T.R
YÜZÜNCÜ YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
CHEMISTRY DEPARTMENT

SYNTHESIS OF 2-(PROP-2-YN-1-YLOXY)BENZALDEHYDE METHYLHYDRAZONE DERIVATIVES AND THEIR ANTIOXIDANT CAPACITIES

M.Sc. THESIS

PREPARED: Jeger Ali OAGAZ
SUPERVISOR: Assoc. Prof. Dr. Arif KIVRAK

VAN-2017

T.R
YÜZÜNCÜ YIL UNIVERSITY
INSTITUTE OF NATURAL AND APPLIED SCIENCES
CHEMISTRY DEPARTMENT

SYNTHESIS OF 2-(PROP-2-YN-1-YLOXY)BENZALDEHYDE METHYLHYDRAZONE DERIVATIVES AND THEIR ANTIOXIDANT CAPACITIES

M.Sc. THESIS

PREPARED: Jeger Ali Oagaz

VAN-2017

ACCEPTANCE AND APPROVAL PAGE

This thesis entitled "**Synthesis of 2-(prop-2-yn-1-yloxy)benzaldehyde methylhydrazone derivatives and their antioxidant capacities**" presented by Jeger Ali Oagaz under supervision of Assoc. Prof. Arif KIVRAK in the department of Chemistry has been accepted as a M. Sc. thesis according to Legislations of Graduate Higher Education on 18/05/2016 with unanimity of votes members of jury.

Chair: Prof. Dr. Metin ZORA Signature:

Member: Assoc. Prof. Arif KIVRAK Signature:

Member:Asist. Prof. Dr. Can YILMAZ. Signature:

This thesis has been approved by the committee of The Institute of Natural and Applied Science on 24../..05../..2017 with decision number .2017/24-1

Signature

...

Director of Institute

THESIS STATEMENT

All information presented in the thesis obtained in the frame of ethical behavior and academic rules. In addition, all kinds of information that does not belong to me have been cited appropriately in the thesis prepared by the thesis writing rules.

Signature

Jeger Ali Oagaz

ABSTRACT

SYNTHESIS OF 2-(PROP-2-YN-1-YLOXY)BENZALDEHYDE METHYLHYDRAZONE DERIVATIVES AND THEIR ANTIOXIDANT CAPACITIES

Jeger Ali OAGAZ

M.Sc. Thesis, Chemistry Science

Supervisor: Assoc. Prof. Dr. Arif KIVRAK

May 2017, 49 page

1-Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine analogues were readily prepared in good yields by the reaction of 2-(Prop-2-yn-1-yloxy)benzaldehydes and methyl hydrazine. The reaction tolerates a variety of substituent on the 2-hydroxybenzaldehyde to form nitro-, halo-, methoxy- and naphthyl-substituted 1-Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazines. The *in vitro* antioxidant capacity measurements exhibited that among all the analyzed hydrazine analogues which surpassed trolox orm y , 1-(2-(But-3-ynyl)-5-nitrobenzylidene)-2-methylhydrazine had the maximum value which was approximately 1.7 more of trolox result.

Keywords; ABTS, Antioxidant capacities, Biological properties**,** Hydrazines, Hydrazones.

ÖZET

2-(PROP-2-İN-1-İLOKSİ)BENZALDEHİT METİLHİDRAZON TÜREVLERİNİN SENTEZİ ve ANTİOKSİDANT KAPASİTELERİ

Jeger Ali OAGAZ
Yüksek Lisans Tez: Kimya Bölümü
Danışman: Doç. Dr. Arif KIVRAK
Mayıs 2017, 49 sayfa

Yapısında heteroatom bulunan yapıların tasarımı, sentezi ve bunların biyolojik özelliklerinin bulunması son yıllarda özellikle ilaç araştırmaları için büyük önem arzetmektedir. Hidrazon ve türevleri çok uzun süredir sentezlenen ve farklı biyolojik aktiviteleri bulunmuş önemli bir sınıfı oluşturmaktadır. Bu çalışmada, 2-(Prop-2-in-1-iloksi)benzaldehit ve metilhidrazin kondenzasyon tepkimesine sokularak 1-Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine türevleri yüksek verimler ile sentezlenmiştir. Tepkime yapısında nitro-, halo-, metoksi, naftil gibi substituentleri bulunduran yapıların elde edilmesi içinde kullanılarak, yeni türevlerin sentezide gerçekleştirilmiştir. Elde edilen yapıların *in vitro* antioksidant kapasiteleri bulunmuştur. Bulunan sonuçlara göre 1-(2-(But-3-ynyl)-5-nitrobenzylidene)-2-methylhydrazine yapısı referans olarak alınan troloksa göre 1.7 kez daha aktivite göstermiştir.

Anahtar kelimeler: ABTS, Antioksidant kapasitesi, Biyolojik özellikler, Hidrazinler, Hidrazonlar.

PREFACE

Foremost, I would like to extend my sincerest thanks and appreciation to those patient souls who helped me accomplish this study; I would like to orm y my sincere gratitude to my advisor Doç. Dr. Arif KIVRAK orm y continuous support of my master study and research, orm y patience, motivation, enthusiasm, and immense knowledge. Him guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a orm advisor and mentor orm y study. I would like to extremely thank Yard. Doç. Dr. Can Yılmaz and Yard. Doç. Dr. Metin Konuş for biological tests.

May 2017

Jeger Ali OAGAZ

TABLE OF CONTENTS

Pages

ABSTRACT ……...……...i

ÖZET ……..……iii

PREFACE ...…....v

TABLE OF CONTENTS ……..vii

LIST OF FIGURES……...…….....xi

SYMBOLS ……..…….....xii

ABBREVIATIONS. ……..…..... xi

1. INTRODUCTION ……..……..1

1.1 Hydrazones ……..…….....1

1.2 Preparation of hydrazones……..…….....1

1.3 Reactivity of hydrazones……..... 3

2. LITERATURE REVIEWS…….....10

2.1 Antimicrobial activity of hydrazones…….....10

2.2 Anti-inflammatory activity of hydrazones……..…….....12

2.3 Anti-cancer activity of hydrazones……..…….....13

2.4 Central nervous system activity…….…….....14

2.5 Other biological activities of hydrazones…….....15

2.6 Aim of the study…….....16

3. MATERIALS AND METHODS ……..……..……..18

3.1 Experimental Section ……..…….....18

3. 2. Synthesis of compounds ……..…….....19

3.2.1. General procedure for the synthesis of 2-(prop-2-ynyloxy) benzaldehydes ……..……...…….....19

3.2.2. General procedure for the synthesis of 1-(2-(but-3-ynyl)benzylidene)-2-methylhydrazines…..……..…….....22

3.3. Trolox Equivalent Antioxidant Capacity (ABTS Assay)……..…….....25

4. RESULTS AND DISCUSSION …….…….....26

4.1 Chemistry……..……..…….....26

4.2 Antioxidant capacities……..…..…….....29

Pages

5. CONCLUSION……..……..32
REFERENCES.. ……..……..33
APPENDIX INDEX ……..……..……..39
EXTENDED TURKISH SUMMARY…….39
CURRICULUM VITAE……..…….50

LIST OF FIGURES

Fıgures **Pages**

Figure 1. Structures of hydrazones……..…1
Figure 2. Synthesis of hydrazones……..…….....3
Figure 3. The Japp–Klingemann reactions…….…….....4
Figure 4. Active centers of hydrazones……..…….....4
Figure 5. Synthesis of *N*-aryl-*N*-tosyl hydrazones…….....5
Figure 6. Synthesis of *N*-aryl hydrazone derivatives…….....6
Figure 7. Fischer Indole Synthesis…….....6
Figure 8. Synthesis of 4-thiazolidin-4-ones…….....7
Figure 9. Synthesis of azetidines via cycloaddition reactions…….…….....7
Figure 10. Synthesis of heterocyclic compounds via cycloaddition reactions…….....…8
Figure 11. The Shapiro reaction……..…….....8
Figure 12. The Wolff-Kishner Reduction…….....9
Figure 13. Synthesis of pyrazoles and dihydropyridazine…….....9
Figure 14. Synthesis of pyrazoles via electrophilic cyclization reactions from acetlynic hydrazones……..…….....10
Figure 15. Synthesis of benzofulvenes…….…….....11
Figure 16. Structure of hydrazones as antimicrobial agents…….....13
Figure 17. Structure of hydrazones as anti-inflammatory agents…….....15
Figure 18. Structure of hydrazones as anti-cancer agents…….....16
Figure 19. Structure of hydrazones as CNS agents……..…….....17
Figure 20. Some biologically important hydrazone derivatives. ……..….....18
Figure 21. Synthesis of novel hydrazones…….....19
Figure 22. Synthesis of 2-(prop-2-ynyloxy)benzaldehydes (3A)…….....21
Figure 23. Synthesis of 5-bromo-2-(prop-2-ynyloxy)benzaldehyde (3B)……..….....21

pages

Figure 24. Synthesis of 5-nitro-2-(prop-2-ynyloxy)benzaldehyde (3C)…….....,.22

Figure 25. Synthesis of 4-methoxy-2-(prop-2-ynyloxy)benzaldehyde (3D)…….....22

Figure 26. Synthesis of 2-(ethynyloxy)-1-naphthaldehyde (3E)……..……..….. 23

Figure 27. Synthesis of 1-(2-(but-3-ynyl)benzylidene)-2-methylhydrazine (4A)…….....24

Figure 28. Synthesis of 1-(5-bromo-2-(but-3-ynyl)benzylidene)-2-methylhydrazine (4B)……..... ……..……..…….....25

Figure 29. Synthesis of 1-(2-(but-3-ynyl)-5-nitrobenzylidene)-2-methylhydrazine (4C)……..……..…….....25

Figure 30. Synthesis of 1-(2-(but-3-ynyl)-4-methoxybenzylidene)-2-methylhydrazine (4D)…….....26

Figure 31. Synthesis of 1-((2-(ethynyloxy)naphthalen-1-yl)methylene)-2-methylhydrazine (4E)……..…….....27

Figure 32. Synthesis of 1-(2-(but-3-ynyl)benzylidene)-2-methylhydrazine 4A-E…….....30

Figure 33.The comparison of ^{1}H NMR Spectra for 2-(prop-2-ynyloxy)benzaldehydes 3A and 1-(2-(but-3-ynyl)benzylidene)-2-methylhydrazine 4A…….....…31

Figure 34. The comparison of ^{13}C NMR Spectra for 2-(prop-2-ynyloxy)benzaldehydes 3a and 1-(2-(but-3-ynyl)benzylidene)-2-methylhydrazine 4A..…….....32

Figure 35. Proposed ABTS cation radical scavanging mechanism of hydrazone derivatives……..…….....33

Figure 36. Antioxidant capacities of sythesized hydrazine derivatives. EC_{50} values of derivatives were calculated as the concentration (µg/ml) exhibiting 50% inhibiton of ABTS radical. Each value represents mean ± Standard Deviation (SD). All the measurements were done triplicated.....34

SYMBOLS

Some symbols used in this study are presented below, along with descriptions.

