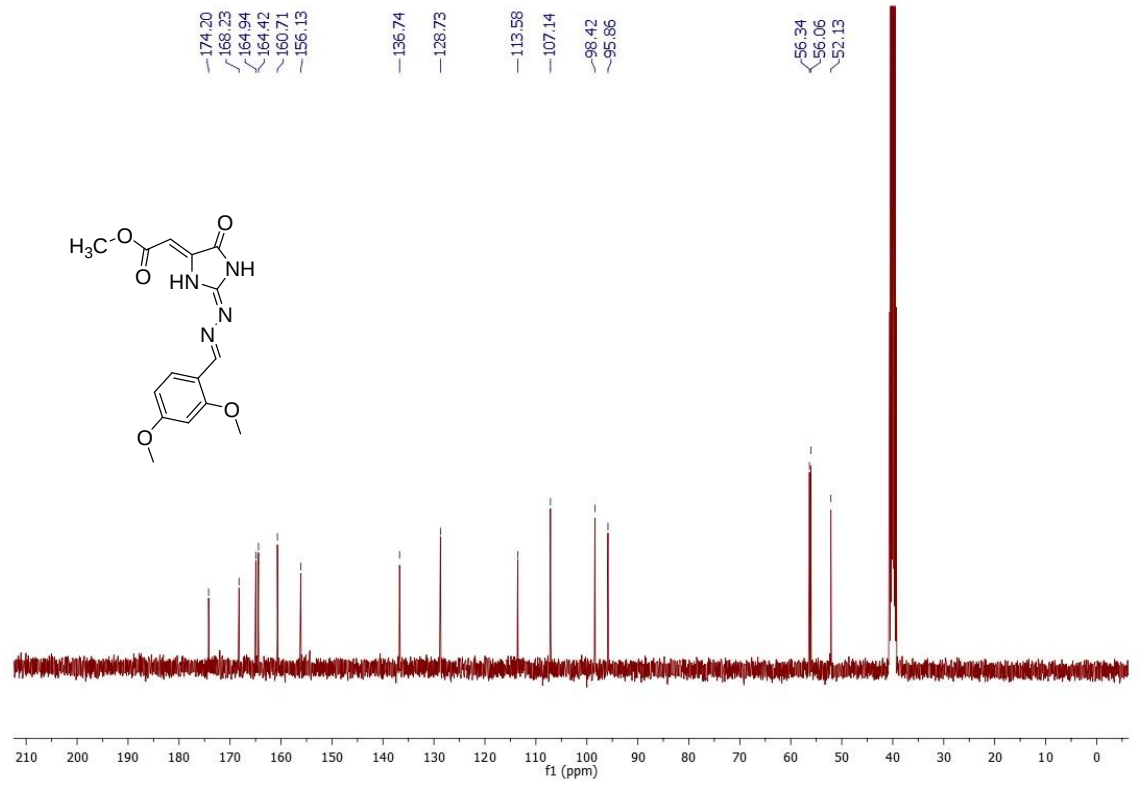


Figure 3.8. ^{13}C-NMR spectrum of A3

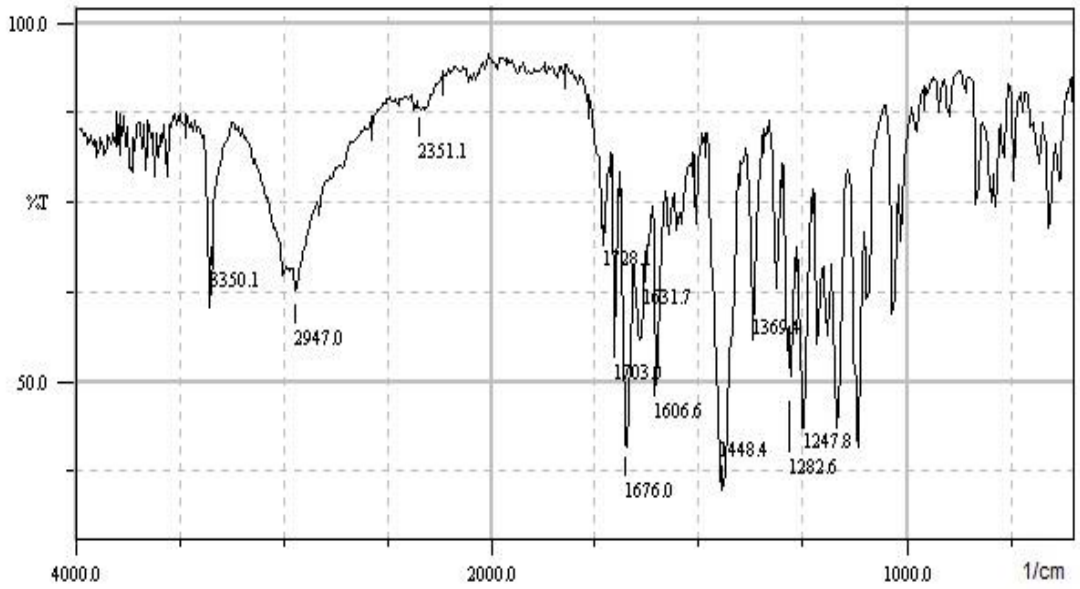


Figure 3.9. FT-IR spectrum of A3

3.2.1.5. Methyl {2-[(2-chlorolbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate(A4)

Light yellow solid; yield 78%; melting point: 220-222^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.31 (s, 1H, NH), 8.68 (s, 1H, NH), 8.42 (d, J = 7.6 Hz, 1H, Ar), 8.04 (s, 1H, HC=N), 7.63 – 7.43 (m, 3H, Ar), 5.89 (s, 1H, HC=C), 3.62 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 173.96, 168.06, 164.95, 153.78, 136.34, 134.92, 133.39, 130.43, 130.06, 128.55, 127.95, 96.75, 52.44. IR (cm^{-1}) 3438-3377 N-H stretch, 2947 =C-H stretch, 1737-1685 C=O stretch, 1613-1544 C=N stretch. Calculated elemental analysis for $C_{13}H_{11}N_4O_3Cl$: C, 50.91; N, 18.27; H, 3.61. Found: C, 50.78; N, 18.19; H, 3.54

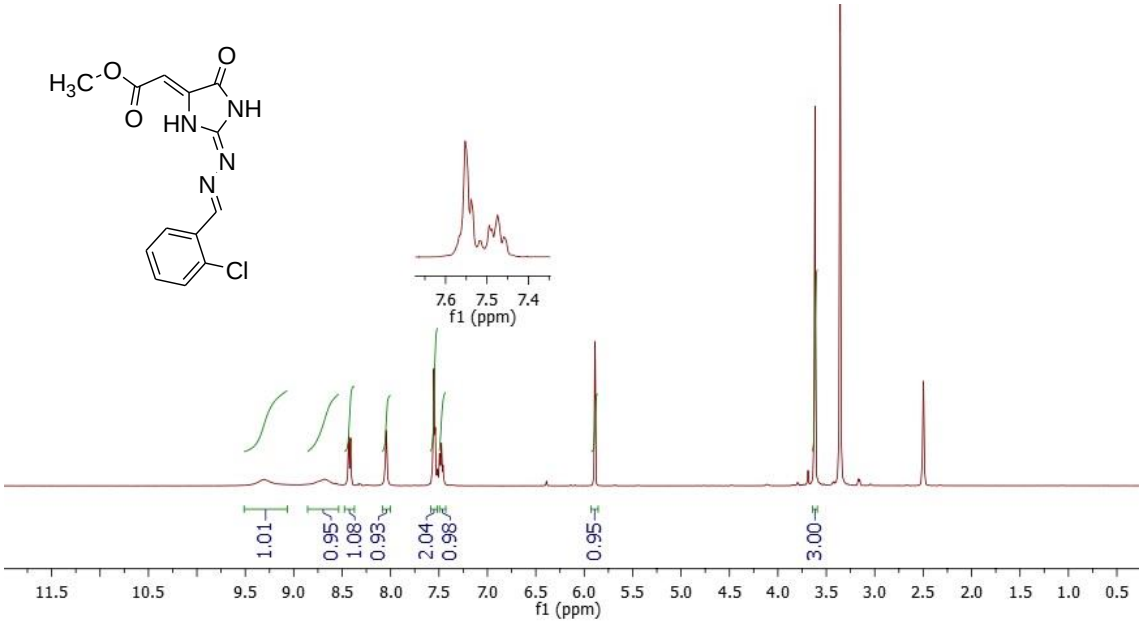


Figure 3.10. ^{1}H-NMR spectrum of A4

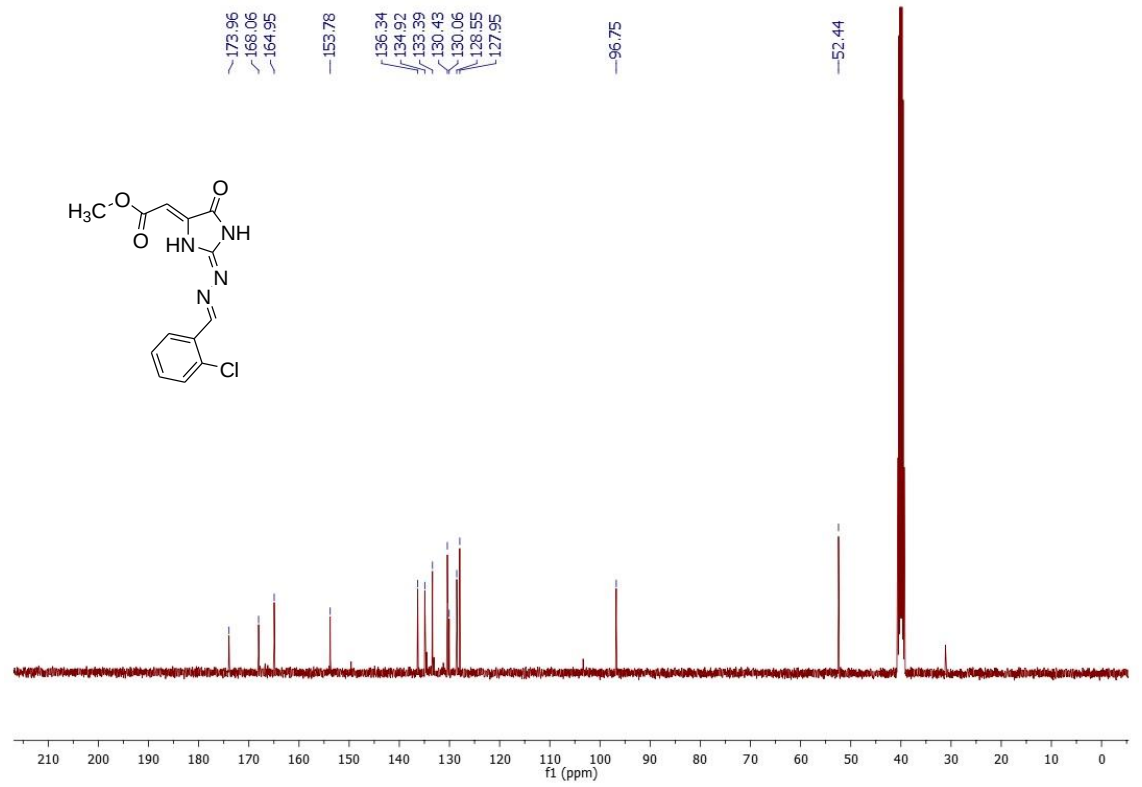


Figure 3.11. ^{13}C-NMR spectrum of A4

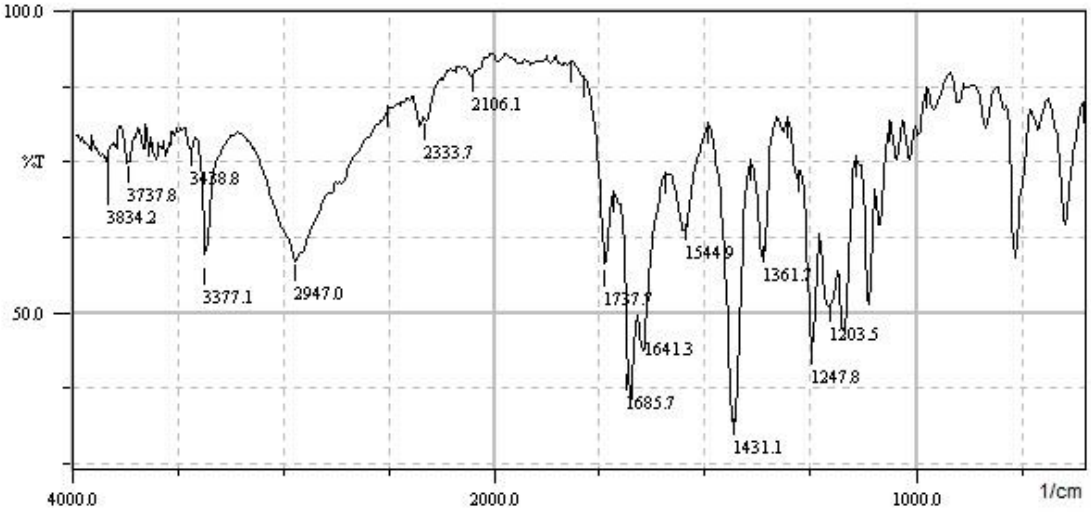


Figure 3.12. FT-IR spectrum of

3.2.1.6. Methyl {2-[(4-nitrobenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A5)

Light yellow solid; yield 71%; melting point:239-240^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.34 (s, 1H, NH), 8.72 (s, 1H, NH), 8.33 (d, J = 7.2 Hz, 2H, Ar), 8.20 (d, J = 7.5 Hz, 2H, Ar), 8.15 (s, 1H, HC=N), 5.88 (s, 1HHC=C), 3.58 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 173.89, 167.86, 165.08, 157.05, 149.23, 139.36, 136.20, 129.88, 124.28, 97.54, 52.38. IR (cm^{-1}) 3411 N-H stretch, 2947 =C-H stretch, 1740-1693 C=O stretch, 1658-1582 C=N stretch. Calculated elemental analysis for $C_{13}H_{11}N_5O_5$: C, 49.21; N, 22.08; H, 3.50. Found: C:49.04; N, 21.94; H, 3.41