Symbols	Description
Na_2SO_4	Sodium sulfate
CH_3COOH	Acetic acid
H_3PO_4	Phosphoric acid
H_2SO_4	Sulfuric acid
KCI	Potassium chloride
HNO_3	Nitric acid
$LiClO_4$	Lithium perchlorate
Na_2HPO_4	Disodium hydrogen phosphate
NaOH	Sodium hydroxide
H_3BO_3	Boric acid
HCl	Hydrochloric acid
$HClO_4$	Perchloric acid
Hg_2Cl_2	Mercury (I) chloride
KNO_3	Potassium nitrate
L	Liter
mL	Milliliter
µL	Microliter
M	Molarity
µg	Micro gram
V	Volt
Mv	Millivolt
°C	Centigrade degrees
Hz	Hertz
S	Second

ABBREVIATIONS

Some abbreviations used in this study are presented below, along with descriptions.

Abbreviations	Description
DEAD	Diethyl azodicarboxylate
SD	Standard Deviation
PET	Polyethylene terephthalate
ABTS	2,2-Azinobis(3-ethylbenzo thiazoline-6-sulfonic acid)diammonium salt
DMF	*N*,*N*-Dimethylformamide
TLC	Thin-layer chromatography
UV	Ultravoilet
TMS	Trimethylsilane
CNS	Central nervous system
WHO	World Healthy Organization

1. INTRODUCTION

1.1. Hydrazones

Hydrazones have gained considerable interest in recent years due to their wide variety of biological and pharmacological properties **(**Figure 1) (Werengoeska et al., 2005; Tatum et al., 2014; Le Goff et al., 2014;Yang et al., 2016; Mohanraj et al., 2016). Hydrazones are important sources for the synthesis of heterocyclic compounds (Zora et al., 2011, 2016) and they are members of Schiff base family which were comprehensively studied because of their catalytic properties in various fields and partly for their biological activity (Narang et al., 2012; Su et al., 2014; Maia et al., 2014; Lane et al., 2014; Rhoda et al., 2015; Bingul et al., 2016). These versatile organic compounds have a general formula of $R_1R_2C{=}NNR_3R_4$ at which there are two amino type nucleophilic nitrogen atoms and a carbon atom with nucleophilic and electrophilic character (Enders et al., 1996). Both of them constitute the active centers of hydrazines; they generate the characteristic physical and chemical properties of hydrazones (Cere et al., 1999; Fries et al., 2005).

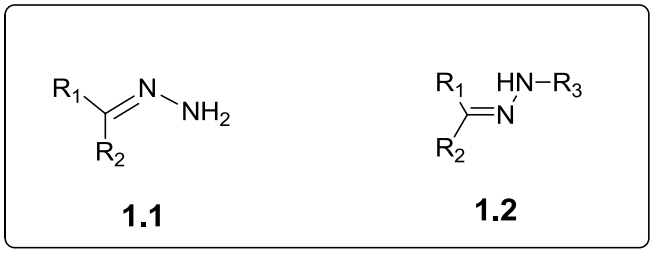

Figure 1**.** Structures of hydrazones.

1.1. Preparation of Hydrazones

Hydrazones have some common properties of their being easy to be prepared, tendency toward crystallinity and better hydrolytic stability relative to imines. Their synthesis is generally performed by the reaction of hydrazine with aldehydes, ketones and such other carbonyl compounds in solvents like ethanol, methanol and butanol (Altintop et al., 2012; Coa et al., 2015; Kaplanek et al., 2015). The reaction includes addition-elimation mechanism for the formation of corresponding hydrazones like imine formation. Hydrazone derivatives are easily purified because they are usually crystalline solids. Therefore, hydrazones can be quickly determined by comparing melting points of starting aldehyde or ketones. If aldehydes/ketones are reacted with hydrazine, only hydrazones are formed. When carbonyl groups undergone condensation reaction with different hydrazone derivatives such as phenylhyrazine etc.,the corresponding *N*-aryl substituted hydrazones are obtained (Xin et al., 2014). If semicarbazides are used for these reactions, semicarbazone compounds are prepared (Figure 2).

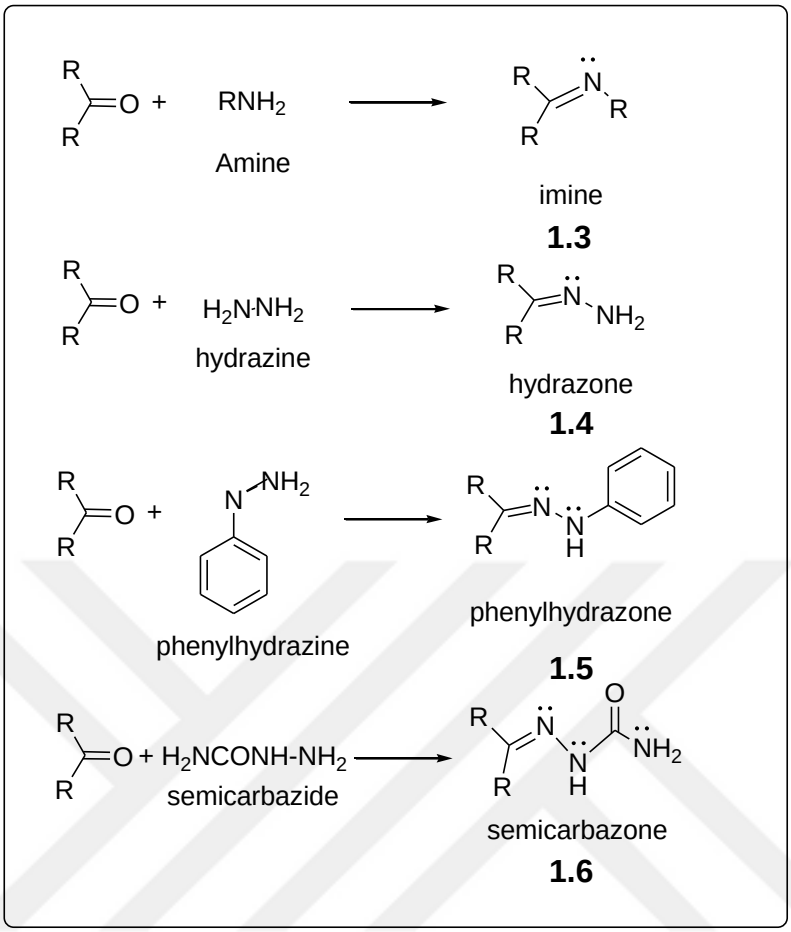

Figure 2. Synthesis of hydrazones.

Hydrazones can also be synthesized by using the Japp–Klingemann (Francis Robert Japp and Felix Klingemann) reaction (Meyer et al., 1984). When aryl diazonium salts are reacted with β-keto esters or acids, the corresponding hydrazone derivatives are formed in good yields (Figure 3). The Japp–Klingemann reactions are very important synthetic methods for the preparation of hydrazone intermediates which could be used in the syntheses of more complex organic molecules.

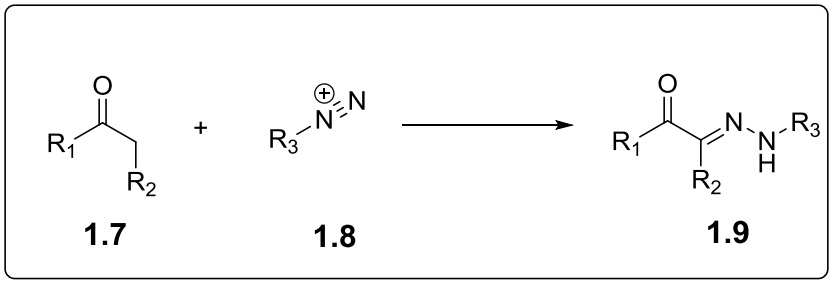

Figure 3**.** The Japp–Klingemann reactions.

1.1. Reactivity of Hydrazones

Hydrazones have two connected nitrogen atoms; one is in the C-N double bond which is conjugated with a lone electron pair of terminal nitrogen atom. Other is primary, secondary or tertiary amines. The structural fragments create different physical and chemical properties of hydrazones. Both nitrogene atoms of the hydrazone group display nucleophilicity, and the carbon atom of hydrazone group give not only electrophilic, but also nucleophilic reactions (Figure 4) (Belskaya et al., 2010).

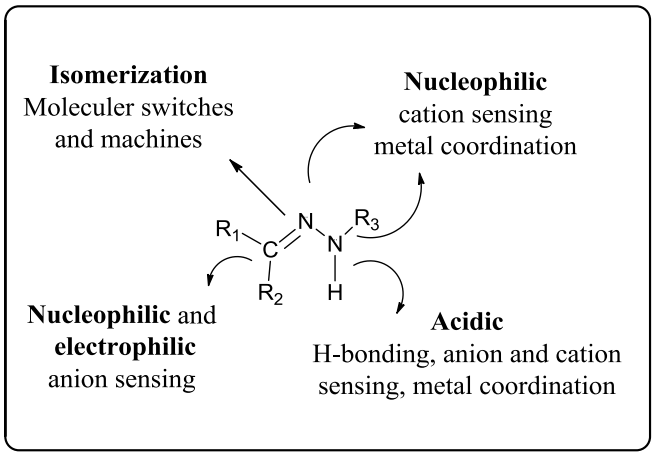

Figure 4. Active centers of hydrazones.

Hydrazone derivatives are mostly used in organic synthesis such as substitution reactions, cycloaddition reactions and intramolecular cyclization reactions with different catalysts. They are known as important intermediates for the formation of a variety of heterocyclic compounds. In addition, hydrazones are good cheating agents for metal complexes (Lane et al., 2014; Narang et al., 2012).

Recently, Keith et al. reported the synthesis of *N*-aryl-*N*-tosyl substituted hydrazone derivatives from corresponding hydrazone and alcohols (Figure 5). Tosyl hydrazones reacted with primary and secondary alcohols in the presence of DEAD and PPh_3 catalyst systems. This reaction is a good example for nucleofilic substitution reactions of hydrazones (Keith et al., 2006).

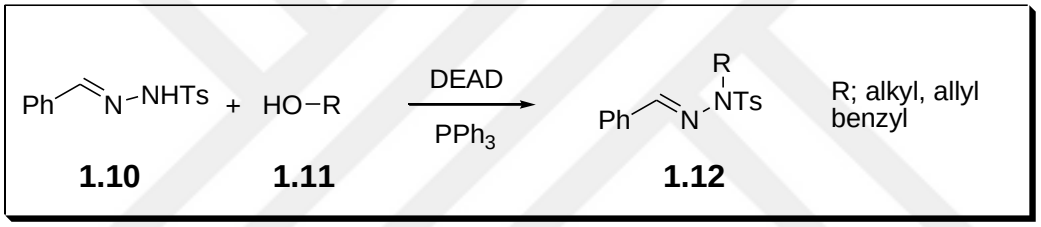

Figure 5. Synthesis of *N*-aryl-*N*-tosyl hydrazones.