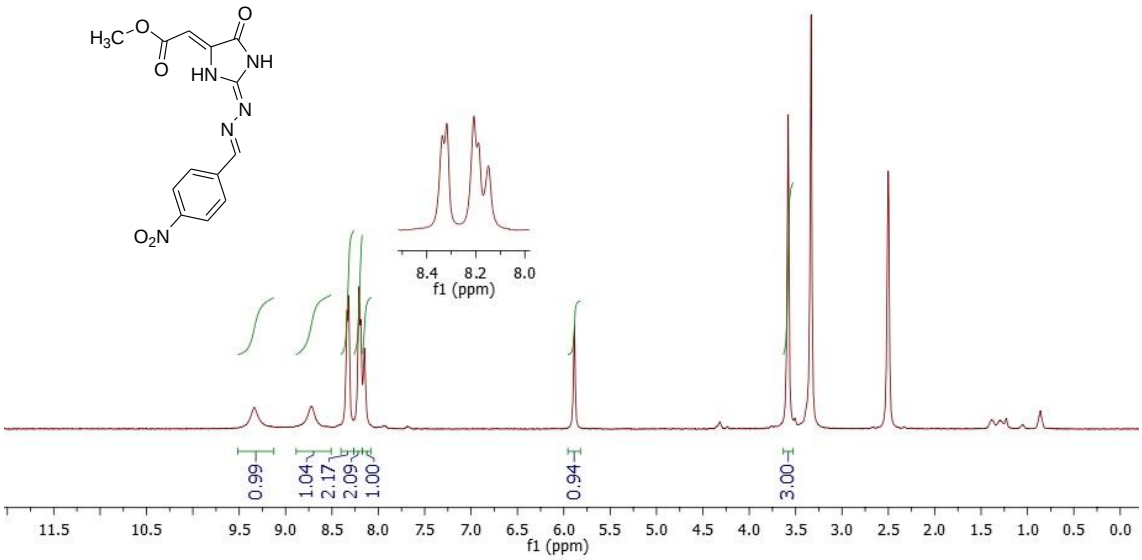


Figure 3.13. ^{1}H-NMR spectrum of A5

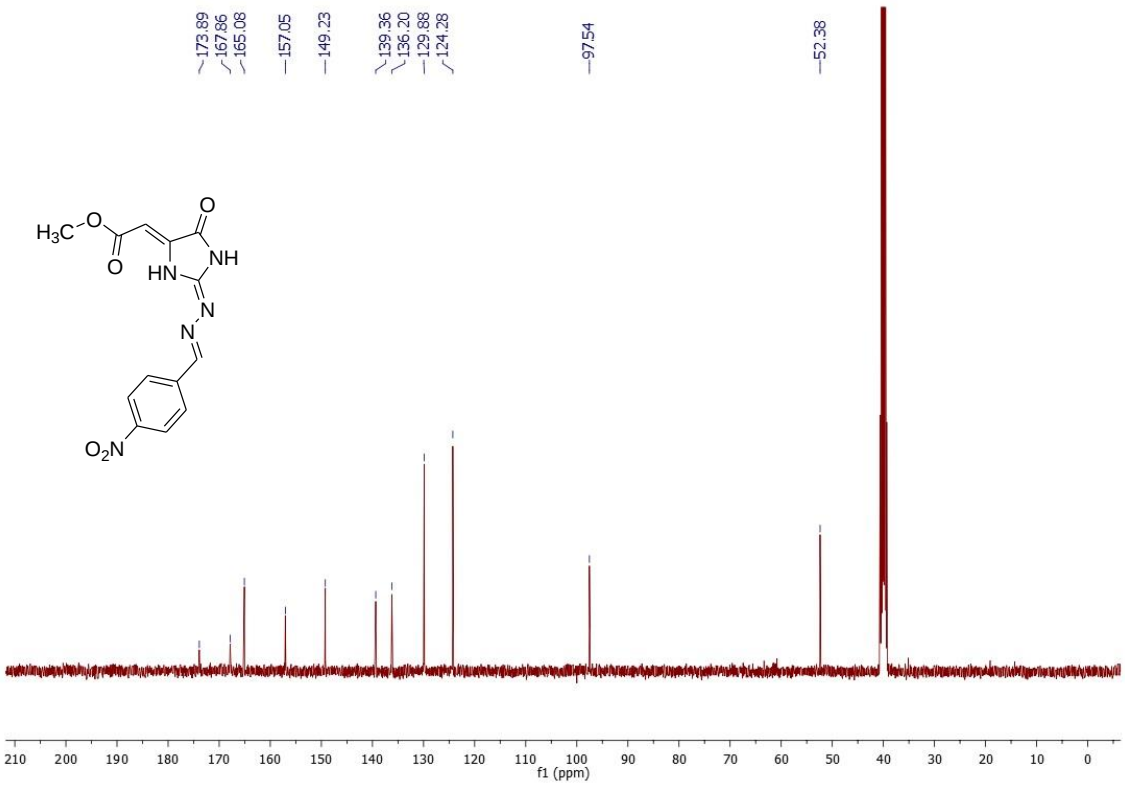


Figure 3.14. ^{13}C-NMR spectrum of A5

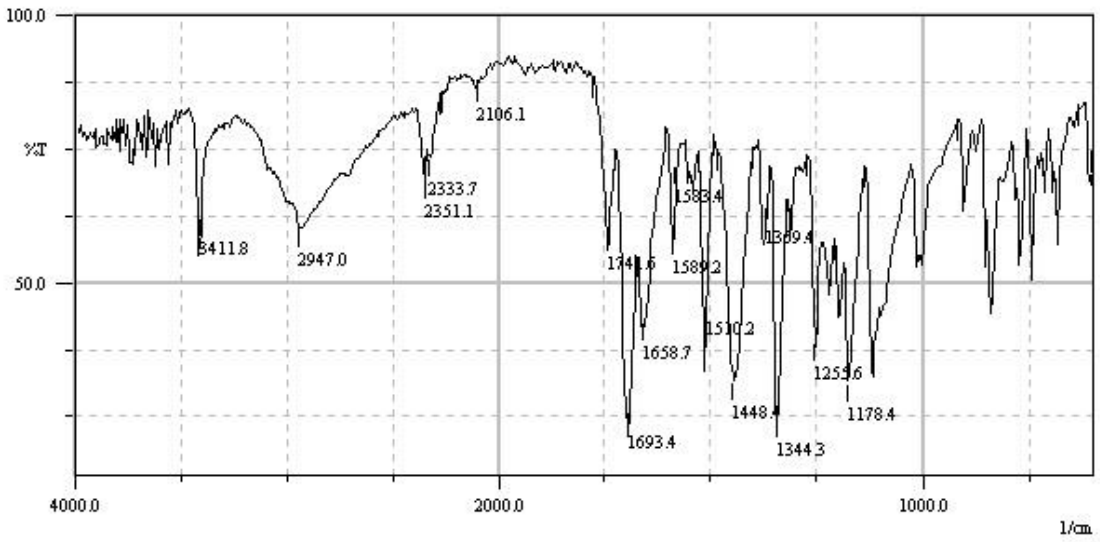


Figure 3.15. FT-IR spectrum of A5

3.2.1.7. Methyl {2-[(2,4-dichlorobenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A6)

Beige solid; yield 83%; melting point: 221-224^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.33 (s, 1H, NH), 8.71 (s, 1H, NH), 8.46 (d, J = 8.5 Hz, 1H, Ar), 7.95 (s, 1H, HC=N), 7.76 (s, 1H, Ar), 7.59 (d, J = 8.5 Hz, 1H Ar), 5.88 (s, 1H, HC=C), 3.62 (s, 3H, OCH_3). ^{13}C-NMR (100 MHz, DMSO) δ 173.88, 168.00, 164.97, 152.49, 137.17, 136.27, 135.60, 129.96, 129.77, 129.21, 128.37, 96.86, 52.47. IR (cm^{-1}) 3386 N-H stretch, 2999-2948 =C-H stretch, 1737-1693 C=O stretch, 1650-1579 C=N stretch. Calculated elemental analysis for $C_{13}H_{10}N_4O_3Cl_2$: C, 45.77; N, 16.42, H, 2.96. Found: C, 45.52; N, 16.27; H, 2.70.

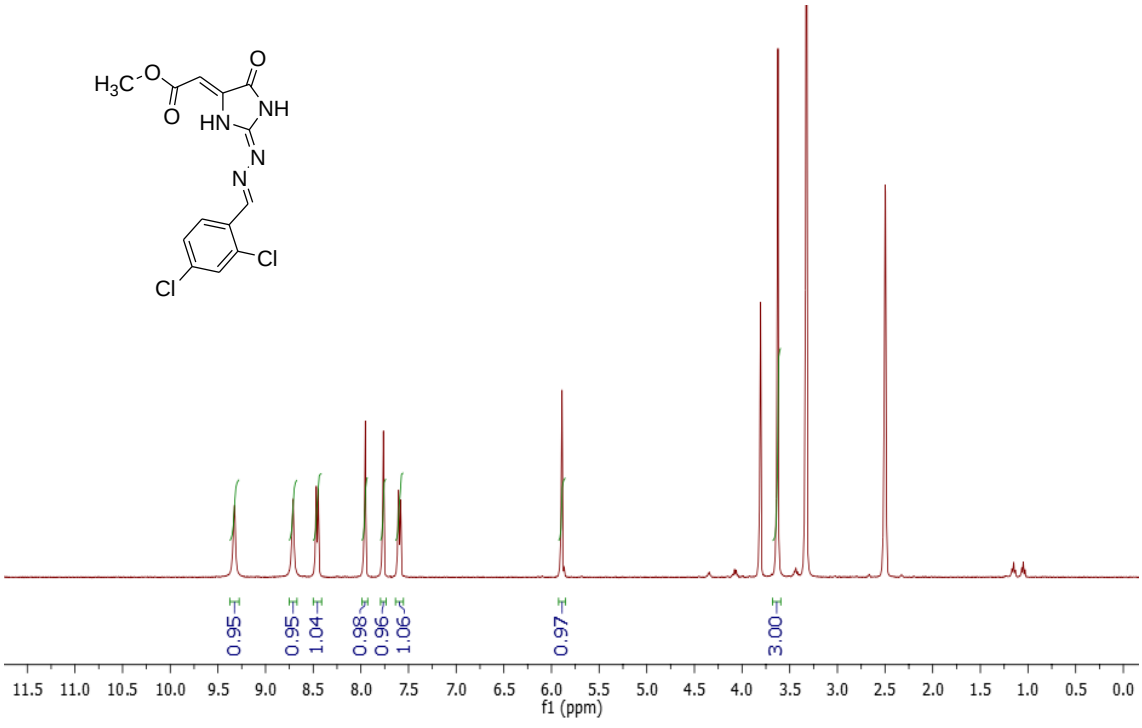


Figure 3.16. ^{1}H-NMR spectrum of A6

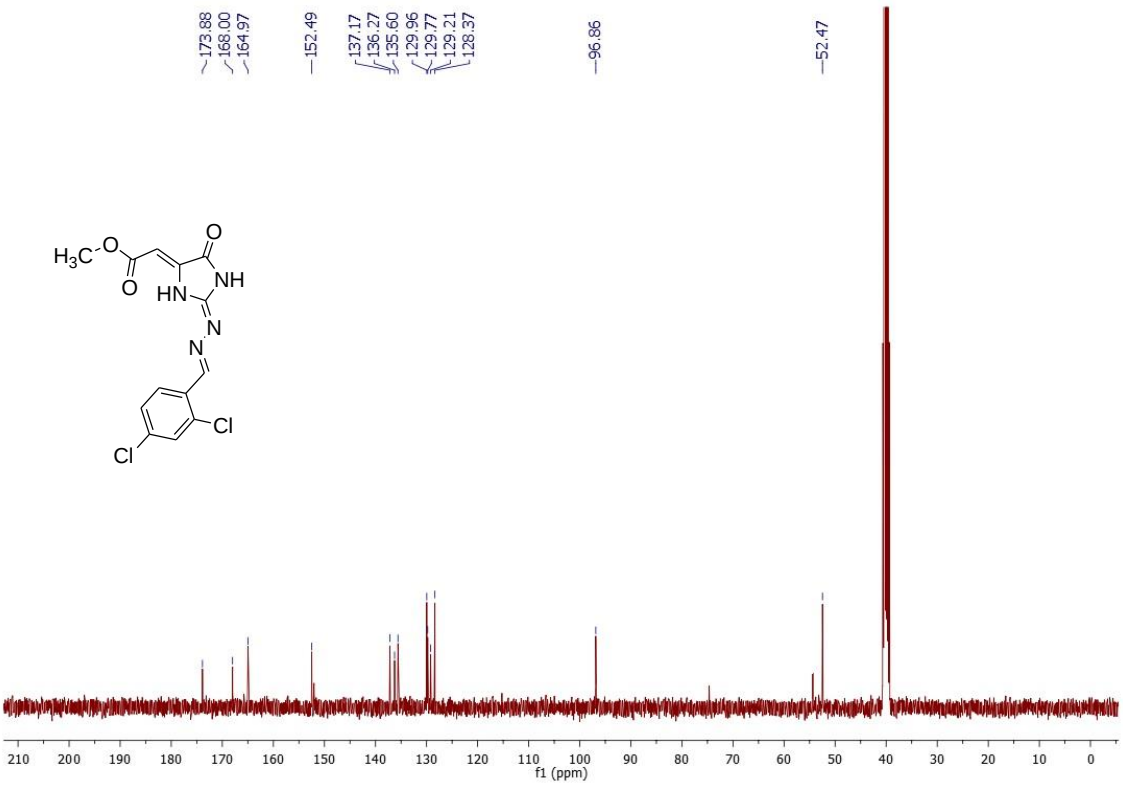


Figure 3.17. ^{13}C-NMR spectrum of A6

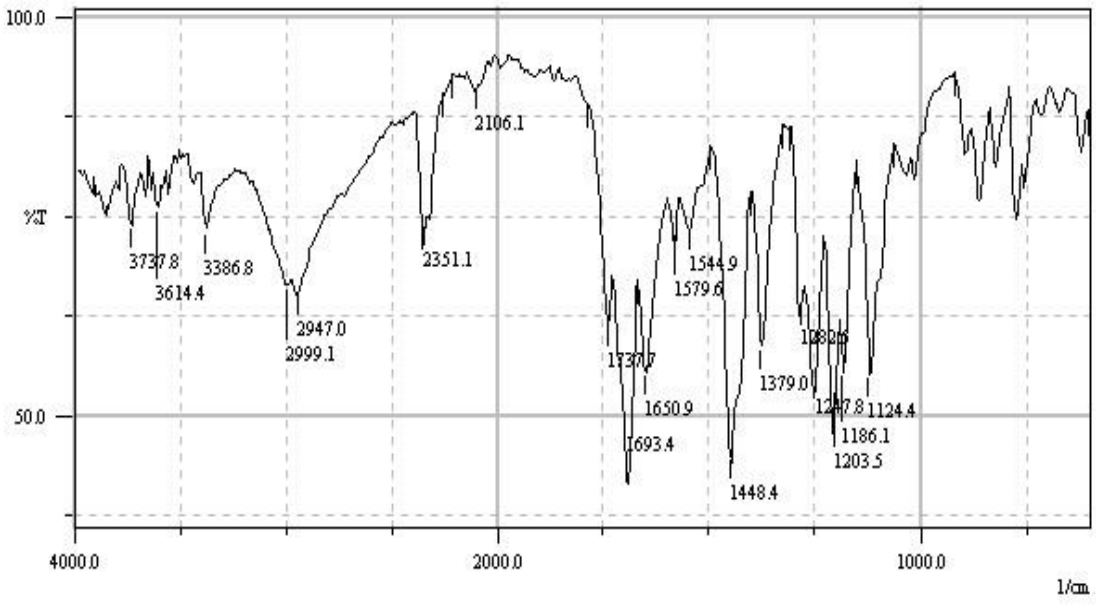


Figure 3.18. FT-IR spectrum of A6

3.2.1.8. Methyl {2-[(4-isopropylbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A7

Light yellow solid; yield 69%; melting point: 205-206^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 8.81 (s, 2H, 2NH), 8.20 (s, 1H, HC=N), 7.82 (s, 2H, Ar), 7.38 (s, 2H, Ar), 5.78 (s, 1H, HC=C), 3.54 (s, 3H, OCH_3), 2.97 (s, 1H, CH), 1.25 (s, 6H, 2xCH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.14, 168.06, 165.04, 162.28, 142.18, 137.02, 130.41, 129.73, 129.05, 96.35, 52.84, 52.18, 21.64. IR (cm^{-1}) 3246 N-H stretch, 2947 =C-H stretch, 1710-1650 C=O stretch, 1606-1554 C=N stretch. Calculated elemental analysis for $C_{16}H_{18}N_4O_3$: C, 61.14; N,17.82; H, 5.77. Found: C, 61.02; N, 17.69; H, 5.66