As shown in Figure 6, Wagaw et al. and Lefebvre et al. were reported new S_NAr type reactions of hydrazines with arylbromides (Wagaw et al., 1998; Lefebvre et al., 2010). These reactions produce *N*-aryl hydrazones which could be used for the synthesis of indole derivatives (Figure 6). Fischer indolizations (Fischer indole synthesis) from *N*-arylhydrazones occur in the presence of Brønsted or Lewis acids. Moreover, the conversion of aryl hydrazones to indoles requires mild reaction conditions (Figure 7) (Fischer., 1883; Allen et al., 1943).

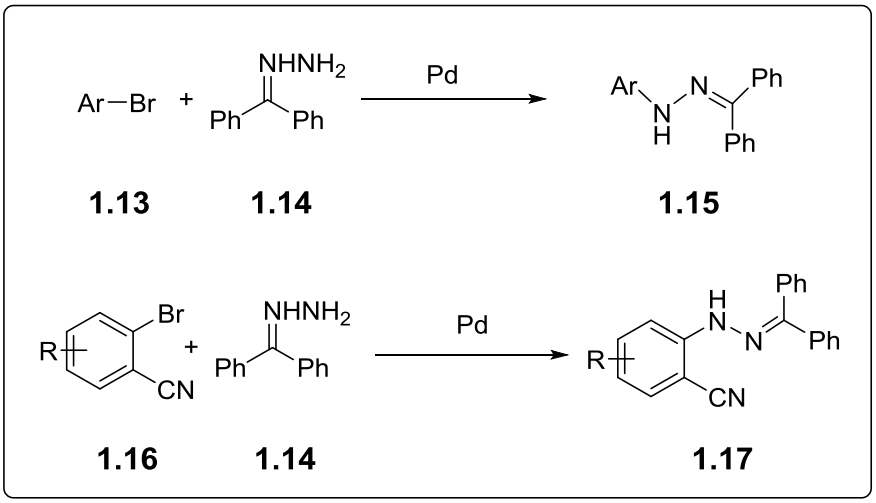

Figure 6**.** Synthesis of *N*-aryl hydrazone derivatives.

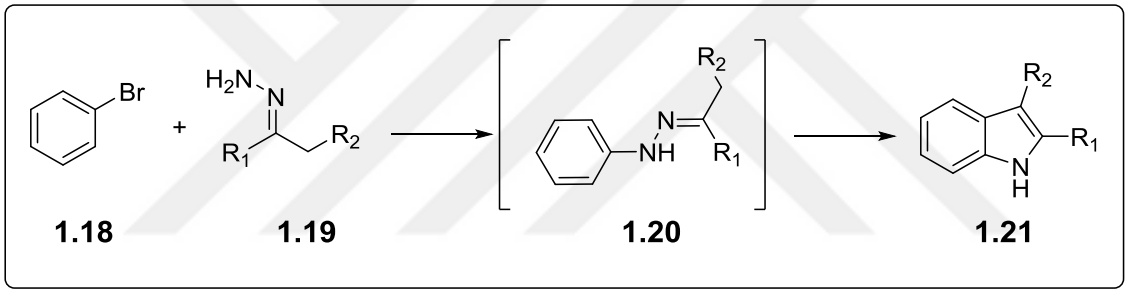

Figure 7**.** Fischer indole synthesis.

There are different synthetic routes for the formation of substituted thiazolidinones in literature. Sadou et al. reported two-steps synthesis of thiazolidin-4-ones from α-tetralone or thiochroman-4-one, catalyzed by acids (Figure 8). In the first part, thiosemicarbazones were obtained from the reactions of α-tetralone with substituted thiosemicarbazides. When thiosemicarbazones were treated with sulfuric acid or heteropolyacid catalysis, 4-thiazolidinones were obtained in good yields in relatively short times (Sadou et al., 2016).

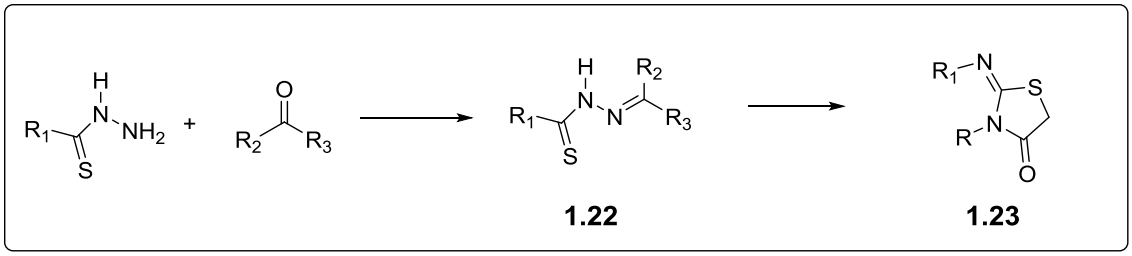

Figure 8. Synthesis of 4-thiazolidin-4-ones.

Hydrazones also have critical intermediates for cycloaddition reactions to give the four or six membered natural and biologically active heterocyclic compounds (Figure 9) (Martin-Zamora et al., 2004). As shown in (Figure 10), hydrazone imtermediates could be used as precursors for generating the active components for the hetero-Diels-Alder reaction (with 1,2-diazabuta-1,3- dienes) or [3+2]-cycloaddition (with azomethine imines, nitrile imines, azomethine ylides) (Belskaya et al., 2010).

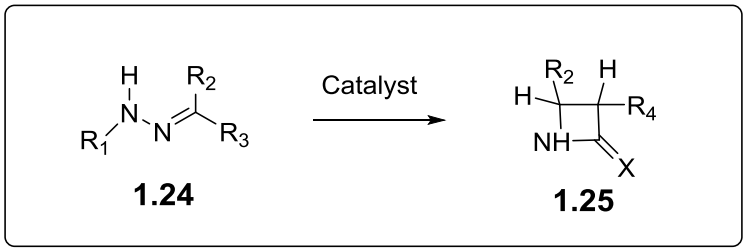

Figure 9**.** Synthesis of azetidines via cycloaddition reactions.

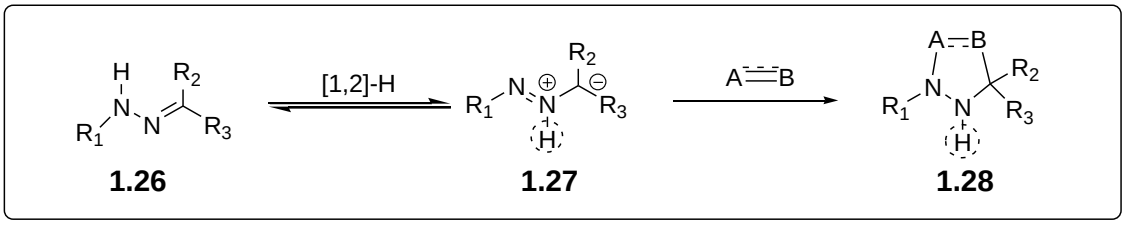

Figure 10. Synthesis of heterocyclic compounds via cycloaddition reactions.

As seen (Figure 11), tosyl hydrazones are critical intermediates for the formation of alkenes. This reaction is named as Shapiro reaction which was discovered by Robert H. Shapiro in 1975. Ketone or aldehyde is converted to an alkene through an intermediate hydrazone in the presence of strong base such as n-butyl lithium (Shapiro et al., 1975).

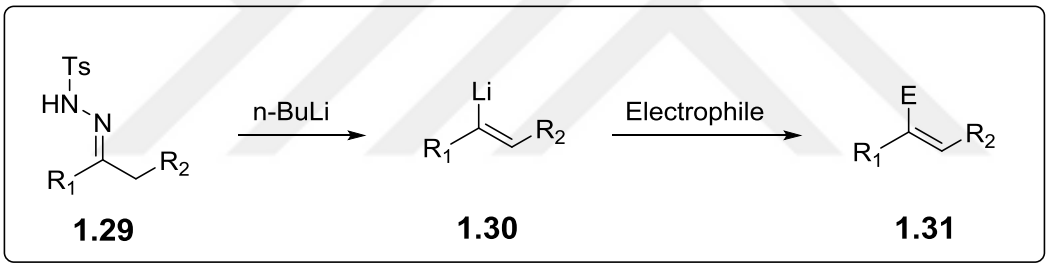

Figure 11. Shapiro reaction.

Wolff-Kishner Reduction is a method which aldehydes or ketones can be converted to corresponding alkanes via their hydrazones in the presence of bases at higher temperature (Figure 12). Firstly, aldehydes or ketones undergo condensation reactions with hydrazines to form hydrazone intermediates, then treatment with base induces the reduction of the carbon coupled with oxidation of the hydrazine to gaseous nitrogen, to yield the corresponding alkane (Furrow and Meyers., 2010).

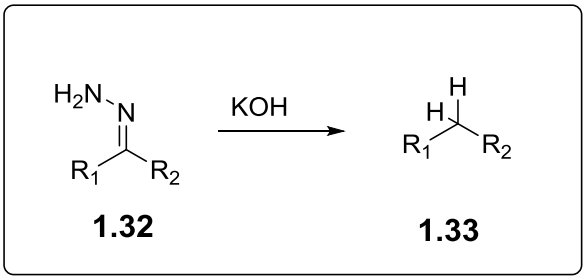

Figure 12. The Wolff-Kishner Reduction.

Pyrazole and dihydropyridazine derivatives are obtained by [3+2] cycloaddition reactions or intramolecular cyclization reactions (Figure 13). When diazo compounds react with alkynes, the corresponding pyrazoles are obtained via cycloaddition reaction. Moreover, the reaction between *N*-aryl hydrazones and heterocyclic compounds gives the dihydropyridazines in good yields.

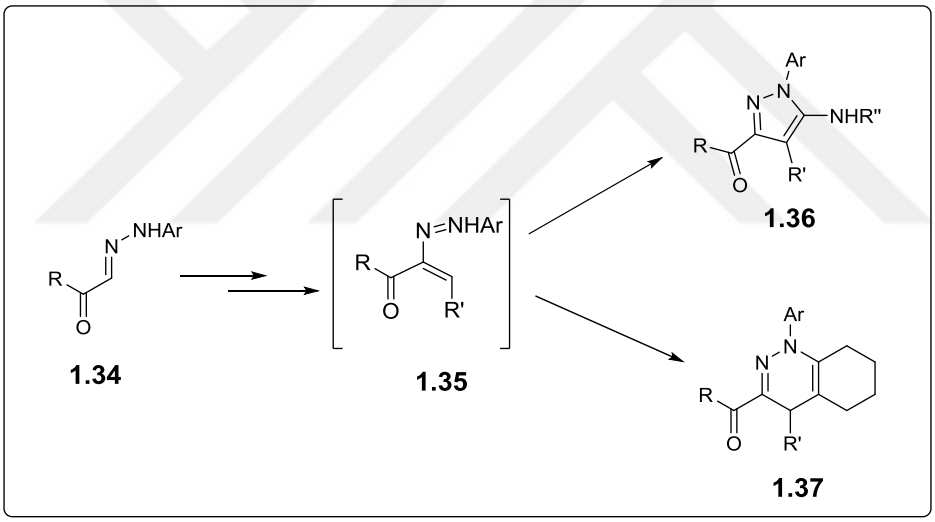

Figure 13**.** Synthesis of pyrazoles and dihydropyridazine.