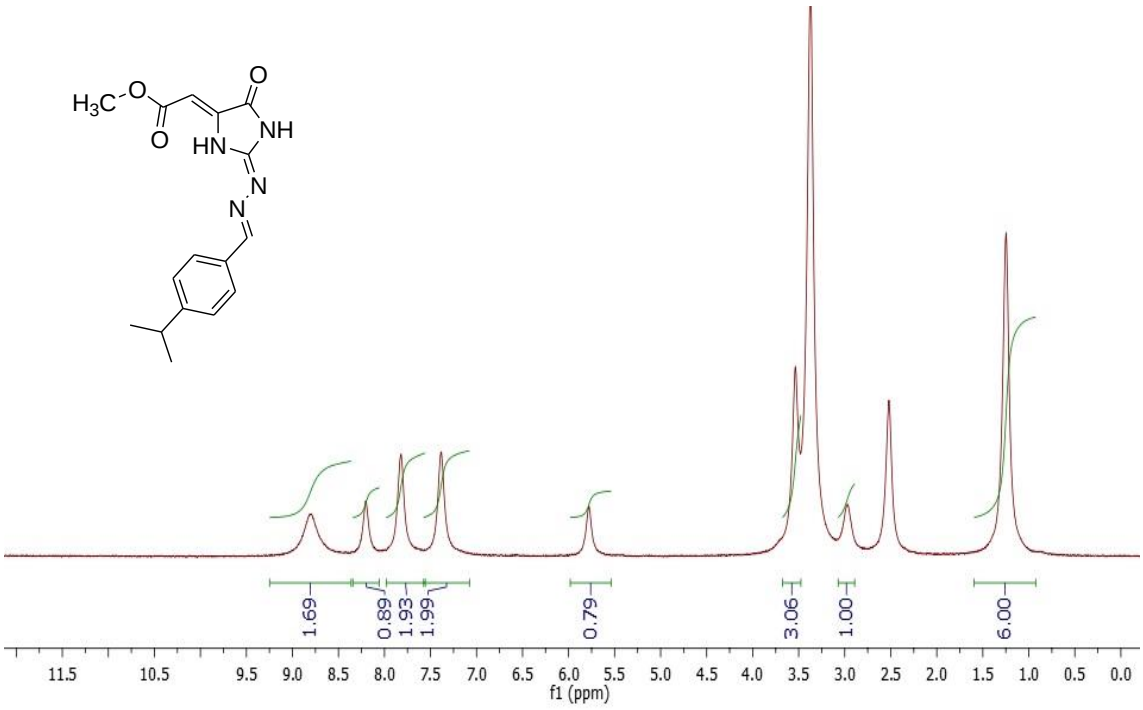


Figure 3.19. ^{1}H-NMR spectrum of A7

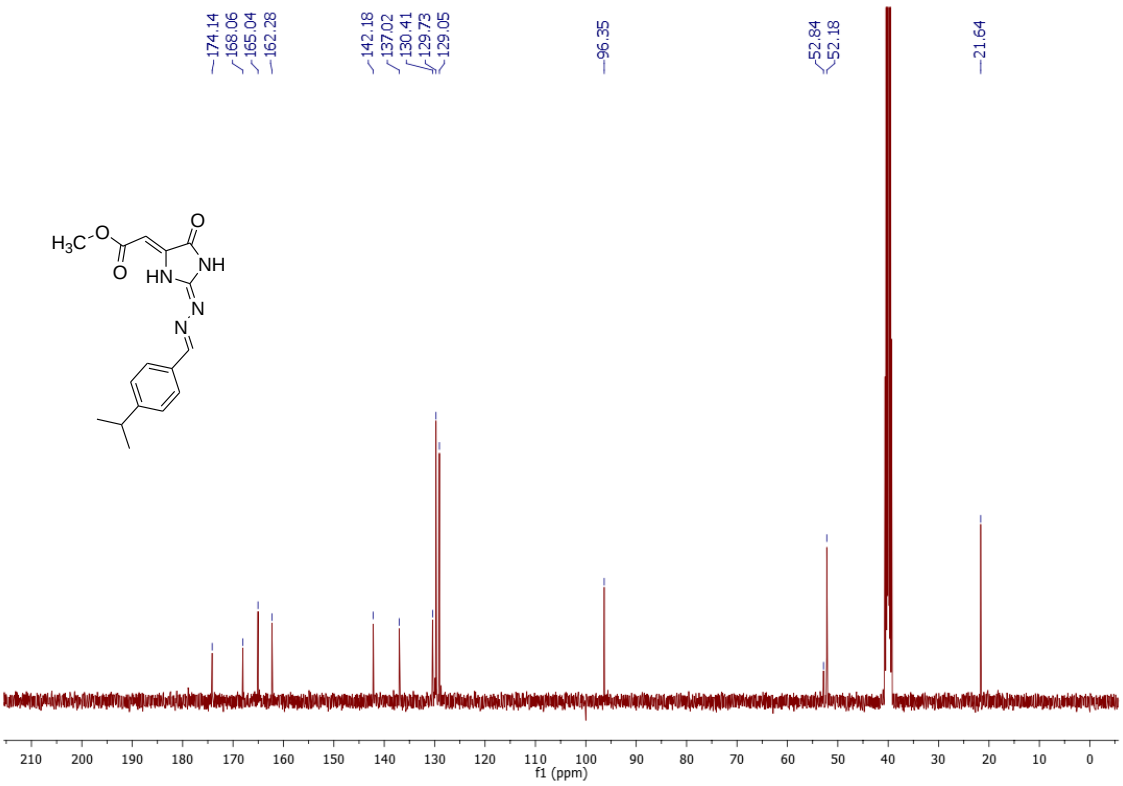


Figure 3.20. ^{13}C-NMR spectrum of A7

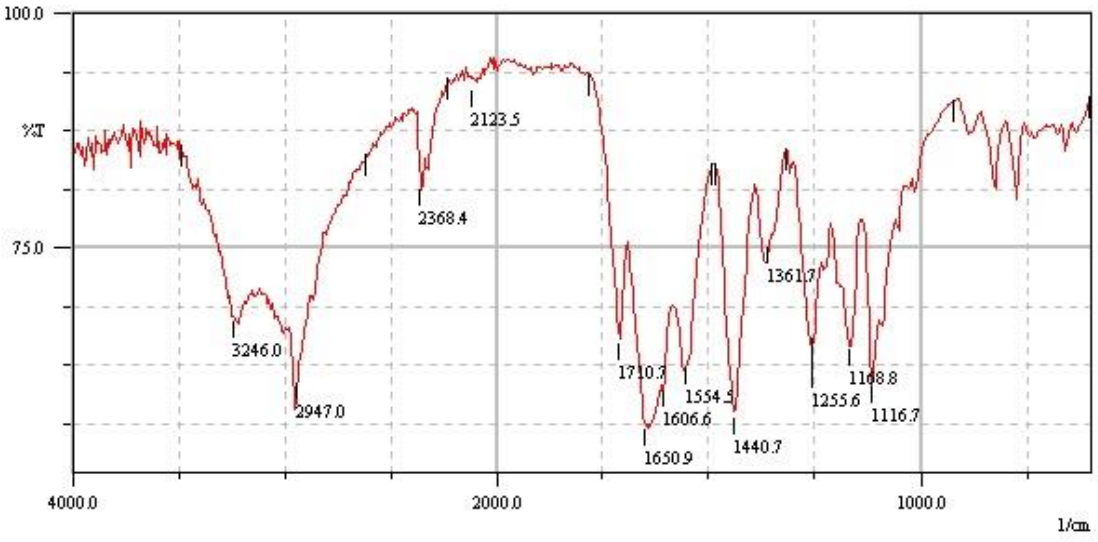


Figure 3.21. FT-IR spectrum of A7

3.2.1.9. Methyl {2-[(4-acetamidolbenzylidene) hydrazinylidene]-5-oxoimidazolidin-4-ylidene} acetate (A8)

Light yellow solid; yield 81%; melting point: 219-221^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 10.21 (s, 1H, NH), 9.15 (s, 1H, NH), 8.42 (s, 1H, NH), 8.12 (s, 1H, HC=N), 7.81 (d, J = 8.3 Hz, 2H, Ar), 7.69 (d, J = 8.4 Hz, 2H, Ar), 5.76 (s, 1H, HC=C), 3.49 (s, 3H, OCH_3), 2.08 (s, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.19, 169.24, 166.56, 165.06, 162.46, 142.82, 137.17, 129.94, 129.58, 119.07, 96.28, 52.18, 24.57. . IR (cm^{-1}) 3404 N-H stretch, 3035 =C-H stretch, 1703-1650 C=O stretch, 1630-1589C=N stretch. Calculated elemental analysis for $C_{15}H_{15}N_5O_4$: C, 54.71; N, 21.27; H, 4.60. Found: C54.62; N, 21.17; H, 4.52

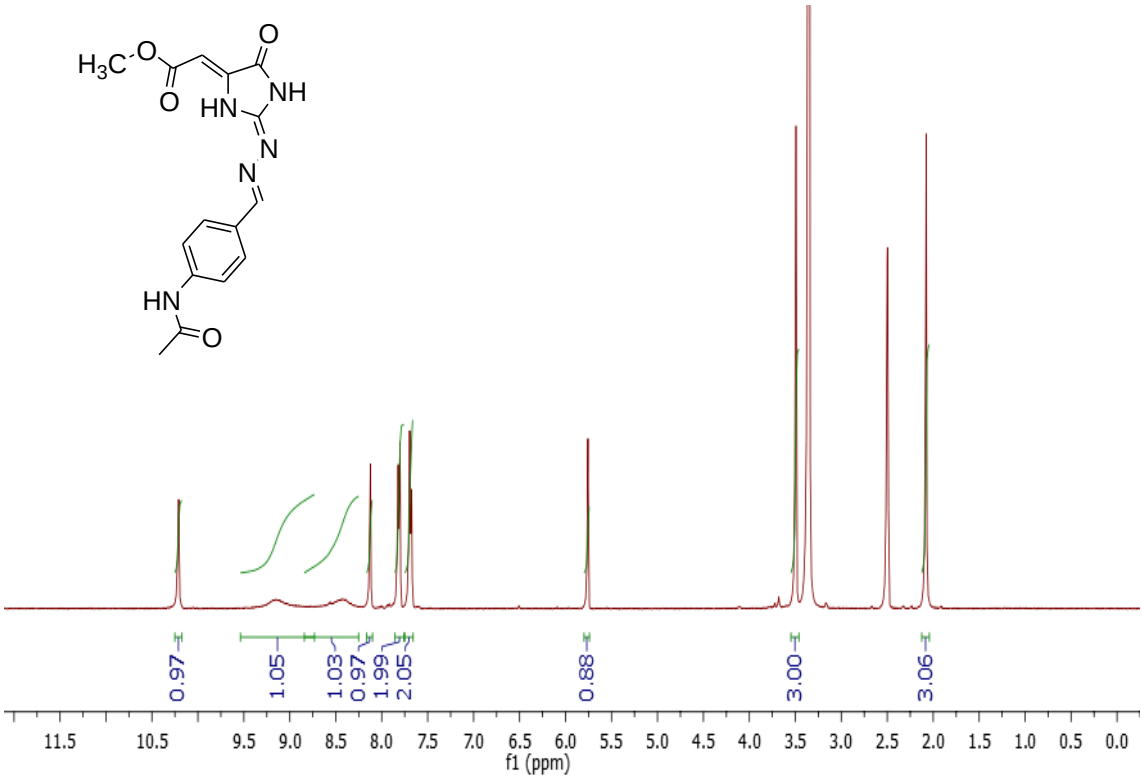


Figure 3.22. ^{1}H-NMR spectrum of A8

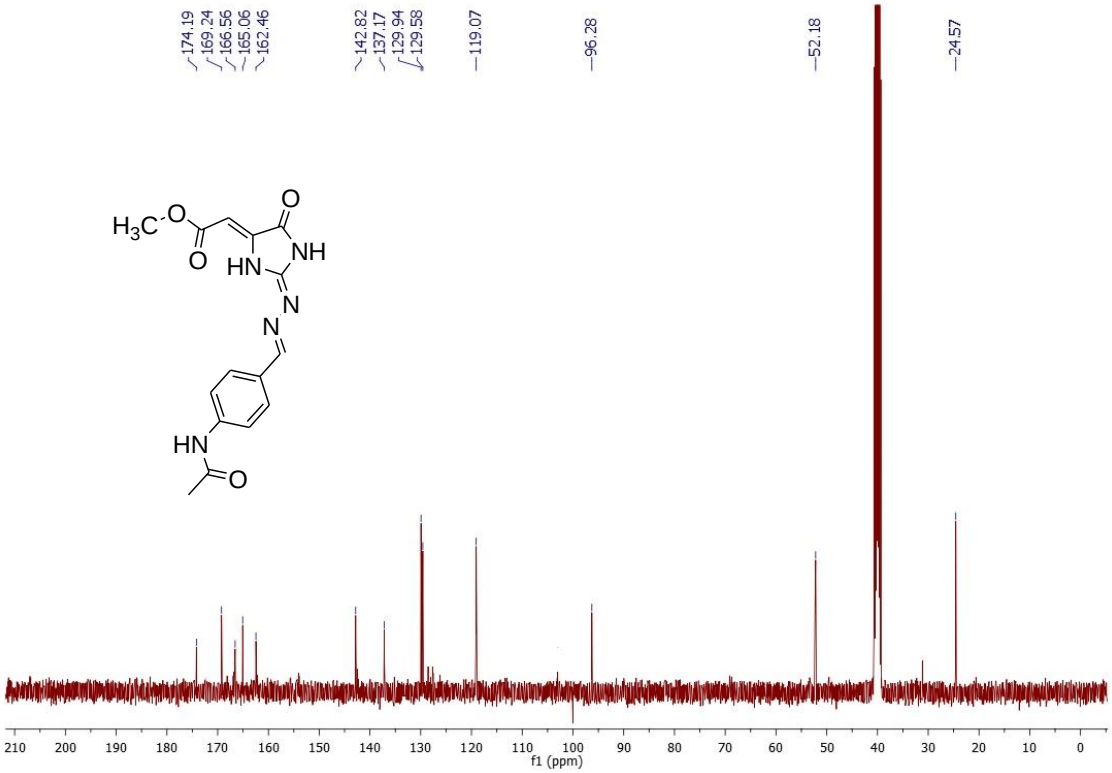


Figure 3.23. ^{13}C-NMR spectrum of A8

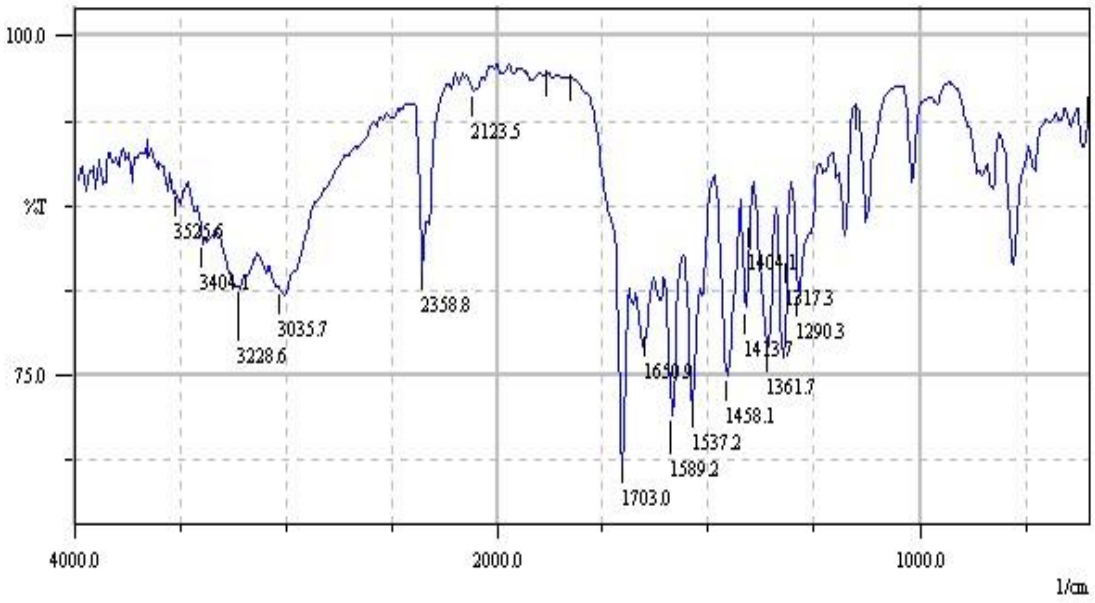
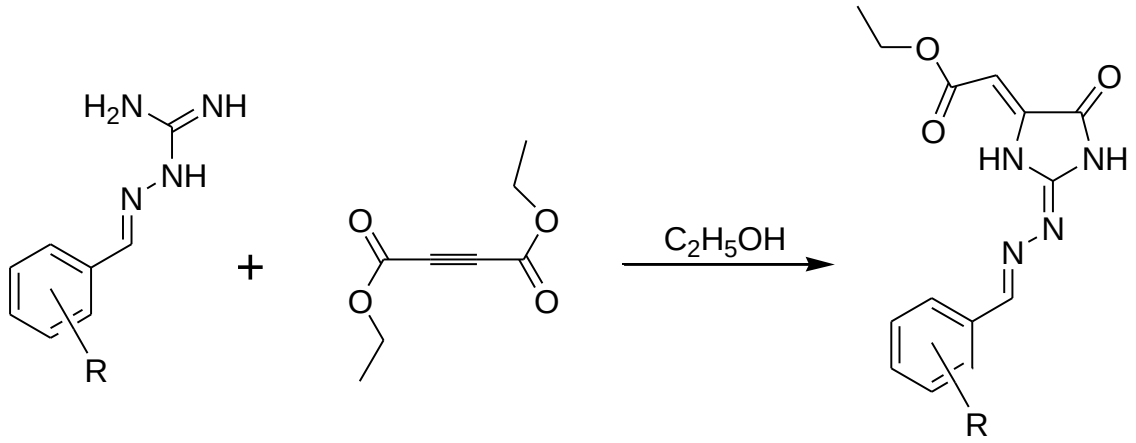


Figure 3.24. FT-IR spectrum of A8

3.2.2. Reaction with diethyl acetylenedicarboxylate (DEAD)

3.2.2.1. General Procedure

Equimolar freshly prepared aminoguanidine derivatives and DEAD were and added in a 100 mL reaction flask and stirred for 10-60 minutes in ethanol at room temperature. Then, precipitated solid was filtered and purified by recrystallization.