Recently, Zora et al. reported novel synthetic methodologies for the synthesis of biologically important pyrazole derivatives by using electrophilic cylization reactions (Figure 14) (Zora et al., 2011, 2016). Firstly, alkynic hydrazones were obtained from the condensation reaction between propargyl aldehydes and hydrazines. Then, acetylenic hydrazones underwent electrophilic cyclization reactions in the presence of molecular iodine. This reaction yielded regioselectively 4-iodopyrazoles, On the other hand, when CuI was used as a catalyst, only pyrazole product was formed

in excellent yields. For the synthesis of 4-selenyl substituted pyrazoles, arylselenyl chloride was employed for electrophilic cyclization reactions as an electrophilic reagent.

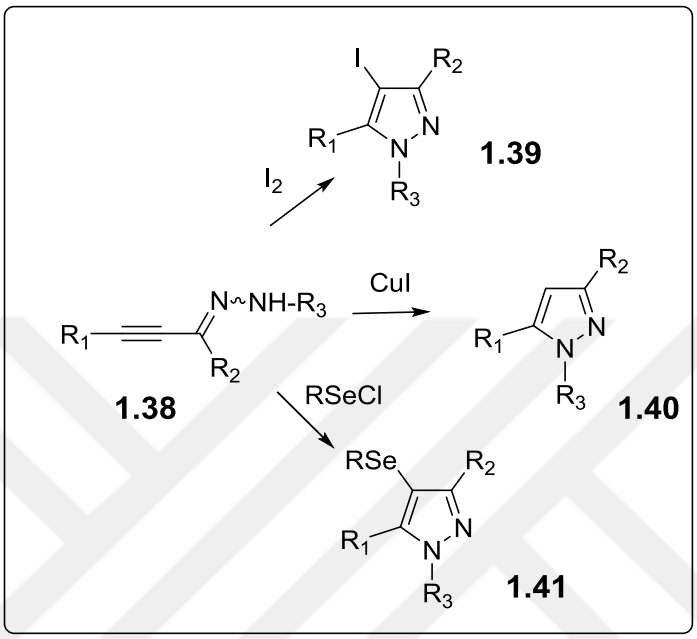

Figure 14. Synthesis of pyrazoles via electrophilic cyclization reactions of acetylenic hydrazones.

Aziz et al. reported the synthesis of benzofulvenes through a squence of palladium catalyzed coupling reaction and palladium catalyzed 5-exo-dig cyclization. Initially, 2-iodoacetophenone was reacted with tosylhydrazine to give the hydrazone intermediates, then palladium catalyzed Sonogashira coupling reaction with terminal alkynes was used for the formation of new carbon-carbon bond. Finally, hydrazones underwent palladium catalyzed cyclization reactions with aryl halides to form 5-exo-dig products (Figure 15) (Aziz et al., 2015).

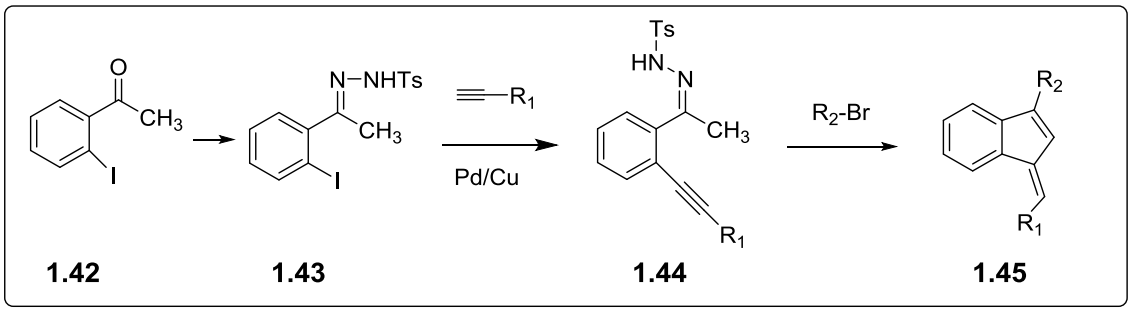

Figure 15. Synthesis of Benzofulvenes.

2. LITERATURE REVIEWS

The synthesis and the evaluation of possible antimicrobial (Gurkok et al., 2009; Shirinzadeh et al., 2011; Wang et al., 2014), antifungal (Wang et al., 2014), antitumoral (Coco et al., 2006; Montenegro et al., 2011) , anti-inflammatory (Rajitha et al., 2011; Navidpour et al., 2014), analgesic (Sondhi etal., 2006), antiproliferative (Onnis et al., 2016) and antitubercular (Sonar et al., 2009; Pinheiro et al., 2011; Pathak et al., 2012) activities of hydrazone derivatives have growing popularity for organic chemists and pharmaceutical experts. Those compounds perform their actions through diverse biochemical ways mainly based on their being effective chelating agents (Liu et al., 2016) and metal ion scavengers (Su et al., 2014), pharmacophoric inhibitors of some key enzymes in metabolic pathways and factors leading cytotoxicity that could be used in pharmacological strategies against many diseases and disorders (Rollas et al., 2007). No matter which mode of operation they have, most efforts spent on those molecules to offer alternative drugs with less toxicity and higher activity lead researchers, first, to evaluate the basic properties of new derivatives such as antioxidant capacities (Serafini et al., 2004; MacDonald et al., 2006).

2.1. Antimicrobial Activity of Hydrazones

Hydrazone and their derivatives have gained huge importance for the treatment of various infections last decades. The bacterial resistance changes every day and development of new organic molecules can be very critical to decrease the effects of bacteria. As shown in Figure 16, a variety of hydrazones may be good candidate as anti-microbial agents.

Recently, sulfonyl containing hydrazones were reported for their antimicrobial activity by Aslan et al. (2.1) (Aslan et al., 2012). Khan also investigated steroidal hydrazones (2.2 and 2.3) which could be a new class of anti-bacterial agent (Khan et al., 2008). Compounds 2.2 and 2.3 were prepared from the reaction of cholest-5-en-3-one

semicarbazone/thiosemicarbazone with 2,3-dichloroquinoxaline. In 2011, the antimicrobial, antioxidant, anti-hemolytic, and cytotoxic activities of hydrazone bearing imidazoles (2.4) were found, and they displayed an antibacterial activity for all the tested bacteria with minimal inhibitory concentration (Abdel-Wahab et al., 2011). In addition, Plaker et. al. developed an easy and useful method to synthesize antibacterial active derivatives containing novel series of thiadiazoles (2.5**)** from terephthalic dihydrazide which is being obtained from PET waste (Plaker et al., 2009). Related with previous studies, Wang *et al*. investigated significant antimicrobial properties of new hydrazones including 1,3,4-thiadiazole moieties (2.6) (Wang et al., 2013).

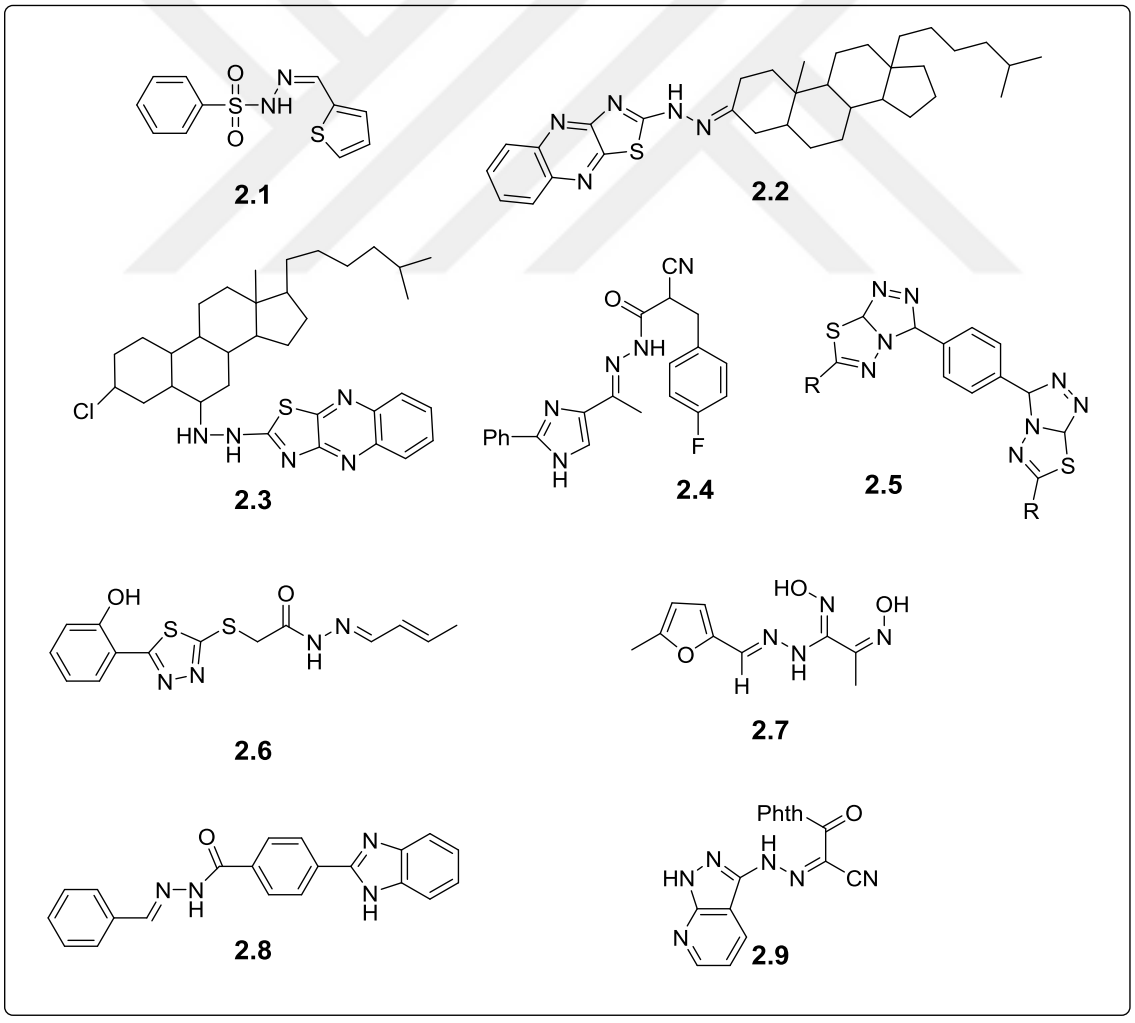

Figure 16**.** Structures of some hydrazine derivatives as antimicrobial agents.