3.2.2.2. Ethyl [2-(benzylidenehydrazinylidene)-5-oxoimidazolidin-4-ylidene]acetate (B2)

Beige solid; yield, 87%; melting point: 185-187^{0}C . ^{1}H-NMR (400 MHz, DMSO δ_6) 9.21 (s, 1H, NH), 8.50 (s, 1H, NH), 8.14 (s, 1H, HC=N), 7.89 (d, J = 7.0 Hz, 2H, Ar), 7.61 – 7.40 (m, 3H, Ar), 5.79 (s, 1H, HC=C), 3.97 (q, J = 7.0 Hz, 2H, OCH_2), 1.12 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.10, 168.01, 164.63, 161.38, 136.70, 133.14, 131.99, 129.12, 128.96, 96.99, 60.95, 14.34. . IR (cm^{-1}) 3438 N-H stretch, 2981-2912 =C-H stretch, 1731-1685 C=O stretch, 1650 C=N stretch Calculated elemental analysis for $C_{14}H_{14}N_4O_3$: C, 58.74; N, 19.57; H,4.93. Found: C, 58.59; N, 19.50; , H, 4.81

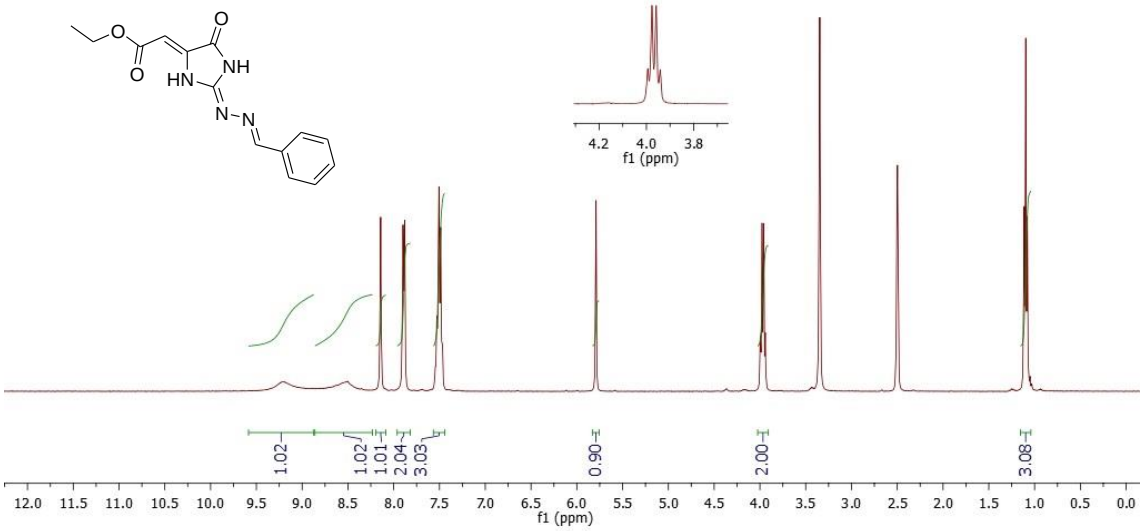


Figure 3.25. ^{1}H-NMR spectrum of B1

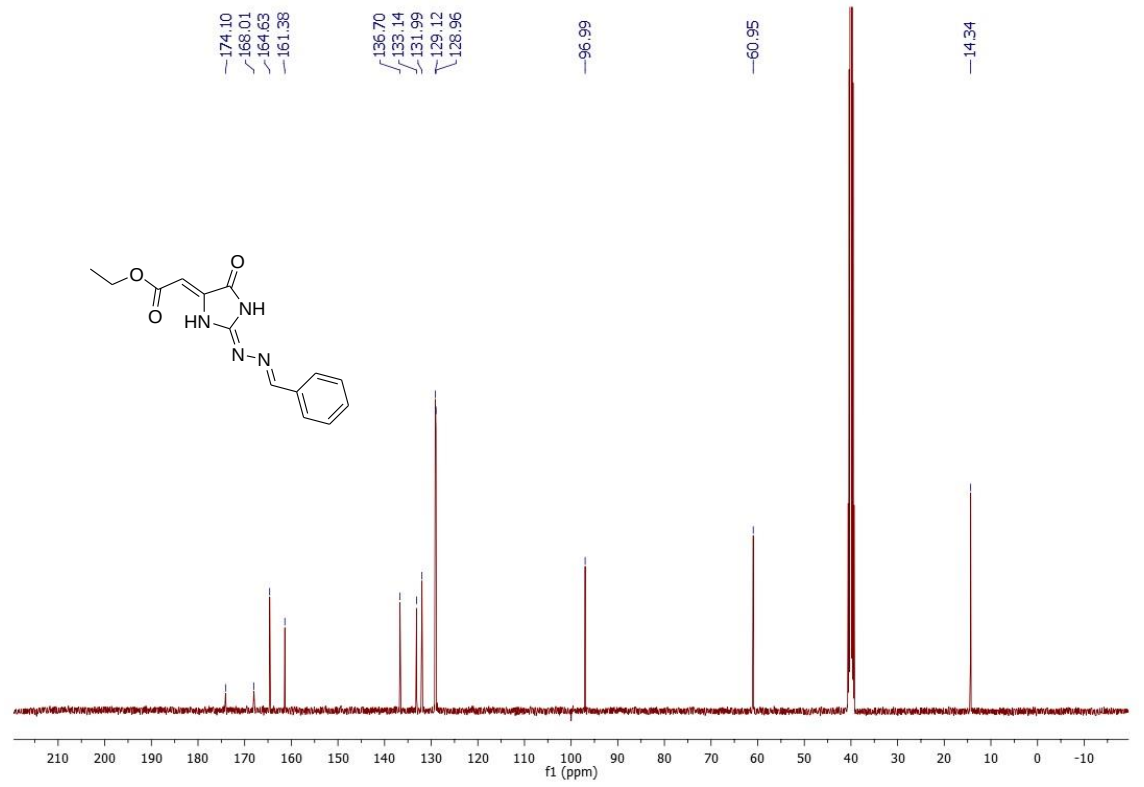


Figure 3.26. ^{13}C-NMR spectrum of B1

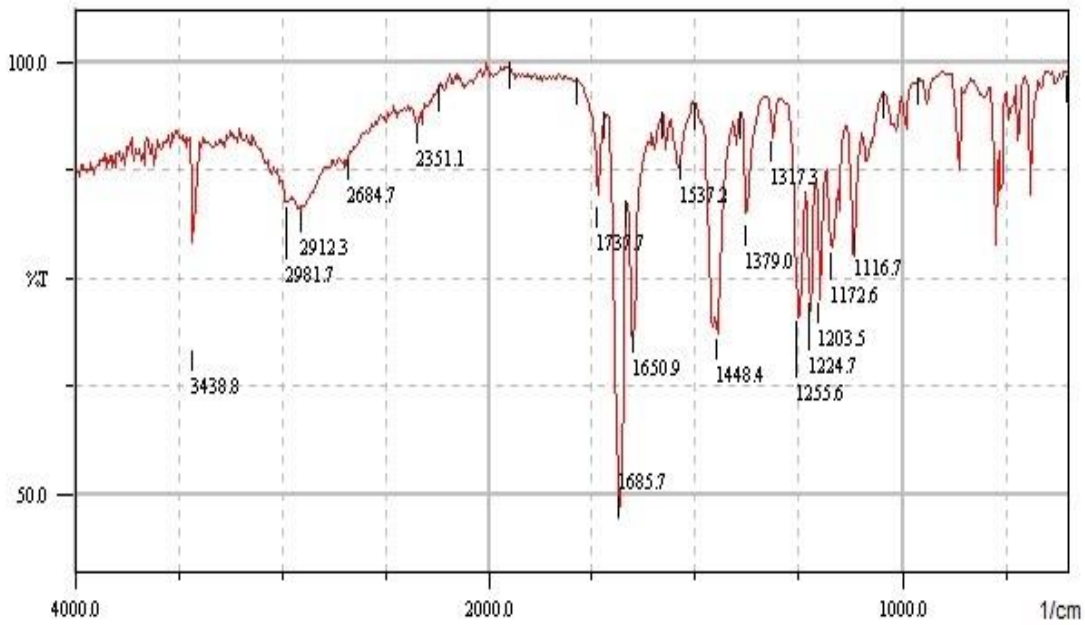


Figure 3.27. FT-IR spectrum of B1

3.2.2.3. Ethyl {2-[(4-triflouromethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B2)

Light yellow solid; yield, 69%; melting point: 217-218^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.25 (s, 1H, NH), 8.70 (s, 1H, NH), 8.20 – 8.09 (m, 3H, HC=N and Ar), 7.86 (d, J = 7.9 Hz, 2H, Ar), 5.84 (s, 1H, HC=C), 4.01 (q, J = 6.8 Hz, 2H, OCH_2), 1.13 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 173.97, 167.92, 164.64, 158.28, 137.15, 136.28, 131.53, 129.47, 126.04, 123.09, 97.57, 61.04, 14.36. IR (cm^{-1}) 3355 N-H stretch, 2981 =C-H stretch, 1693-1631 C=O stretch, 1579 C=N stretch. Calculated elemental analysis for $C_{15}H_{13}N_4O_3F_3$: C, 50.85; N, 15.81; H, 3.70. Found: C, 50.70; N, 15.71; H3.59.

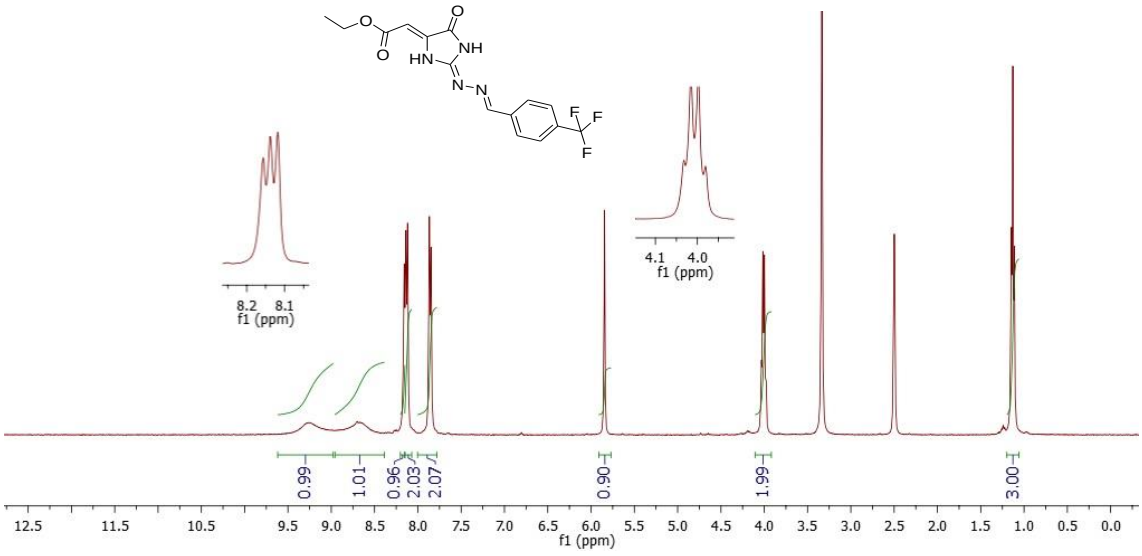


Figure 3.28. ^{1}H-NMR spectrum of B2

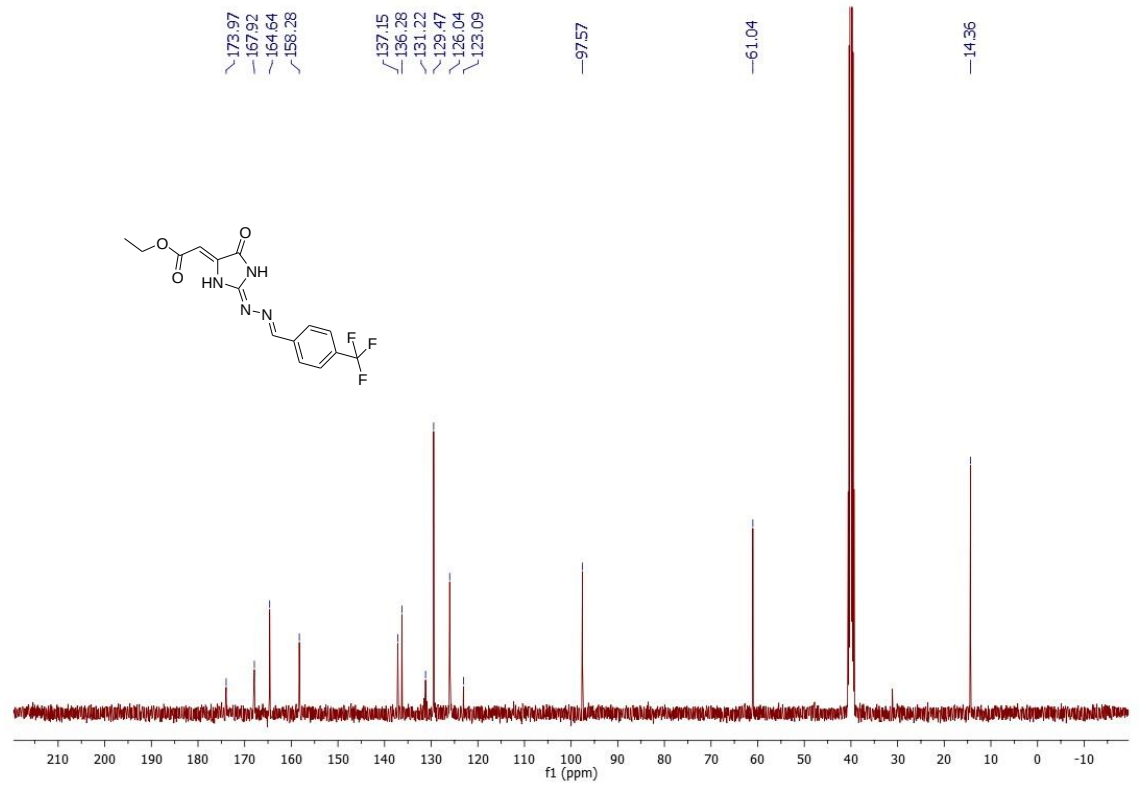


Figure 3.29. ^{13}C-NMR spectrum of B2

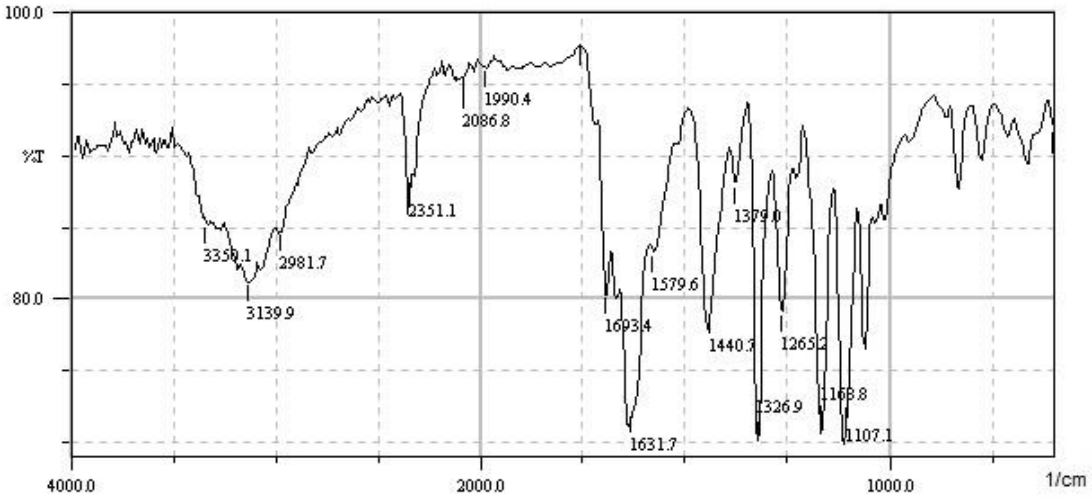


Figure 3.30. FT-IR spectrum of B2

3.2.2.4. Ethyl {2-[(4-acetamidomethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B3)

Yellow solid; yield, 81%; melting point: 197-198^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 10.21 (s, 1H, NH, Amid), 8.71 (s, 2H, 2xNH), 8.18 (s, 1H, HC=N), 7.79 (d, J = 8.1 Hz, 2H, Ar), 7.68 (d, J = 7.7 Hz, 2H, Ar), 5.70 (s, 1H, HC=C), 3.94 (q, J = 6.8 Hz, 2H, OCH_2), 2.07 (s, 3H, CH_3, Acetate), 1.07 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.09, 169.23, 167.95, 164.75, 161.54, 142.72, 137.27, 129.79, 127.71, 119.03, 96.37, 60.86, 24.59, 14.32. IR (cm^{-1}) 3438-3350 N-H stretch, 2981 =C-H stretch, 1720-1676 C=O stretch, 1641-1591 C=N stretch. Calculated elemental analysis for $C_{16}H_{17}N_5O_4$: C, 55.97; N, 20.40; H, 4.99. Found: C, 55.72; N, 20.28; H, 4.86

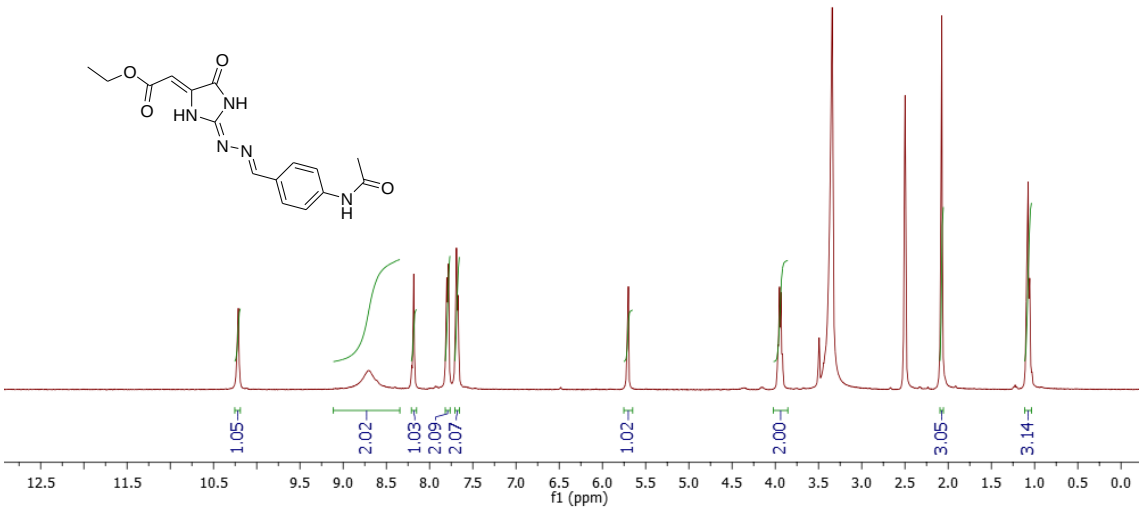


Figure 3.31. ^{1}H-NMR spectrum of B3

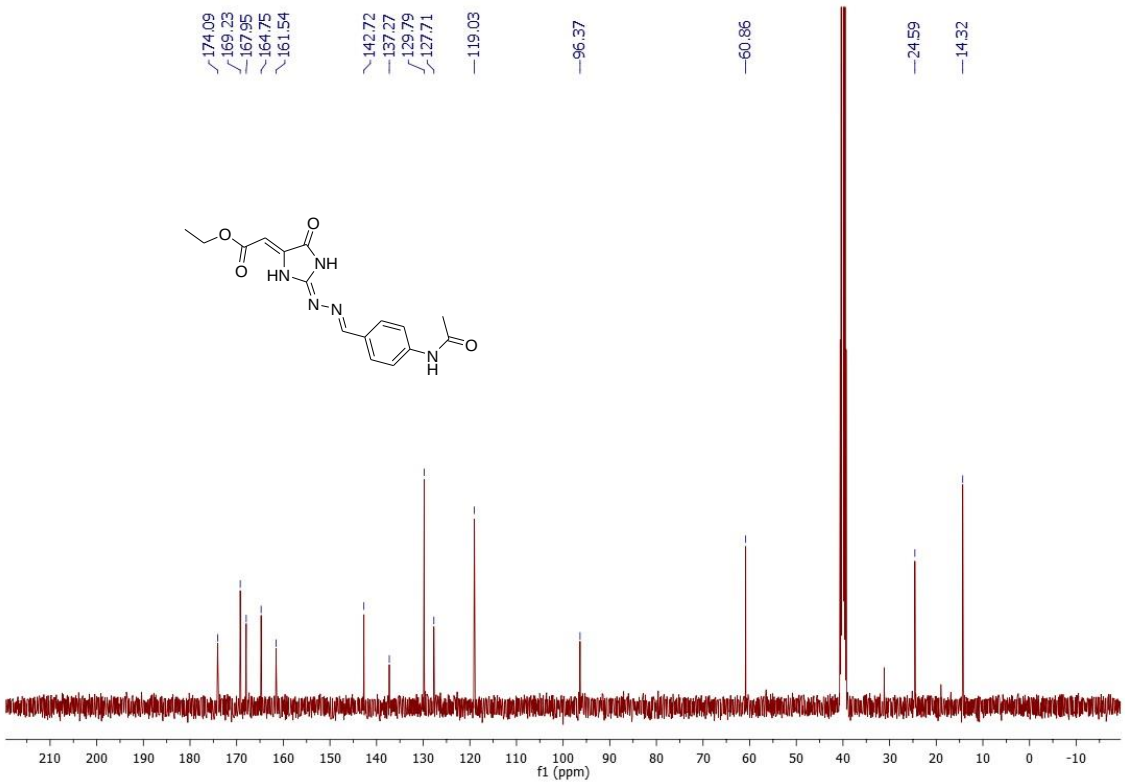


Figure 3.32. ^{13}C-NMR spectrum of B3

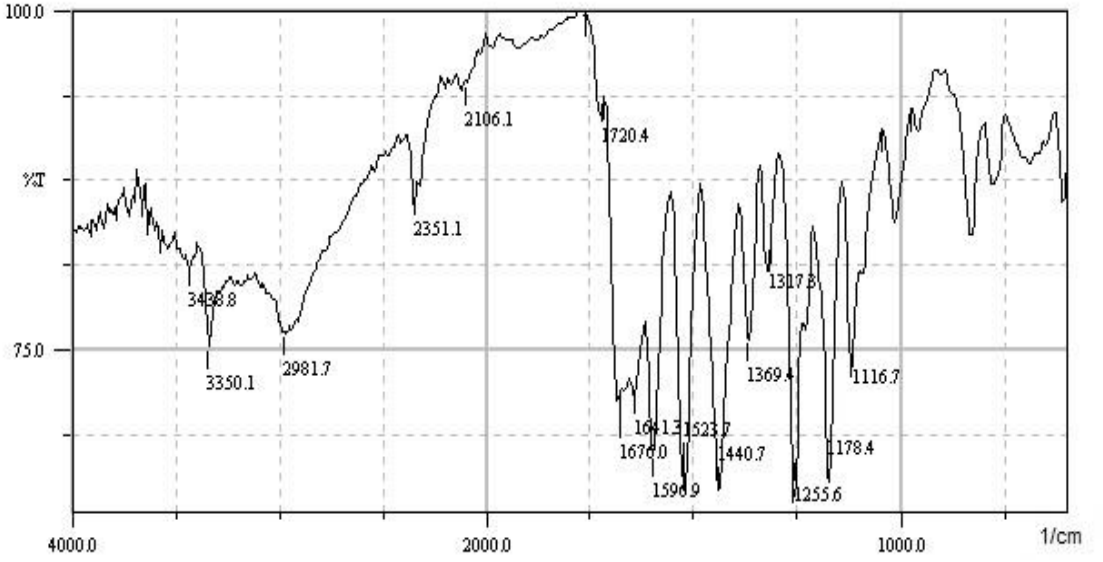


Figure 3.33. FT-IR spectrum of B3

3.2.2.5. Ethyl {2-[(2,4-dichloromethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B4)

Light yellow solid; yield, 83%; melting point: 216-217^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 8.91 (s, 2H, 2xNH), 8.40 (d, J = 7.9 Hz, 1H, Ar), 8.17 (s, 1H, HC=N), 7.75 (s, 1H, Ar), 7.58 (d, J = 7.7 Hz, 1H, Ar), 5.81 (s, 1H, HC=C), 4.07 (d, J = 6.2 Hz, 2H, OCH_2), 1.14 (s, 1H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 173.71, 167.80, 164.70, 151.80, 137.02, 136.52, 135.44, 129.92, 129.63, 129.44, 128.36, 96.87, 61.10, 14.46. IR (cm^{-1}) 3332 N-H stretch, 2981 =C-H stretch, 1720-1703 C=O stretch, 1631-1579 C=N stretch. Calculated elemental analysis for $C_{14}H_{12}N_4O_3Cl_2$: C, 47.34; N, 15.77; H, 3.41. Found: C, 47.16; N, 15.64; H, 3.32.