Hydrazones are also known as useful intermediates for the preparation of metal complexes with different metals. Babahan et al. recently synthesized three novel heteroaromatic hydrazone derivatives (2.7**)** bearing vic-dioxime groups (L1H2: 5-methyl-2-furfural hydrazone glyoxime, L2H2: 3-acetylpyridine hydrazone glyoxime and L3H2: 4-acetylpyridine hydrazone glyoxime) and their Ni(II), Cu(II) and Co(II) complexes (Babahan et al., 2013).

A variety of benzimidazole derivatives bearing hydrazone moiety (2.8) were prepared and investigated for their possible antibacterial and antifungal activities. After screening six different gram-negative and four different gram-positive bacterial strains, novel benzimidazole-hydrazone derivatives may be big candidates for the treatment of bacterial diseases (Ozkay et al., 2010). Moreover, Khalil et al. investigated the effects of polyheteroaromatics (**2.9**) and they found that these molecules had interesting activities against the different bacteria (Khalil et al., 2009).

2.2. Anti-inflammatory Activity of Hydrazones

Anthranilic acid derivatives (2.10) were synthesized and reported to have significant anti-inflammatory activity by Mohamed Eissa et al. in 2012. In this study, three different anthranilic acids were designed and prepared to find their antiinflammatory activities. In addition, Salgin-Gökşen et al., investigated the biological properties of hydrazones containing 5-Methyl-2 benzoxazolinones (2.11), and these structures displayed good analgesic and anti-inflammatory activities (Salgin-Göksen et al., 2007).

Different kinds of organic compounds with different pharmacophoric properties have been investigated in search of novel anti-inflammatory agents using carrageenan-induced paw edema as a model for acute inflammation. Bhandari and Rajitha reported that the aroyl hydrazones had high more activity (percentage inhibition of more than 80%), and could be next generation anti-inflammatory agents (2.12) (Bhandari et al., 2008; Rajitha et al., 2011).

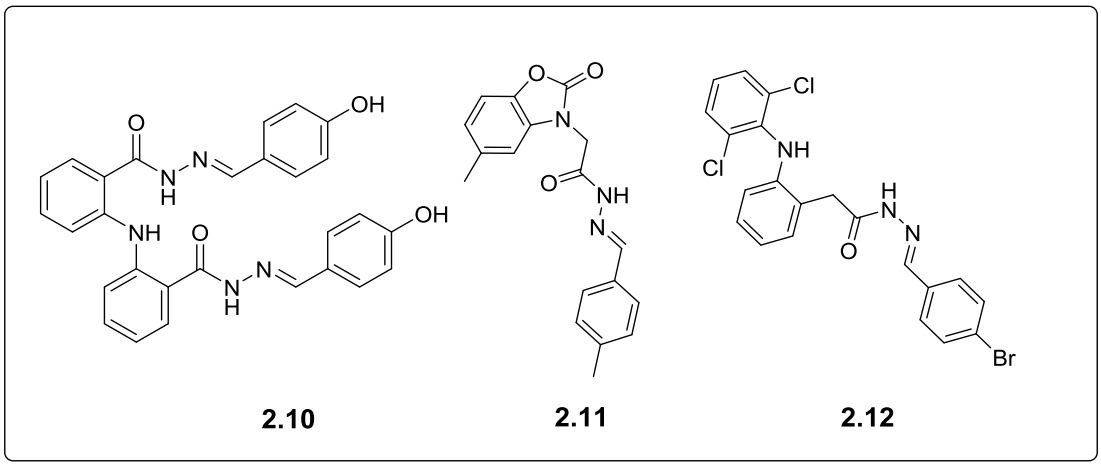

Figure 17. Structure of some hydrazine derivatives as anti-inflammatory agents.

2.3. Anti-cancer Activity of Hydrazones

World Healthy Organization (WHO) has announced that many people in the world were under cancer risk. There are more than 100 different types of cancer such as lung cancer, breast cancer etc. Last decades, many researchers have focused on the design and synthesis of novel small organic molecules for the treatment of cancers. Breast cancer is the most common cancer type for woman. Dandawate et al. synthesized plumbagin hydrazone derivatives (2.13), and they tested them against breast cancer (Dandawate et al., 2012). After screening, it was found that these types of hydrazones had high activity to breast cancer cells. As seen in (Figure 18), flurbiprofen hydrazide derivatives (2.14) were prepared from corresponding starting compounds, and they were evaluated against ovarian and leukemia cancer cell lines (Aydın et al., 2013). In the lights of the previous studies, Cui et al., isolated acylhydrazones (2.15) and found that they had potent activity against the human promyelocytic leukemic cells (Hl-60) (Cui et al., 2010). There are a variety of compounds which have been synthesized and tested for the treatment of cancers in (Figure 18).

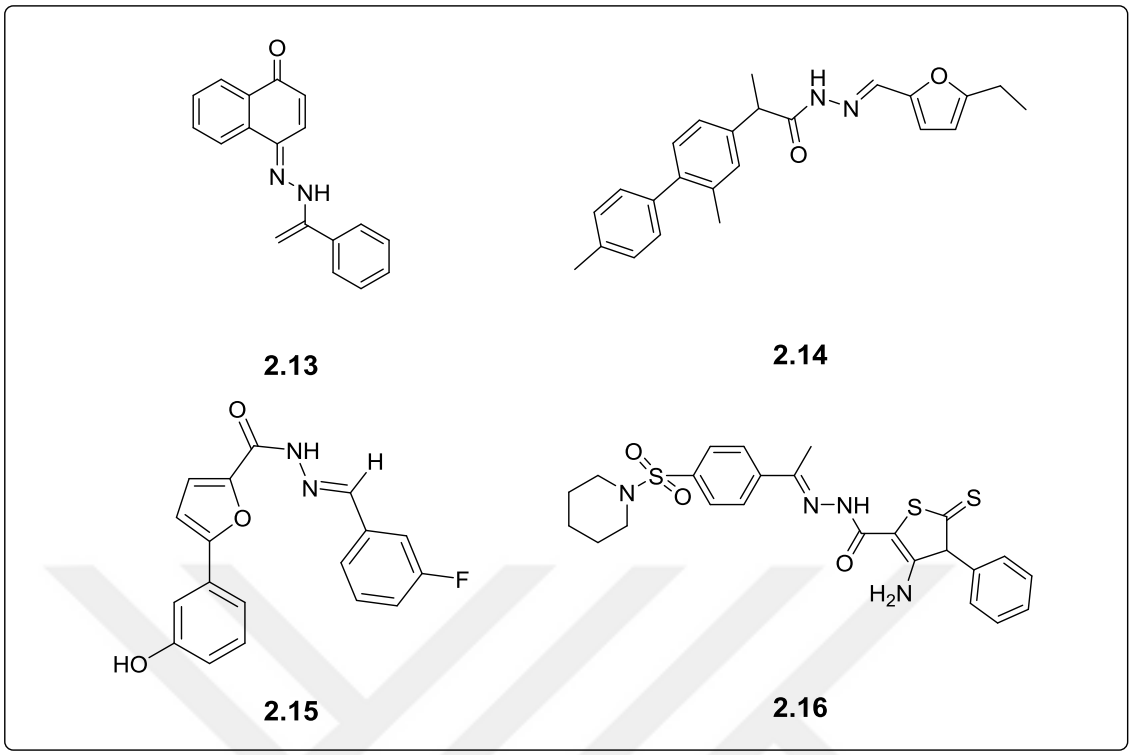

Figure 18**.** Structures of some hydrazones proposed as anti-cancer agents.

2.4. Activities of Hydrozone Derivatives in Central Nervous System

Hydrazones were reported to have activity against various diseases of Central Nervous system (CNS). Salgin-Gökşen *and coworkers* prepared 2-[2-(5-Methyl-2-benzoxazolinone-3-yl)acetyl]-3/4/5-substituted benzylidenehydrazine derivatives (2.17**)** from the reaction between 2-(5-Methyl-2-benzoxazolinone-3-yl)acetylhydrazine and substituted benzaldehydes in neutral and acid/base catalyzed conditions (Salgın-Göksen et al., 2013). They screened them for *in-vitro* monoamine oxidase inhibitory (MAO-B) activity for Parkinson's disease. Moreover compounds 2.18, 2.19 and 2.20 have been investigated for the treatment of schizophrenia and depression, respectively (Figure 19) (Cutshall et al., 2012; Kulandasamy et al., 2009; Oliveira et al., 2011).

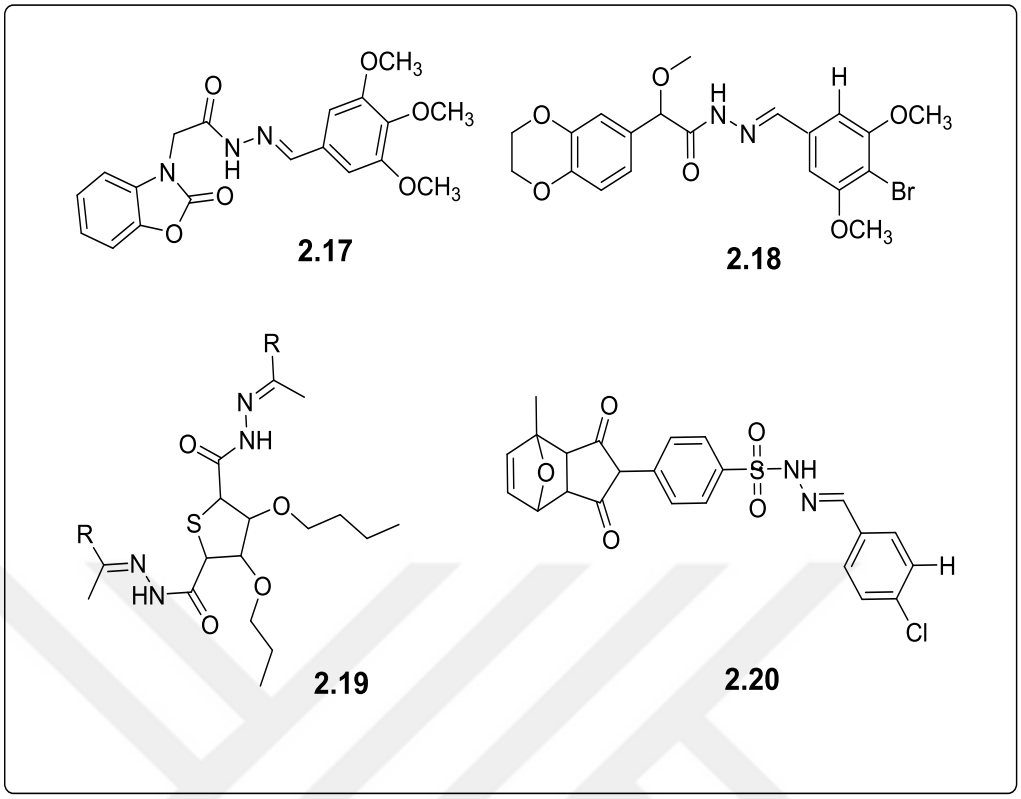

Figure 19**.** Structure of hydrazones as CNS agents.