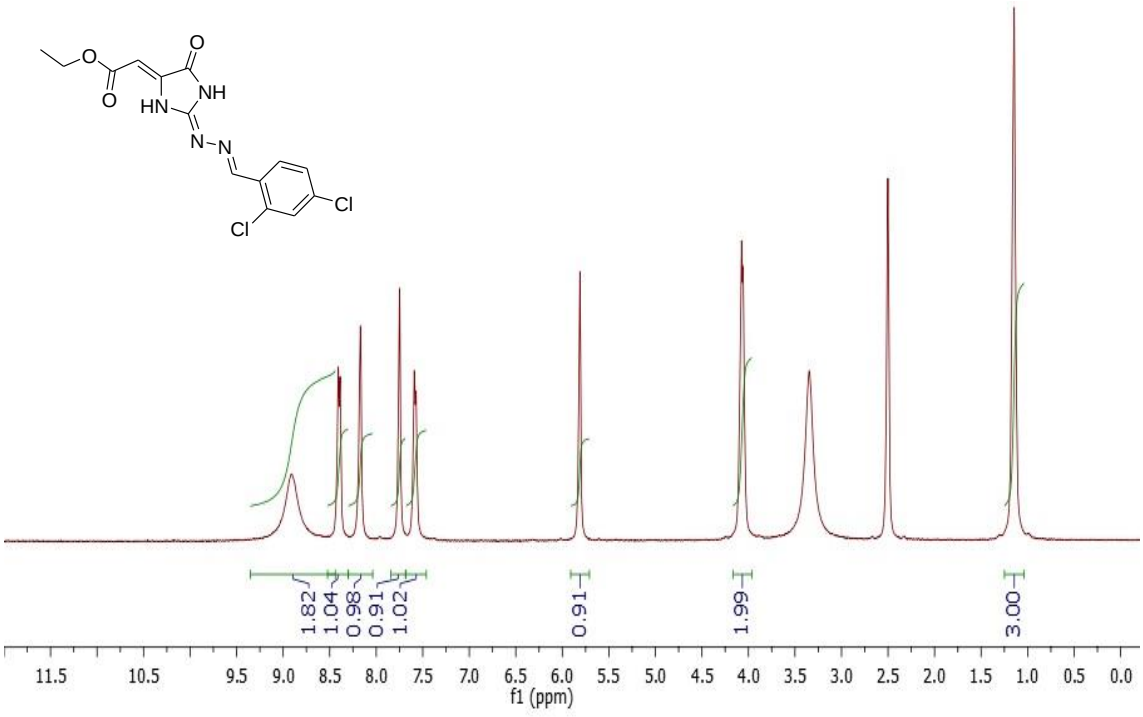


Figure 3.34. ^{1}H-NMR spectrum of B4

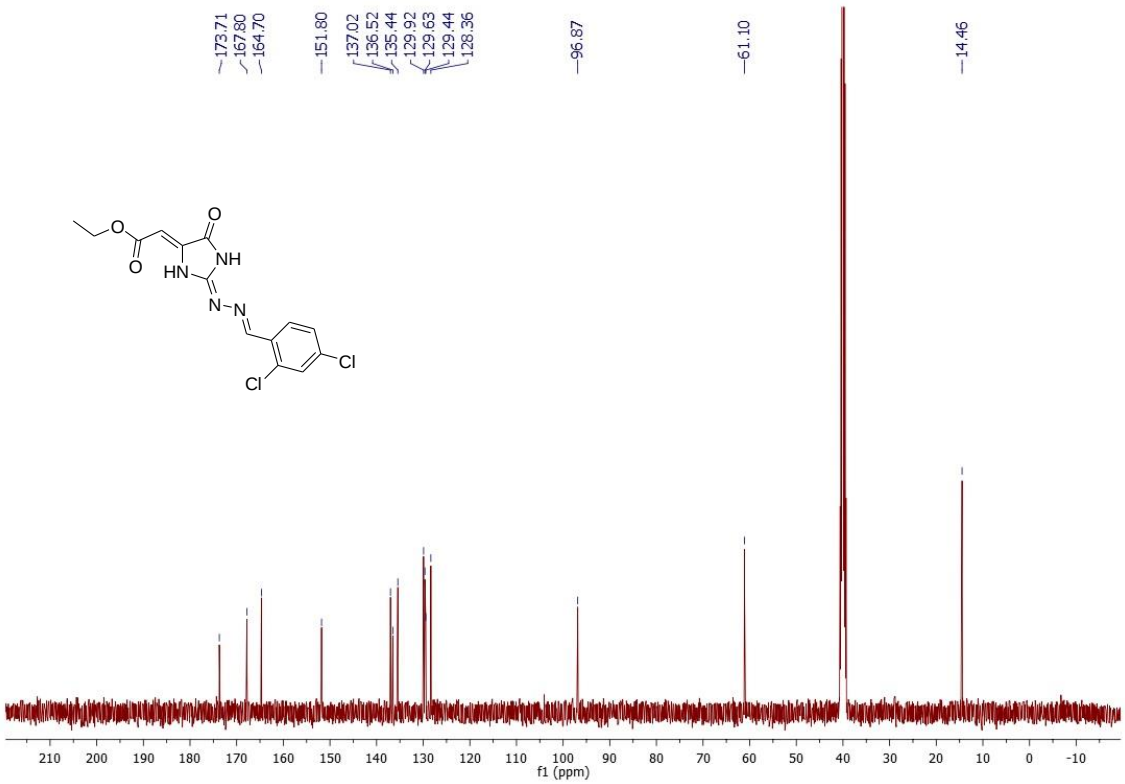


Figure 3.35. ^{13}C-NMR spectrum of B4

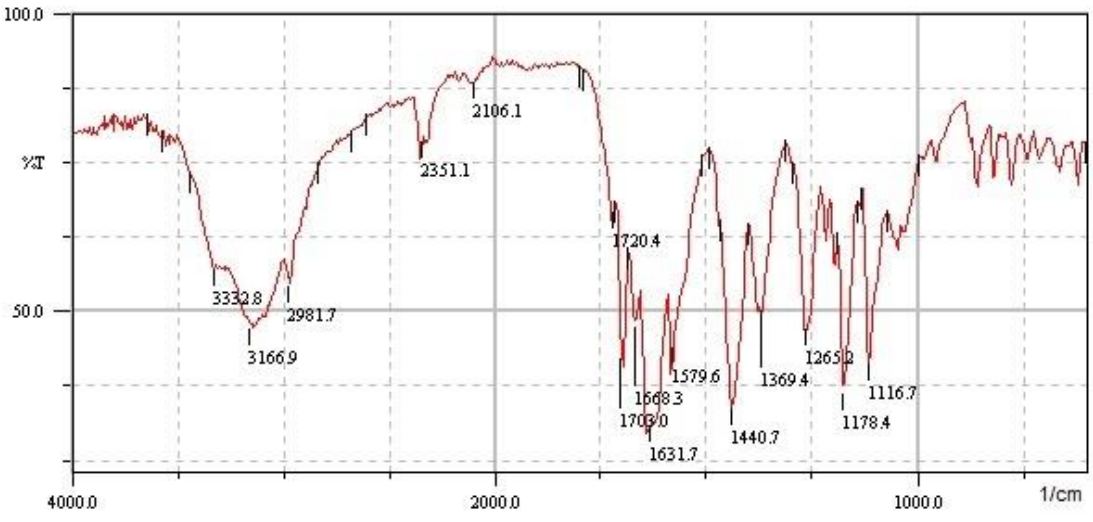


Figure 3.36. FT-IR spectrum of B4

3.2.2.6. Ethyl {2-[(4-methoxymethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B5)

Beige solid; ,yield; 78%; melting point: 195-196^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.07 (s, 1H, NH), 8.44 (s, 1H, NH), 8.16 (s, 1H, HC=C), 7.83 (d, J = 8.0 Hz, 2H, Ar), 7.05 (d, J = 8.0 Hz, 2H, Ar), 5.74 (s, 1H, HC=C), 3.94 (q, J = 6.9 Hz, 2H, OCH_2), 3.83 (s, 3H, OCH_3), 1.08 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.22, 168.12, 164.62, 162.56, 137.09, 130.87, 130.59, 125.63, 114.63, 96.56, 60.86, 55.89, 14.32. IR (cm^{-1}) 3219 N-H stretch, 2981 =C-H stretch, 1710-1641 C=O stretch, 1596-1544 C=N stretch. Calculated elemental analysis for $C_{15}H_{16}N_4O_4$: C, 56.96; N, 17.71; H, 5.10. Found: C, 56.81; N, 17.64; H, 5.01.

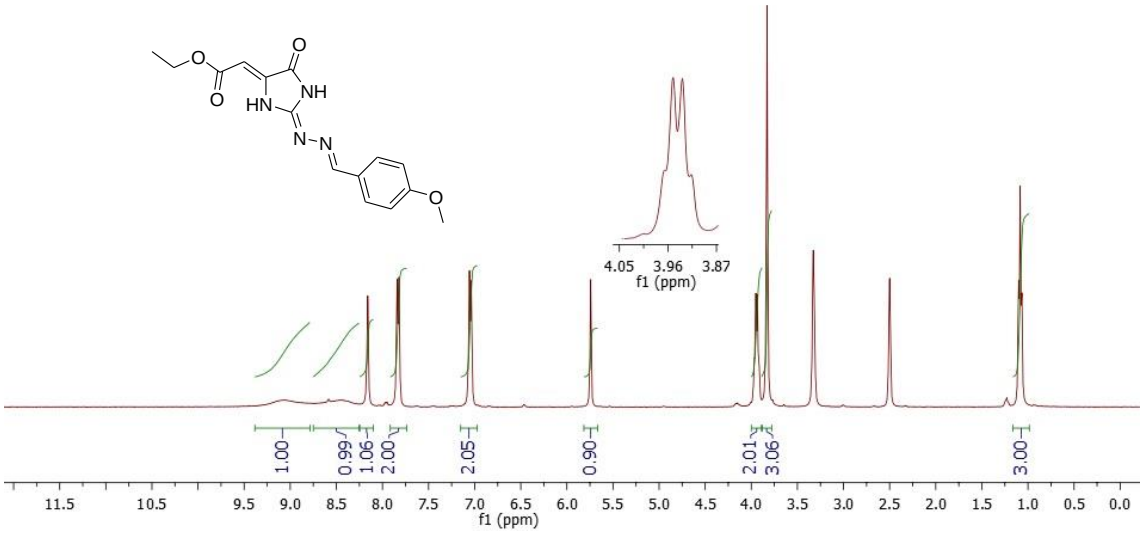


Figure 3.37. ^{1}H-NMR Spectrum of B5

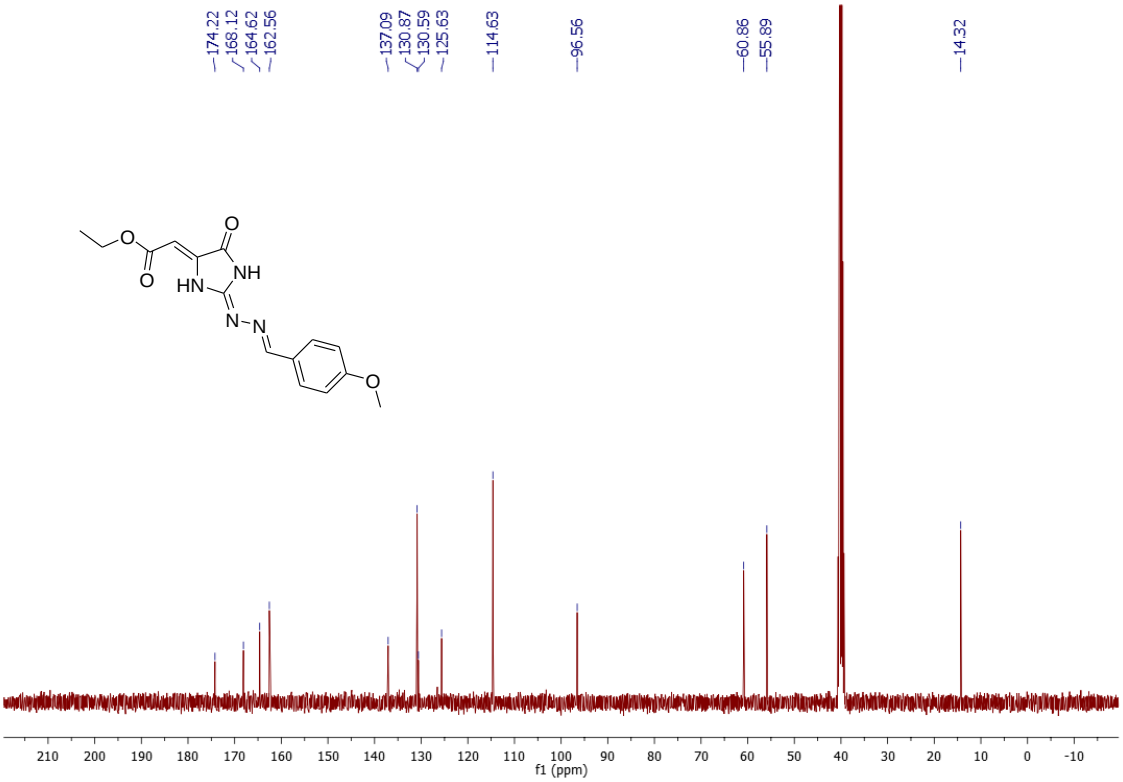


Figure 3.38. ^{13}C-NMR spectrum of B5

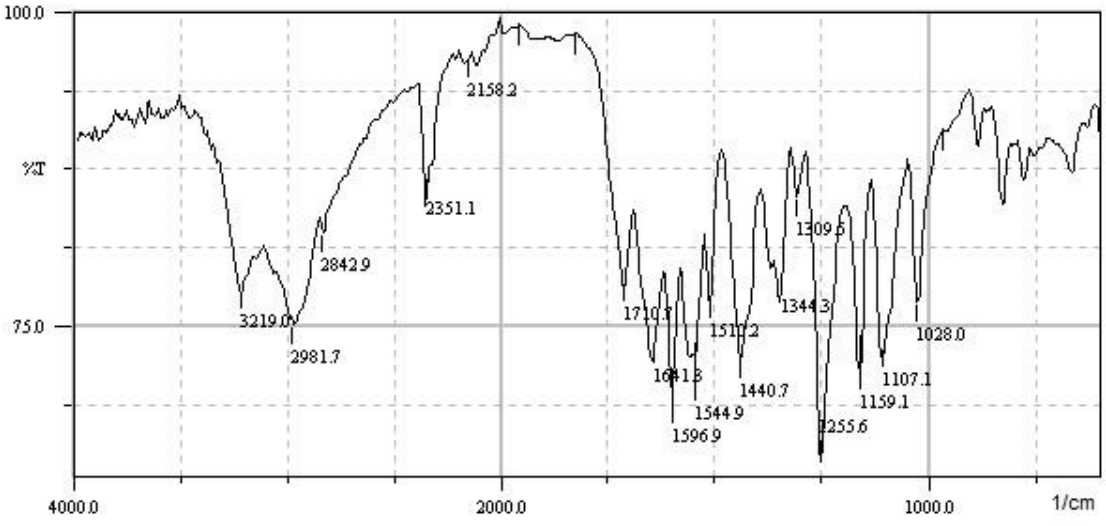


Figure 3.39. FT-IR spectrum of B5

3.2.2.7. Ethyl {2-[(4-ethoxymethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B6)

Light yellow solid; yield, 83%, melting point: 203-204^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.14 (s, 1H, NH), 8.39 (s, 1H, NH), 8.15 (s, 1H, HC=N), 7.81 (d, J = 8.4 Hz, 2H, Ar), 7.03 (d, J = 8.5 Hz, 2H, Ar), 5.74 (s, 1H, HC=C), 4.10 (q, J = 6.7 Hz, 2H, OCH_2, ester), 3.94 (q, J = 7.0 Hz, 2H, OCH_2, ether), 1.35 (t, J = 6.8 Hz, 3H, CH_3), 1.08 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.23, 168.13, 164.63, 162.53, 161.86, 137.09, 130.90, 125.47, 115.02, 96.54, 63.87, 60.87, 14.98, 14.33. IR (cm^{-1}) 3228 N-H stretch, 2964 =C-H stretch, 1703-1650 C=O stretch, 1596-1554 C=N stretch. Calculated elemental analysis for $C_{16}H_{18}N_4O_4$: C, 58.17; N, 16.96; H, 5.49. Found: C, 58.05; N, 16.74; H, 5.34.