2.5. Other Biological Activities of Hydrazones

Hydrazone and their derivatives have fascinating biological properties. Antibacterial, antiimflammataroy, anticancer and CNS activities have been summarized in the previous part. In addition to hydrazones have been used as antitumor, anti-protozoal and anticonvulsant agents. They have also displayed anti-tuberculous and anti-HIV activities. As shown in (Figure 20), there are some biologically active examples of known hydrazone compounds (Verma et al., 2014).

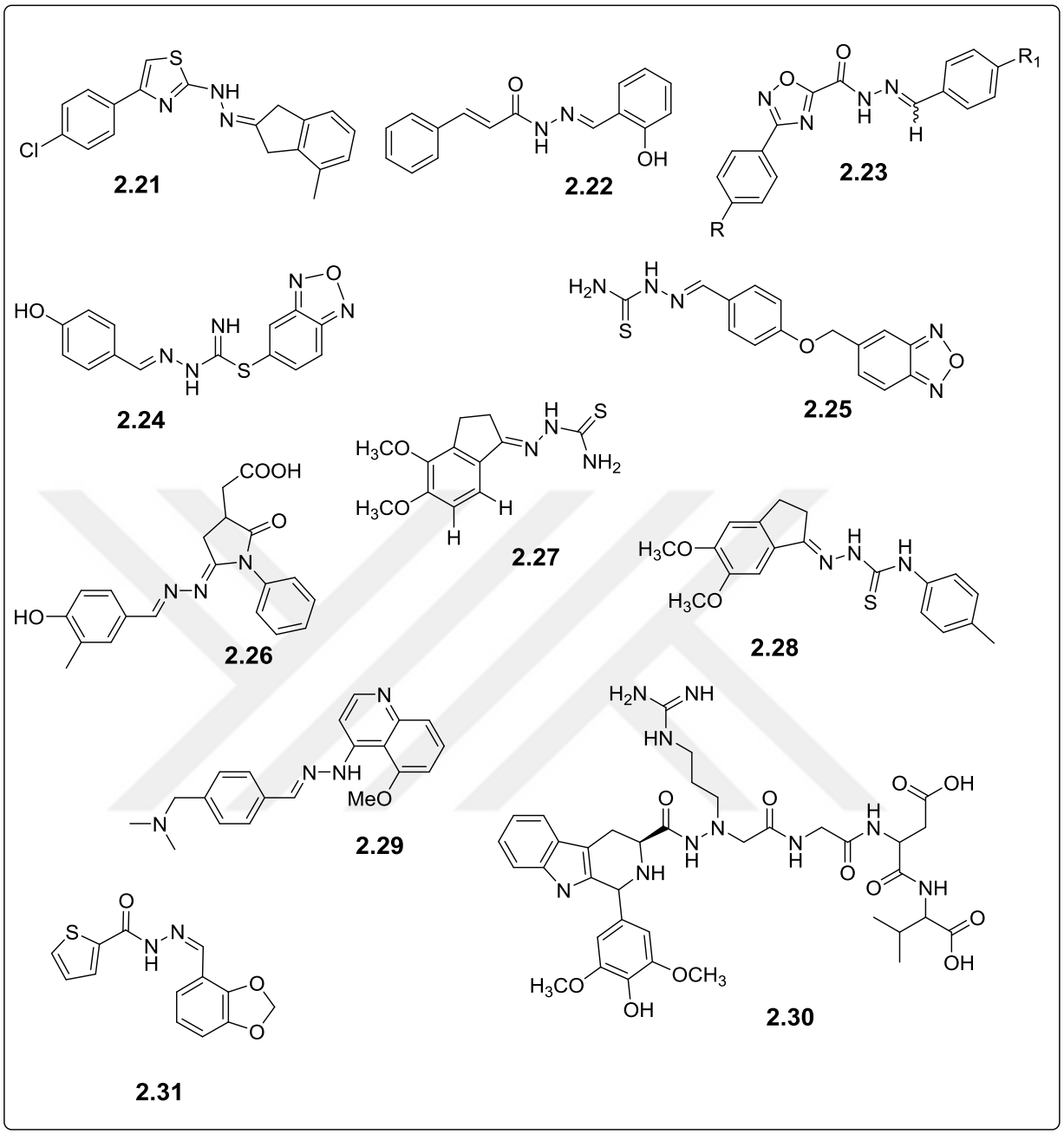

Figure 20. Some biologically important hydrazone derivatives.

2.6. Aim of the Study

In the present study, novel hydrazone derivatives were designed and synthesized via condensation reactions between methyl hydrazine and of 2-(Prop-2-yn-1-yloxy)benzaldehyde derivatives. Their antioxidant potentials were also tested by

using ABTS assay. In this assay, 2,2'-azinobis(3-ethylbenzthiazoline-6-acid) (ABTS) is turned into its blue/green radical cation (ABTS•+) with the action of potassium persulphate which is a strong oxidizing agent. ABTS•+ cation is highly reactive towards antioxidant compounds and soluble in both aqueous and organic solvents. This nature makes it a very useful method for determination of the antioxidant capacity of both lipophilic and hydrophilic antioxidants (Cano et al., 200). In addition, this assay can be applied over a wide pH range without affecting ionic strength of medium (Dawidowicz et al., 2013).

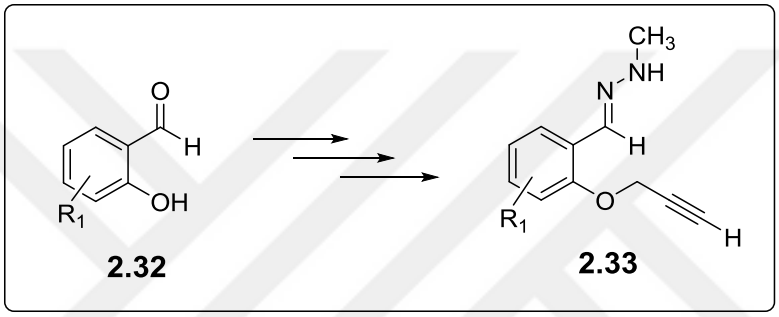

Figure 21. Synthesis of novel hydrazones.

3. MATERIALS AND METHODS

3.1. Experimental Section

The design, synthesis, and biological properties of novel hydrazone derivatives were studied. The structure of the synthesized molecules were determined by ^{1}H and ^{13}C-NMR spectroscopy. ^{1}H and ^{13}C-NMR spectra were recorded on an Agilent NMR (400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (J) were reported in hertz (Hz). In addition, spin multiplicities were presented by the following symbols: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). ^{13}C-NMR information was given in parentheses as C, CH, CH_2, and CH_3. Flash chromatography was performed using thick-walled glass columns and 'flash grade' silica (Merck 230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel plates and visualization was effected with short wavelength UV lamp. The relative proportions of solvents in chromatography solvent mixtures referred to volume to volume ratio. Absorption spectra was measured on a Thermo Scientific Multiskan GO UV–VIS spectrophotometer. All commercially available reagents were used directly without purification unless otherwise stated. All the solvents used in experiments were distilled for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in an oven prior to use.

3.2. Synthesis of Compounds

3.2.1. General procedure for the synthesis of 2-(Prop-2-yn-1-yloxy)benzaldehydes.

The corresponding 2-Hydroxybenzaldehyde (10 mmol) was dissolved in DMF. Then, 3-Bromoprop-1-yne (1.5 equiv.) and potasium carbonate (1 equiv.) were added at room temperature. The resulting mixture was flushed with Argon and stirred at room temperature. After the reaction was over, the reaction mixture was cooled at 0

^{o}C, then, filtered and washed with distilled water to afford the desired corresponding product.

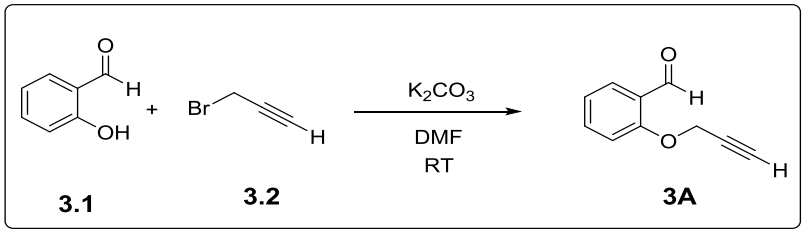

Figure 22**.** Synthesis of 2-(prop-2-yn-1-yloxy)benzaldehydes (3A).

2-(Prop-2-yn-1-yloxy)benzaldehyde (3A): Purification by filtration afforded the product as a light yellow solid (Yield: 82%) : ^{1}H-NMR (400 MHz, CDCl3) δ 10.49 (s, 1H, aldehyde), 7.87 (d, J = 7.7 Hz; 1H), 7.57 (m, 1H), 7.11 (m, 1H), 4.83 (s, 2H, CH_2), 2.58 (s, 1H, alkyn H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.5, 159.7, 135.7, 128.6, 125.4, 121.7, 113.2, 77.6, 76.5, 56.3. IR (ATR) 3268 (acetylenic H), 2873, 2116 (triple bond), 1679 (carbonyl), 1581, 1480, 1456, 1329, 1286, 1220, 1006, 755, 675. The spectral data were in agreement with those reported previously for this compound (Khoshkholgh et al., 2008).

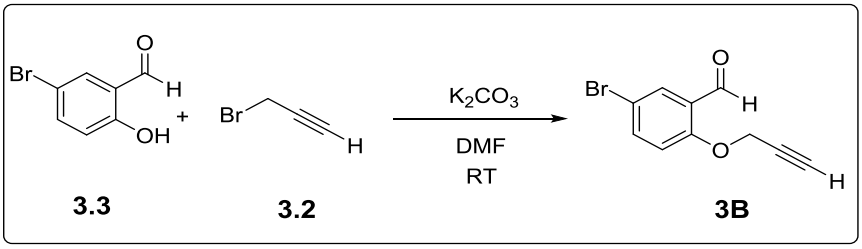

Figure 23. Synthesis of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (3B).

5-Bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (3B): Purification by filtration afforded the product as a white solid (Yield: 58%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ

10.37 (s, 1H, aldehyde), 7.93 (d, *J* = 2.4 Hz, 1H), 7.63 (dd, *J* = 8.8 and 2.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.81 (s, 2H, CH_2), 2.58 (t, *J* = 2.4 Hz, 1H, alkyne's H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.1, 158.6, 138.1, 131.1, 126.7, 115.3, 114.6, 77.3, 76.9, 56.6. IR (ATR) 3234 (acetylenic H), 2883, 2118 (triple bond), 1681 (carbonyl), 1589, 1479, 1406, 1329, 1286, 1219, 1018, 880, 691. The spectral data were in agreement with those reported previously for this compound (Khoshkholgh et al., 2008).

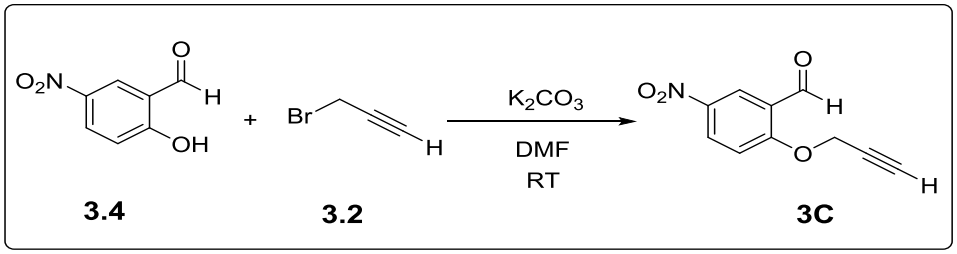

Figure 24. Synthesis of 5-nitro-2-(prop-2-yn-1-yloxy)benzaldehyde (3C).

5-Nitro-2-(prop-2-yn-1-yloxy)benzaldehyde (3C): Purification by filtration afforded the product as a brown solid (Yield: 68%) : 1H-NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H, aldehyde), 8.69 (m, 1H), 8.43 (dt, *J* = 9.2 and 2.5 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 4.97 (s, 2H, CH_2), 2.66 (t, *J* = 2.4 Hz, 1H, alkyne) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 187.2, 163.3, 142.1, 130.3, 125.1, 124.6, 113.7, 77.9, 76.2, 57.1. IR (ATR) 3240 (acetylenic H), 2887, 2114 (triple bond), 1661 (carbonyl), 1575, 1480, 1412, 1315, 1286, 1219, 1018, 885, 705. The spectral data were in agreement with those reported previously for this compound (Khoshkholgh et al., 2008).

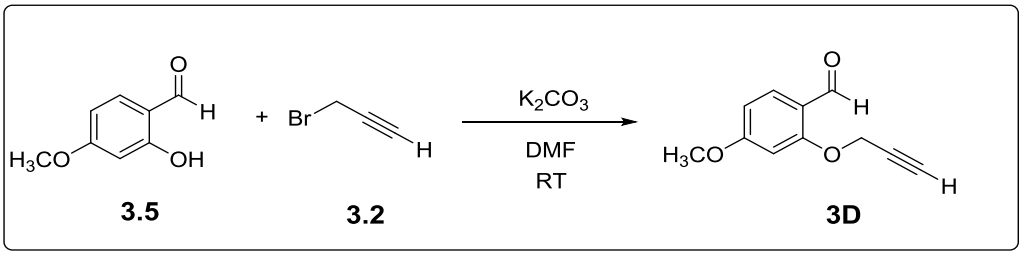

Figure 25**.** Synthesis of 4-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (3D).

4-Methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (3D): Purification by filtration afforded the product as a light yellow (Yield: 92%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H, aldehyde), 7.45 (m, 1H), 7.16 (m, 2H), 4.87 (s, 2H, CH_2), 3.88 (s, 3H, OMe), 2.47 (s, 1H, alkyne); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 152.6, 131.2, 124.9, 118.8, 117.6, 78.2, 76.9, 60.8, 56.0. IR (ATR) 3281 (acetylenic H), 2936, 2119 (triple bond), 1688 (carbonyl), 1588, 1472, 1412, 1345, 1273, 1062, 1065, 990, 785. The spectral data were in agreement with those reported previously for this compound (Vedachalam et al., 2011).

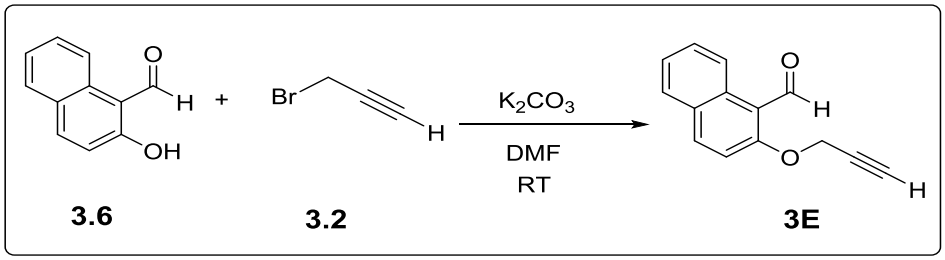

Figure 26**.** Synthesis of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (3E).

2-(Prop-2-yn-1-yloxy)-1-naphthaldehyde (3E): Purification by filtration afforded the product as a light yellow (Yield; 70%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.9 (s, 1H, aldehyde), 9.27 (d, *J* = 8.7 Hz, 1H), 8.07 (m, 1H), 7.80 (m, 1H), 7.63 (m, 1H), 7.44 (m, 1H), 7.37 (m, 1H), 4.94 (s, 2H, CH_2), 2.77 (t, *J* = 2.3 Hz, 1H, alkyne's H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 191.7, 161.9, 137.3, 131.4, 129.9, 129.1, 128.2, 125.2, 125.1, 118.0, 113.9, 77.6, 76.7, 57.4. IR (ATR) 3258 (acetylenic H), 2966, 2123 (triple bond), 1696 (carbonyl), 1495, 1363, 1177, 1227, 1062, 1001, 985, 740. The spectral data were in agreement with those reported previously for this compound (Khoshkholgh et al., 2008).

3.2.2. General procedure for the synthesis of 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine

The corresponding 2-(prop-2-ynyloxy)benzaldehydes (3A**)**: (0.5 mmol) was dissolved in dioxane (2 mL). Then methylhydrazine (2 mL) was added at room temperature. The resulting mixture was flushed with Argon and stirred at room temperature. After the reaction was over, the solvents were removed under vacuum and the desired product was obtained after short flash column chromatography.

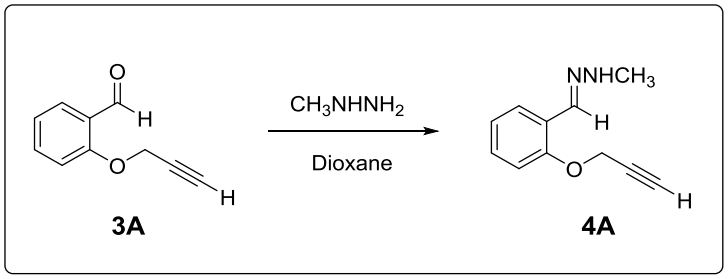

Figure 27**.** Synthesis of 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine (4A).

1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine (4A): The product was isolated as an brown oil (Yield; 98%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H, CH=N), 7.81 (dd, *J* = 8.0 and 1.9 Hz, 1H), 7.20 (m, 1H), 6.97 (m, 2H), 5.60 (brs, 1H, NH), 4.70 (d, *J* = 2.4 Hz, 2H, CH_2), 2.94 (s, 3H, $NHCH_3$), 2.59 (s, 1H, alkyne's H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 154.6, 139.2, 130.9, 128.6, 125.3, 121.8, 112.7, 78.6, 75.7, 56.3, 34.9. IR (ATR) 3284 (acetylenic H), 2960, 2866, 2793, 2116 (triple bond), 1600, 1483, 1463, 1223, 1098, 1021, 762.

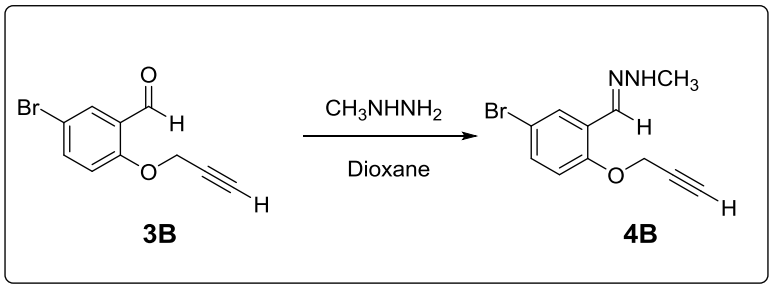

Figure 28. Synthesis of (Z)-1-(5-bromo-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine (4B).

1-(5-Bromo-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine (4B): The product was isolated as an brown oil (Yield; 85%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 2.5 Hz, 1H), 7.72 (s, 1H, CH=N), 7.28 (dd, J = 8.7 and 2.5 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 4.70 (d, J = 2.4, 2H, CH_2), 2.96 (s, 3H, $NHCH_3$), 2.52 (t, J = 2.4 Hz, 1H, alkyne's H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.4, 136.9, 130.8, 128.6, 127.8, 118.2, 114.5, 78.1, 76.0, 56.5, 34.7. IR (ATR) 3290 (acetylenic H), 2980, 2920, 2797, 2120 (triple bond), 1594, 1475, 1406, 1224, 1115, 1020, 799, 633.

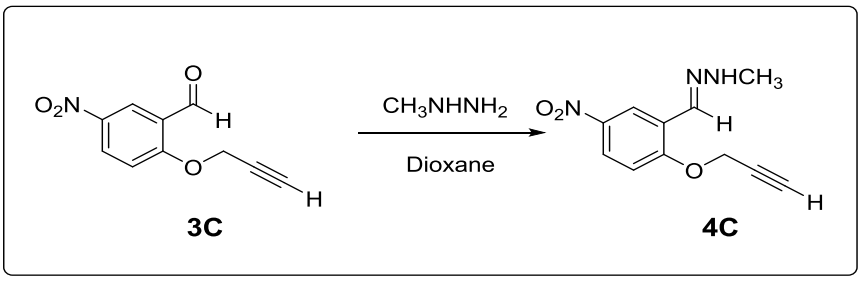

Figure 29**.** Synthesis of 1-methyl-2-(5-nitro-2-(prop-2-yn1yloxy)benzylidene) hydrazine (4C).

1-Methyl-2-(5-nitro-2-(prop-2-yn-1-yloxy)benzylidene)hydrazine (4C): The product was isolated as an brown oil (Yield: 84%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.69 (m, 1H), 8.07 (m, 1H), 7.68 (s, 1H, CH=N) 7.04 (m, 1H), 5.93 (brs, 1H, NH), 4.83 (s, 2H, CH_2), 3.00 (s, 3H, $NHCH_3$), 2.58 (s, 1H, alkyne); ^{13}C-NMR (100 MHz,

$CDCl_3$) δ 158.3, 142.5, 126.8, 123.4, 123.0, 120.9, 111.9, 77.2, 76.8, 56.5, 34.4. IR (ATR) 3280 (acetylenic H), 2940, 2915, 2788, 2117 (triple bond), 1601, 1455, 1450, 1232, 1145, 1060, 787, 702.

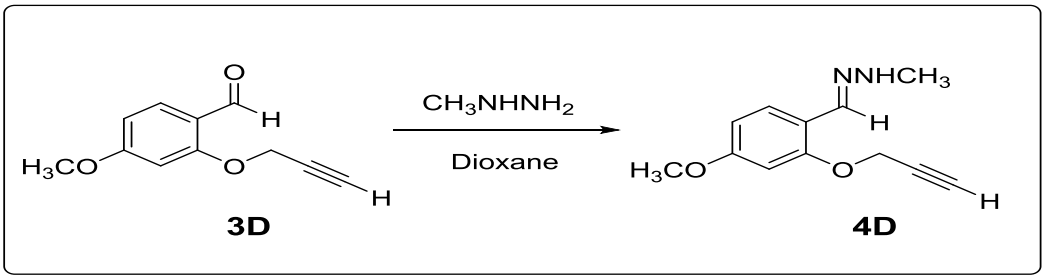

Figure 30. Synthesis of 1-(4-methoxy-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine (4D).