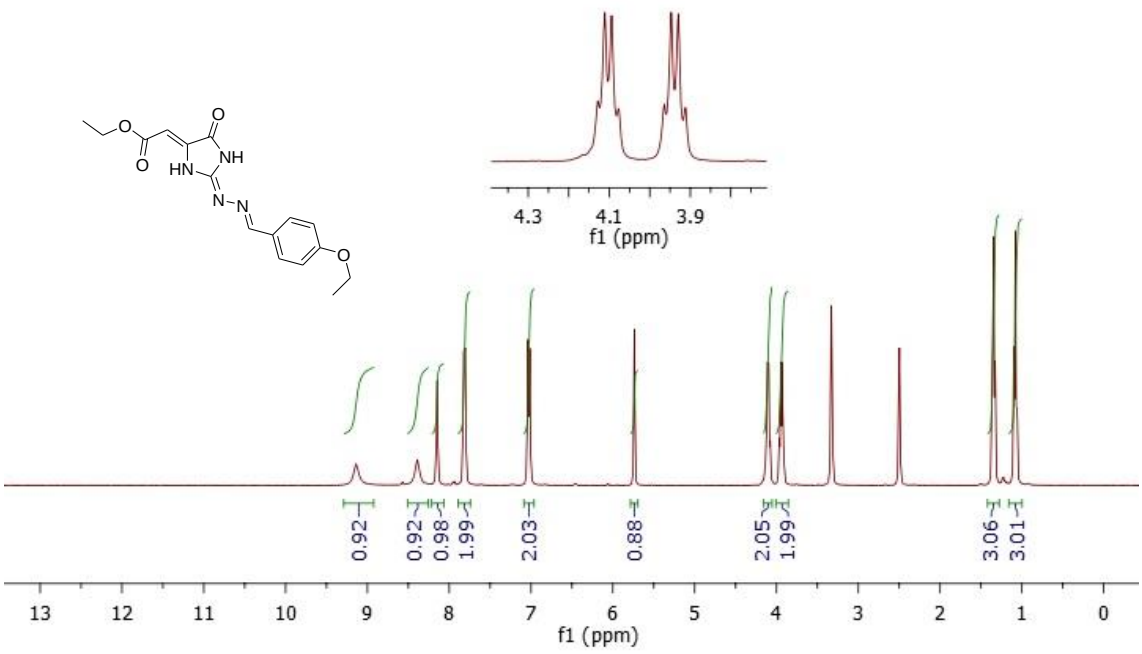


Figure 3.40. ^{1}H-NMR spectrum of B6

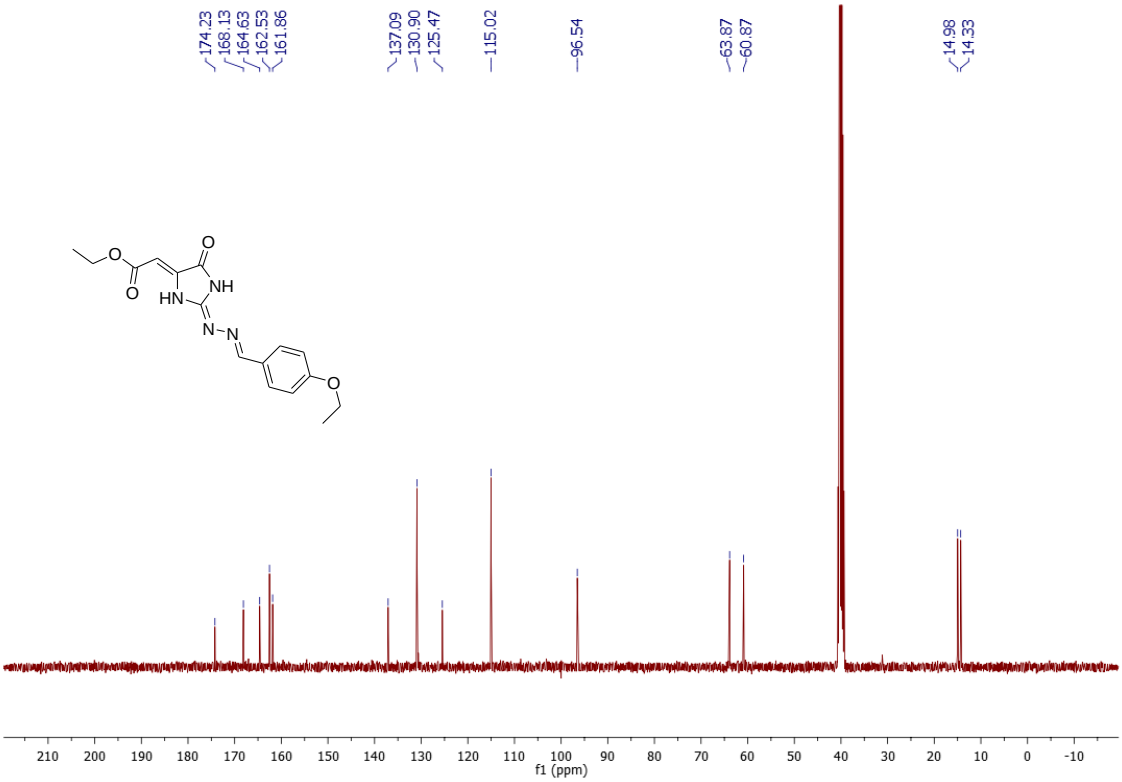


Figure 3.41. ^{13}C-NMR spectrum of B6

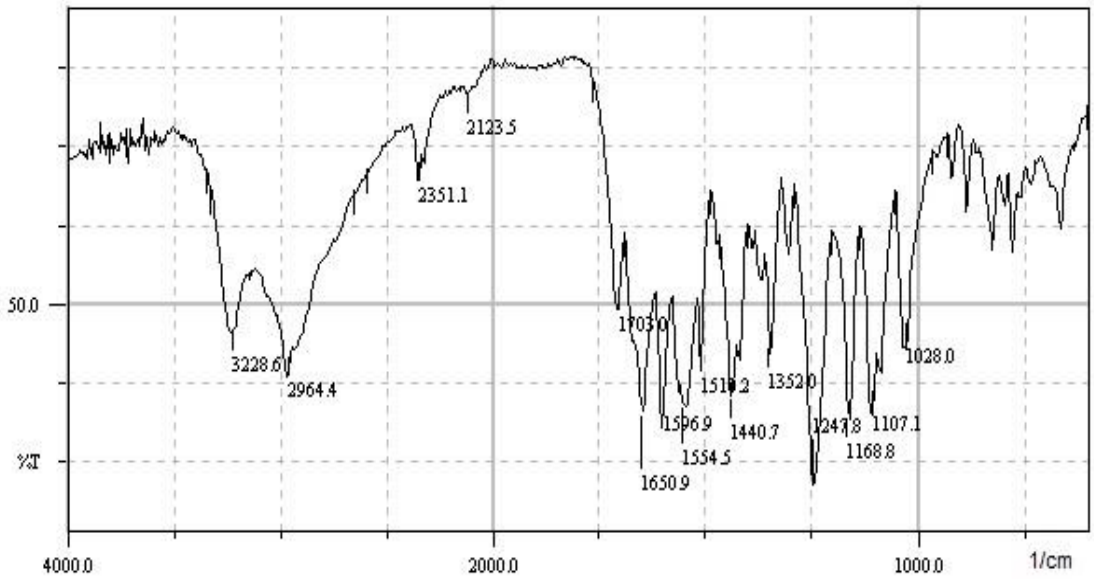


Figure 3.42. FT-IR spectrum of B6

3.2.2.8. Ethyl {2-[(2-choloromethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B7)

Beige solid; yield, 83%; melting point: 219-220^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.30 (s, 1H, NH), 8.64 (s, 1H, NH), 8.42 (d, J = 6.8 Hz, 1H, Ar), 8.06 (s, 1H, HC=N), 7.55 (s, 2H, Ar), 7.48 (s, 1H, Ar), 5.87 (s, 1H, HC=C), 4.07 (q, J = 6.9 Hz, 2H, OCH_2), 1.14 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO) δ 173.98, 168.06, 164.52, 153.55, 136.17, 134.86, 133.37, 130.42, 130.09, 128.54, 127.95, 97.17, 61.14, 14.44. IR (cm^{-1}) 3350 N-H stretch, 2929 =C-H stretch, 1737-1676 C=O stretch, 1641-1554 C=N stretch. Calculated elemental analysis for $C_{14}H_{13}N_4O_3Cl$: C, 52.43; N, 17.47; H, 4.09. Found: C, 52.31; N, 17.36; H, 4.01.

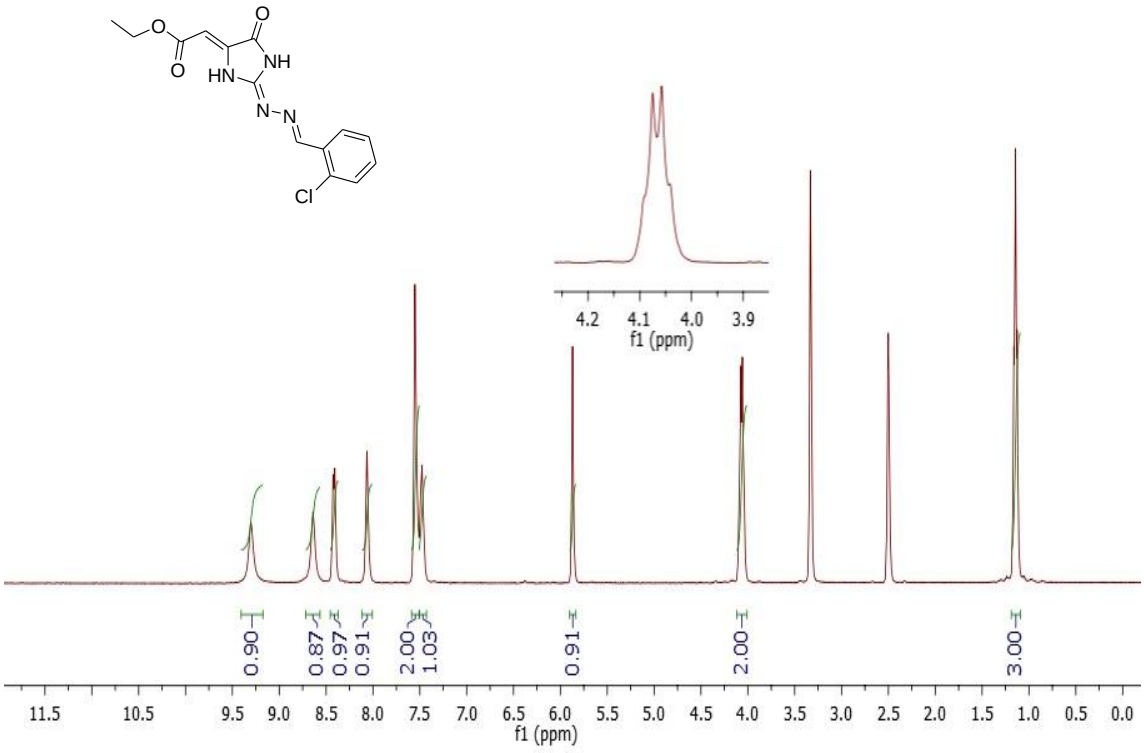


Figure 3.43. ^{1}H-NMR spectrum of B7

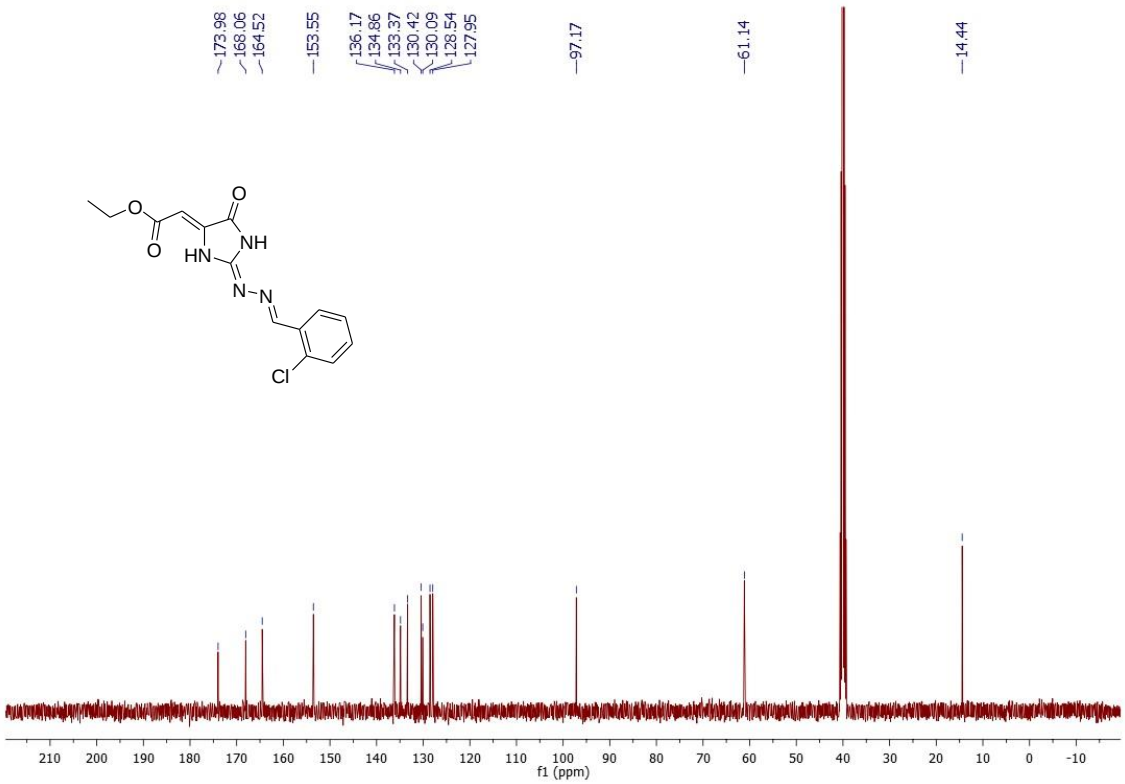


Figure 3.44. ^{13}C-NMR spectrum of B7

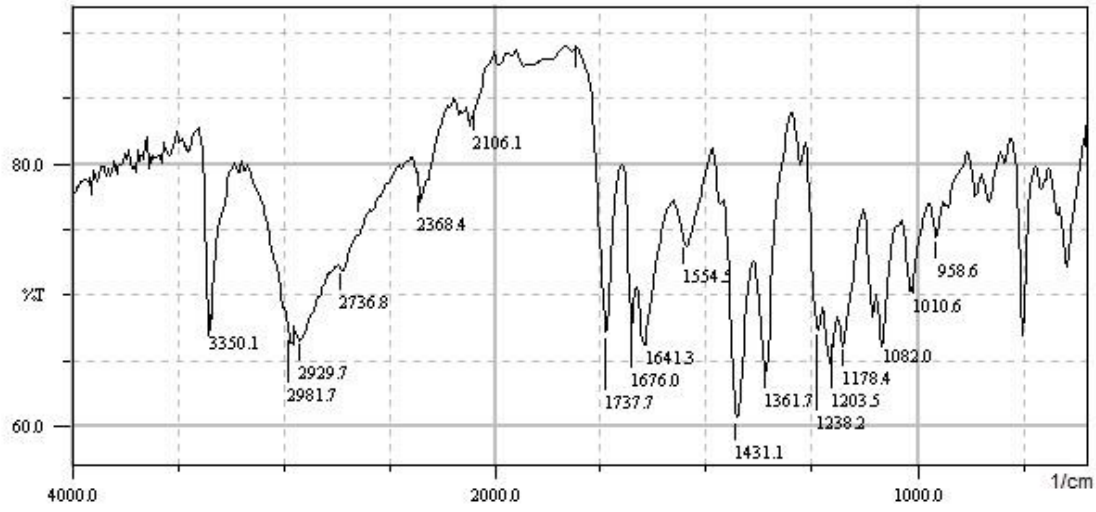


Figure 3.45. FT-IR spectrum of B7

3.2.2.9. Ethyl {2-[(2,4-dimetoxymethylbenzylidene)hydrazinylidene]-5-oxoimidazolidin-4-ylidene}acetate. (B8)

Yellow solid; yield, 88%; melting point: 221-222^{0}C. ^{1}H-NMR (400 MHz, DMSO δ_6) 9.04 (s, 1H, NH), 8.28 (s, 1H, NH), 8.16 (s, 1H, HC=N), 8.06 (d, J = 9.1 Hz, 1H, Ar), 6.65 (s, 2H, Ar), 5.75 (s, 1H, HC=C), 3.97 (q, J = 6.8 Hz, 2H, OCH_2), 3.85 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 1.10 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C-NMR (100 MHz, DMSO δ_6) 174.19, 168.25, 164.51, 164.38, 160.65, 155.72, 136.59, 128.69, 113.60, 107.11, 98.37, 96.24, 60.91, 56.29, 56.06, 14.30. IR (cm^{-1}) 3342 N-H stretch, 2981 =C-H stretch, 1728-1676 C=O stretch, 1641-1596 C=N stretch. Calculated elemental analysis for $C_{16}H_{18}N_4O_5$: C, 55.48; N, 16.18; H, 5.24. Found: C, 55.33; N, 16.16; H, 5.12.

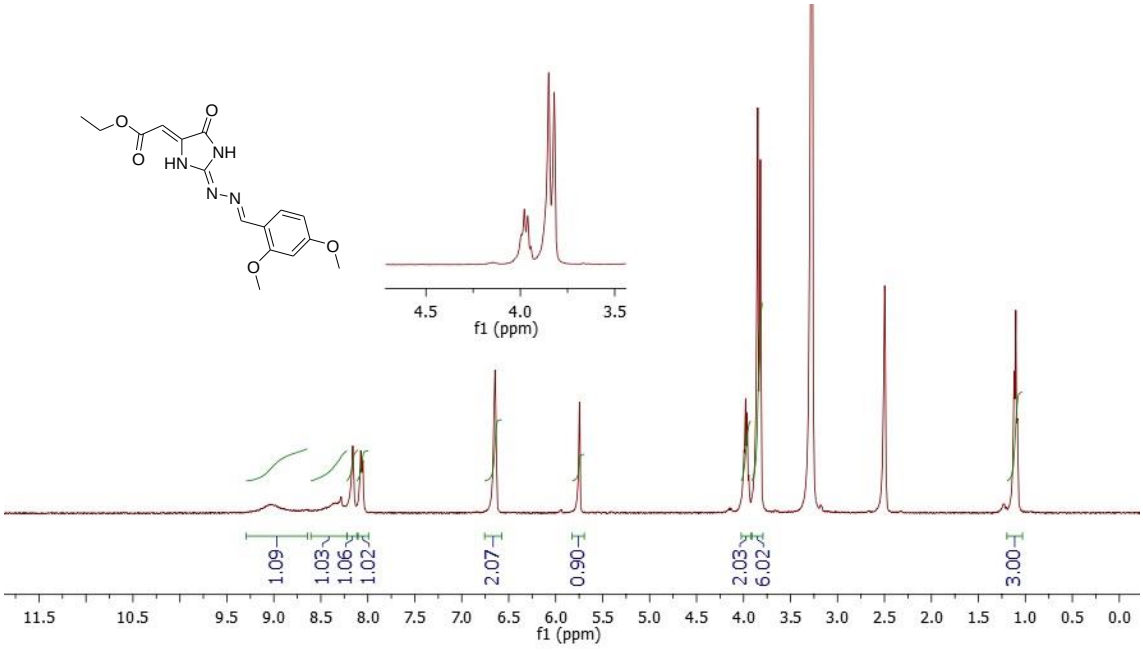


Figure 3.46. 1H-NMR spectrum of B8

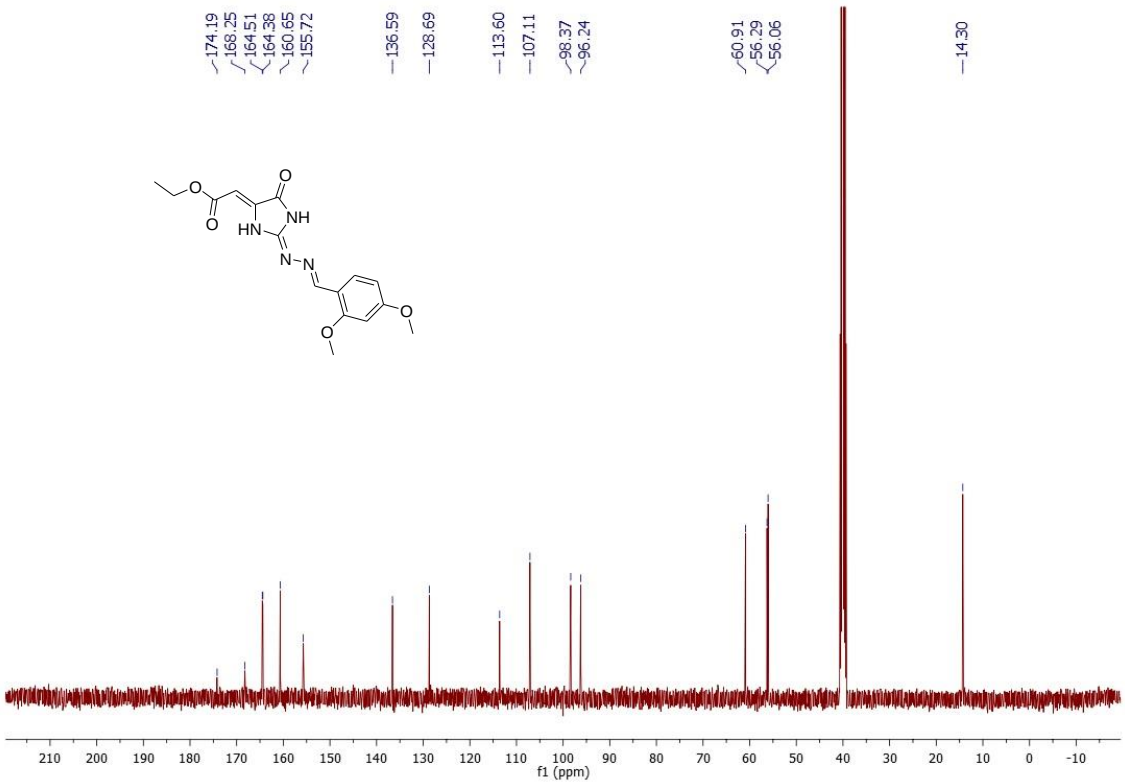


Figure 3.47. 13C-NMR spectrum of B8

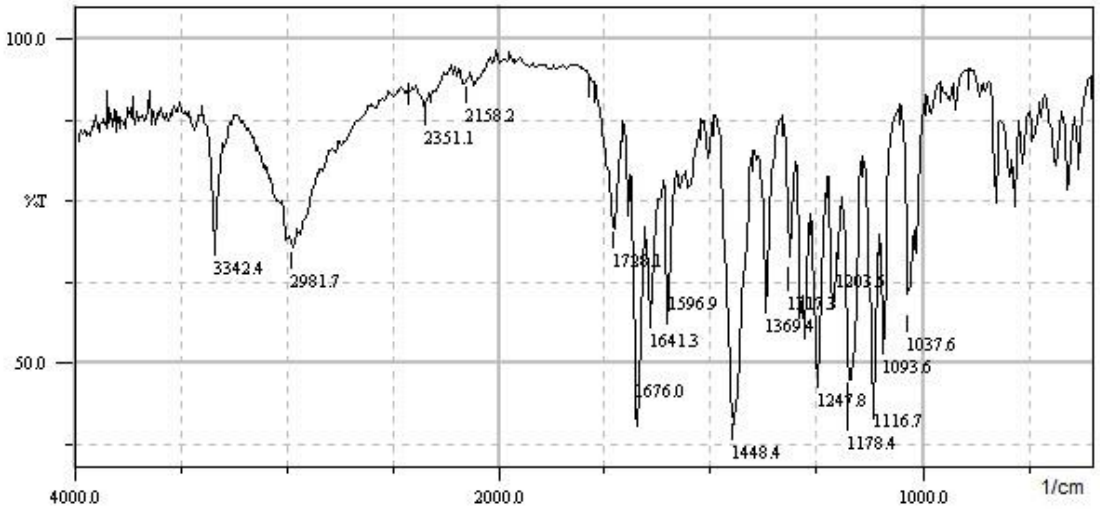


Figure 3.48. FT-IR spectrum of B8

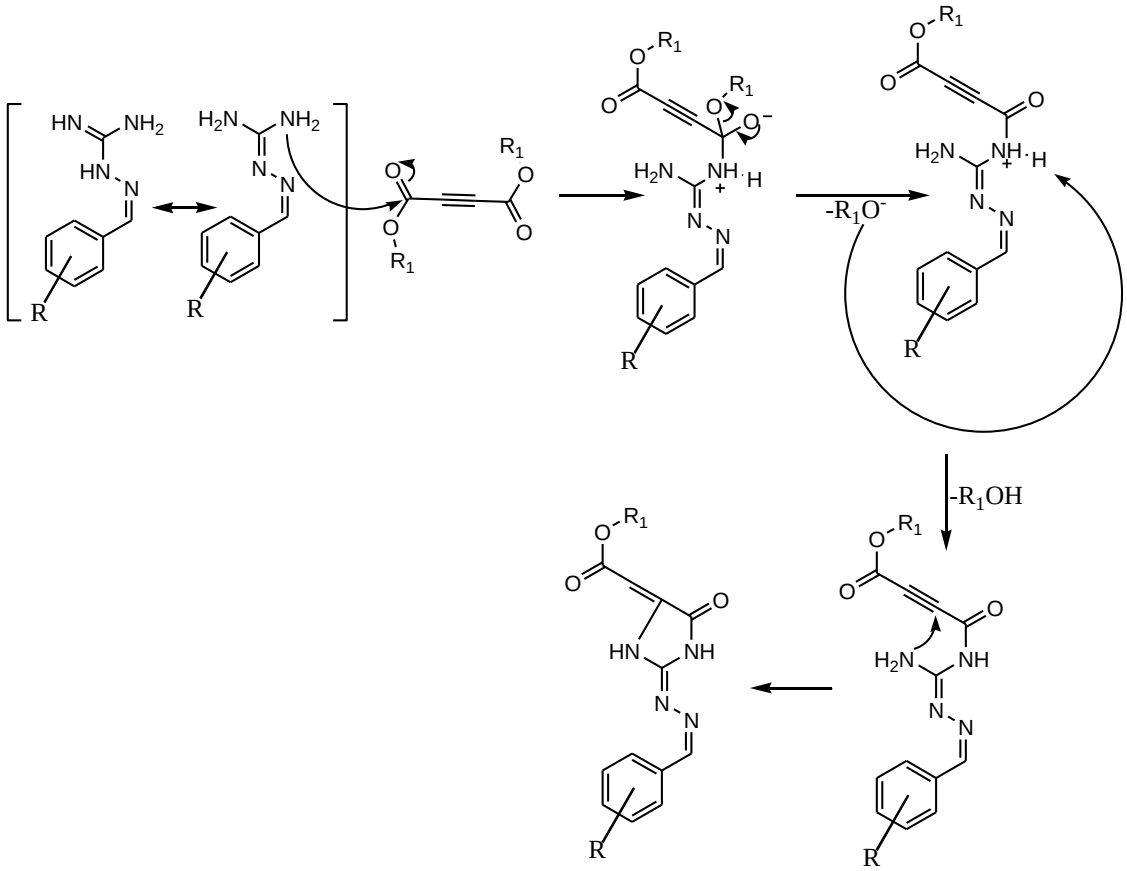


Figure 3.49. The first probable mechanism of reaction

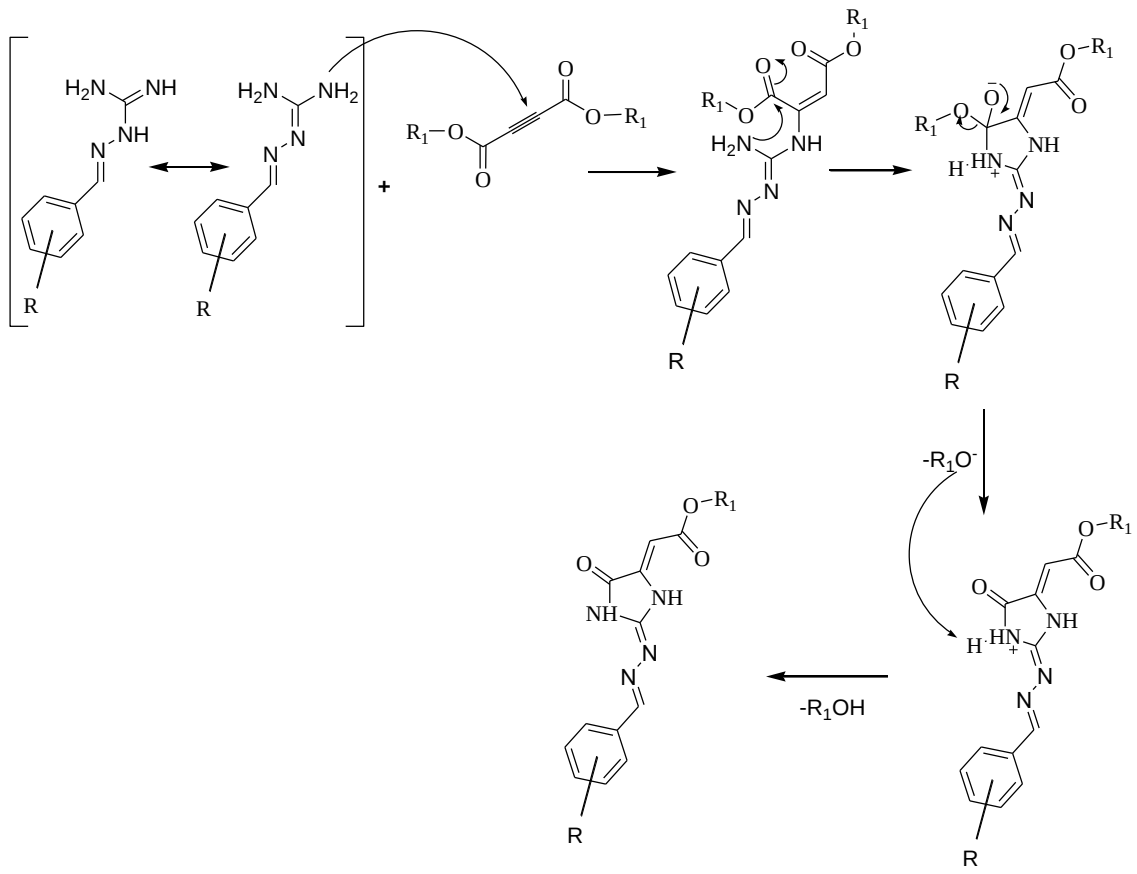


Figure 3.50. The second probable mechanism of reaction

CHAPTER 4

CONCLUSION

Because of the diverse utilization and importance of heterocyclic molecules in our life and specifically their uses as drugs or drug precursors, chemists pay exclusive attention to look for the convenient and basic methods to get them from commercially, versatile and cheaply appropriate materials. Usage of acetylenedicarboxylates, which are electron-deficient acetylenic molecules, having two reactive ester groups, gets advantage to engage readily heterocyclization. Due to the presence of a two ester electron-withdrawing functional group, they easily carry out Michael addition, which is concluded by heterocyclization to obtain functional heterocyclic molecules with diverse ring sizes.

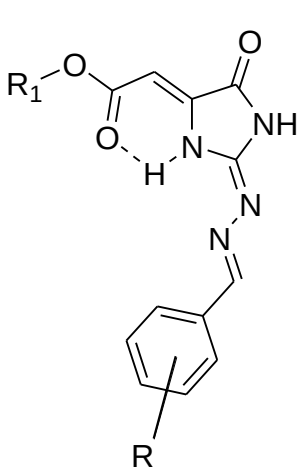
Primarily, we first carried out the reaction of DMAD and DEAD with aminoguanidine derivatives in methanol and ethanol to obtain a single compound which was characterized as 5-oxoimidazolidine derivatives. The structure of the synthesized molecules was determined by ^{1}H-NMR, ^{13}C-NMR, IR and elemental analysis.

The ^{1}H-NMR spectrums of A and B series represented broad N-H peaks at (s, δ 8.00 - 9.50 ppm), amide proton's peak is on the left side on spectrum, and, also, exo methylen peaks at (s, δ 5.50 – 6.00 ppm). The presence of electron withdrawal R groups such as Cl, NO2, CF3, ^{1}H-NMR peaks of aromatic group shift to (s, δ 8.00 - 8.50 ppm). ^{13}C-NMR spectrums demonstrated peaks of carbonyl carbons, guanyl carbon and inime carbon are beyond of (δ 160 ppm). The carbon adjacent to nitrogen in exo methylen gives a peak next to aromatic group, and the other is at (δ 90-100 ppm). The IR spectrums exhibited N-H absorption at 3200-3500 cm^{-1}, aromatic =C-H absorption at 2900-3000 cm^{-1}, C=O peaks at 1650-1750 cm^{-1} and C=N peaks at 1550-1650 cm^{-1}.

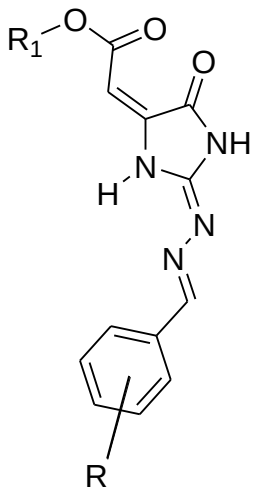
Two probable mechanisms have been added above. In the first one, nucleophilic amino center attacked to carbonyl carbon which is poor in terms of electron and open the

double bond on oxygen. After reclosing the bond alkoxy group leaved and an amide bond have been generated. The other nucleophilic amino center of aminoguanidine attacked electron-deficient alkyne carbon and commence a Michael addition. In the second mechanism, sequence of nucleophilic attacks has been substituted. Transition state on Michael addition phase is not known. According to literature, the latter mechanism is more probable [43]. Nevertheless, more accurate result may be obtained by using computational methods.

From the reaction of aminoguanidine derivatives with acetylenedicarboxylate derivatives two isomers may be obtained. Z isomer is more probable and stable because of intramolecular H bonding between oxygen and enamine hydrogen which is formed hexagonal structure by H bond makes the molecule more stable either. The other is E isomer which has two adjacent carbonyl carbons that triggers steric hindrance and makes molecule less stable.



Z isomer



E isomer

The procedure described in this study, includes the preparation of unique substituted imidazolidine derivatives from commerical and avialable DMAD and DEAD, and easy to prepare aminoguanidine derivatives. The other momentous courses of this process are high yield, modest reaction conditions, availability of the reagents.

For further investigation synthesized molecules will be undergone some biologic test to determine their biological activity. According to results QSAR calculations will be done.

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