1-(4-methoxy-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine (4D); The product was isolated as an brown oil (Yield; 96%) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, CH=N), 7.42 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.04 (td, *J* = 8.0 and 0.5 Hz, 1H), 6.80 (dd, *J* = 8.02 and 1.4 Hz, 1H), 4.71 (d, *J* = 2.5 Hz, 2H, CH2), 3.84 (s, 3H), 2.98 (s, 3H, $NHCH_3$), 2.97 (s, 1H, alkyne's H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 152.5, 131.5, 130.9, 124.7, 116.8, 111.1, 79.4, 75.5, 60.3, 55.7, 34.7. IR (ATR) 3400, 3281 (acetylenic H), 2936, 2838, 2796, 2119 (triple bond), 1588, 1472, 1437, 1302, 1273, 1065, 990, 743.

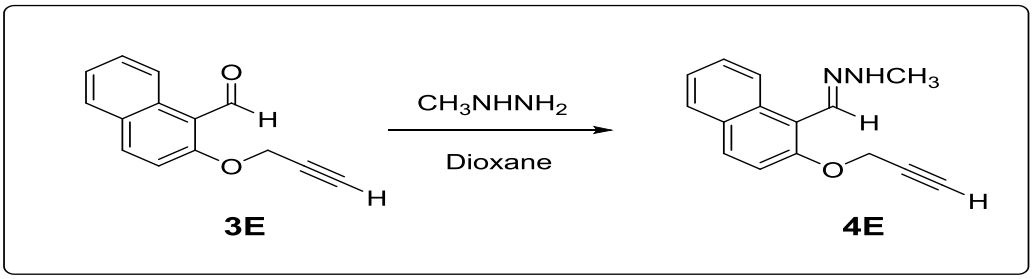

Figure 31. Synthesis of 1-methyl-2-((2-(prop-2-yn-1-yloxy)naphthalen-1-yl)methylene)hydrazine (4E).

1-Methyl-2-((2-(prop-2-yn-1-yloxy)naphthalen-1-yl)methylene)hydrazine (4E): The product was isolated as an brown oil (Yield; 88 %) : ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 8.7 Hz, 1H), 8.28 (s, 1H, CH=N), 7.78 (m, 1H), 7.76 (m, 1H), 7.51 (m, 1H), 7.38 (m, 1H), 7.32 (d, *J* = 9 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 2H, CH_2), 3.09 (s, 3H, $NHCH_3$), 2.52 (t, *J* = 2.4 Hz, 1H, alkyne's H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 153.7, 136.5, 133.5, 129.8, 128.1, 127.2, 126.7, 126.2, 124.3, 122.9, 114.8, 78.7, 75.8, 57.7, 35.4. IR (ATR) 3291 (acetylenic H), 2956, 2865, 2775, 2114 (triple bond), 1577, 1475, 1445, 1377, 1272, 1066, 995, 756.

3.3. Trolox Equivalent Antioxidant Capacity (ABTS Assay)

All chemicals used in ABTS assay including, 2,2'-Azinobis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), potassium persulfate ($K_2S_2O_8$) and methanol (CH_3OH) were purchased from Sigma-Aldrich. Antioxidant capacities of the synthesized hydrazone derivatives were determined according to the modified method of Re et al. (Rea et al. 1999). Firstly, ABTS stock solution was prepared in distal water H_2O, including ABTS (7 mM) and potassium persulphate (2.45 mM), by incubating at room temperature for 12-16 h. Then, in order to obtain working ABTS solution, ABTS stock solution was diluted with methanol to achieve an absorbance of 0.700±0.02 at 734 nm. Hydrazone derivatives and trolox (standard) were dissolved in methanol and diluted with methanol. Finally, standard or

synthesized hydrozone compound was mixed with ABTS working solution (1:1) and incubated in the dark at 25 °C for 30 min. Absorbencies of standard/synthesized compounds and control tube, containing only methanol and ABTS, were measured at 734 nm wavelength. All measurements were done triplicate under dim light. Trolox was used as an antioxidant standard.

The percentage of radical scavenging capability was calculated using the following equation:

$$\text{Radical Scavenging Capability}\,(\%) = \frac{(\text{Control Absorbance} - \text{Sample Absorbance})}{(\text{Control Absorbance})} x100$$

The EC_{50} value is the concentration of compound that is able to reduce the absorbance value of the ABTS•+ radical cation solution to half of its original value. This value obtained from linear curve of radical scavenging capability versus different concentrations of tested compound.

4. RESULTS AND DISCUSSION

4.1. Chemistry

A variety of novel methyl hydrazones, namely, 1-Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine **(**4A**)**, 1-(5-Bromo-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine (4B), 1-Methyl-2-(5-nitro-2-(prop-2-yn-1-yloxy)benzylidene)hydrazine (4C), 1-(4-Methoxy-2-(prop-2-yn-1-yloxy)benzylidene)-2-methylhydrazine **(**4D**)** and 1-Methyl-2-((2-(prop-2-yn-1-yloxy)naphthalen-1-yl)methylene)hydrazine (4E) were synthesized. Initially, a number of 2-(Prop-2-yn-1-yloxy)benzaldehyde 3A-E have been prepared from the corresponding 2-hydroxybenzaldehyde derivatives by using literature procedures. A simple method for the preparation of 2-(Prop-2-yn-1-yloxy)benzaldehyde 3 involves the S_N2 nucleophilic Substitution reactions with propargylbromide 2 under basic conditions. Using this approach, a variety of 2-(Prop-2-yn-1-yloxy)benzaldehydes (3A, 3B, 3C, 3D and 3E) have been synthesized as starting compounds (Scheme 1). When 2-hydroxybenzaldahyde was allowed to react with propargyl bromide 2 in the presence of potassium carbonate, corresponding 3A was formed in 82% yields. While the highest yield (92%) was obtained from the reaction between 2-hydroxy-4-methoxybenzaldehyde 1D and propargyl bromide 2, the bromo substituted aldehydes 1B gave a very low yield of the expected intermediate 3B. Moreover 3A, 3C and 3E were isolated in good yields (Figure 32).

After preparation and characterization of 2-(Prop-2-yn-1-yloxy)benzaldehydes 3, the condensation reactions between 3A-D and methyl hydrazine have been used for the formation of corresponding hydrazone derivatives (4A-E). When 3A underwent condensation reaction with methyl hydrazine in dioxane at room temperature under inert atmosphere, the desired product 4A was obtained in 98% yield. The effects of substituent was tested by using electron withdrawing groups (NO_2), electron donating groups (MeO-), halogen (Br) and poly-aromatic compound (naphthyl). If 3B was

allowed to react with methyl hydrazine for the formation of 4B, the yield was found in %85. When a strong electron-withdrawing nitro group presented on the phenyl 3C react with same hydrazine to form the corresponding hydrazone, the yield (84%) of 4C was found relatively lower than that of electron donating methoxy-substituted aromatic 4D (96%). Moreover, poly-aromatic compound 3E was applied to the synthesis of corresponding hydrazone 4E, the isolated yield was found to be 88% yield. These results displayed that the reactions between 3 and methyl hydrazine can be easily used for the synthesis of novel hydrazone derivatives 4. In addition, these hydrazones may be readily elaborated to more complex products from propargyl groups by using known chemistry.

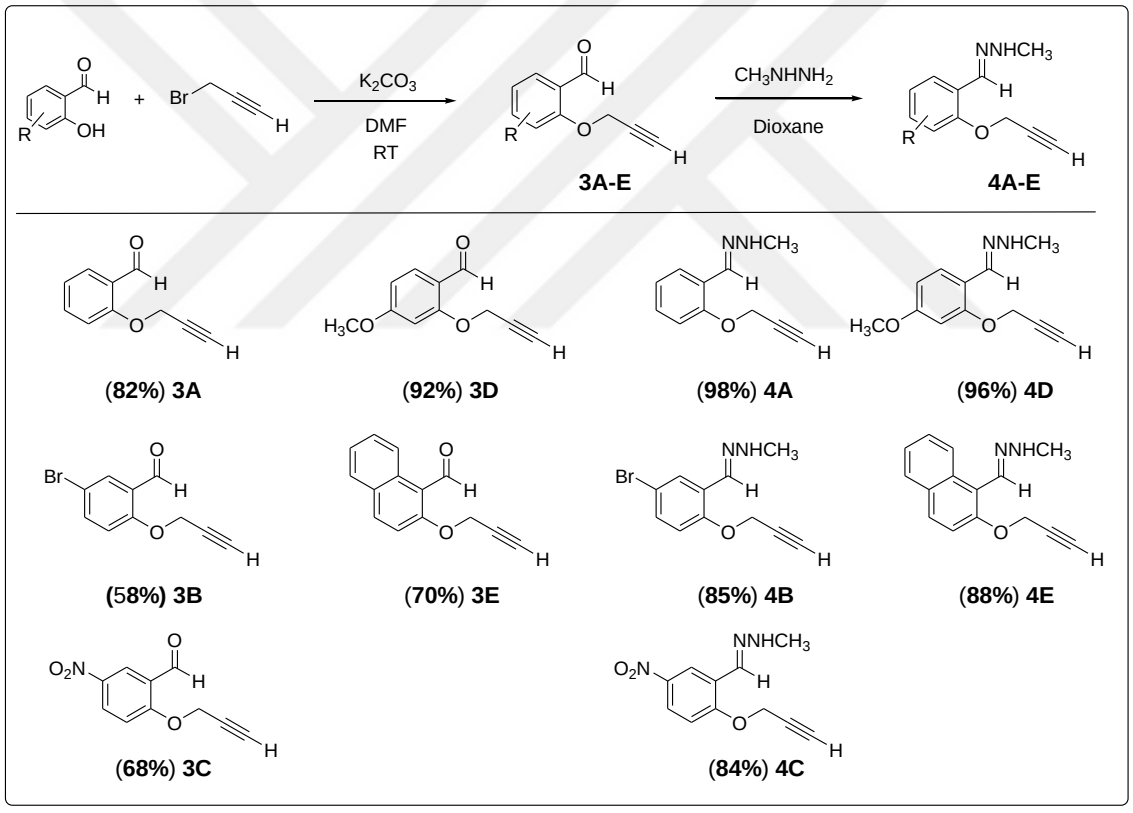

Figure 32. Synthesis of 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazines 4A-E**.**

^{1}H-NMR and ^{13}C-NMR spectra of the 4A-E were recorded in $CDCl_3$ solvent. Aromatic peaks were observed between 7 and 9 ppm. Moreover, acetylenic hydrogens (≡—H) gave rise to shielded hydrogens, or relatively high field chemical shifts for ^{1}H-

NMR. This could be explained by the cylindrical π-π cloud around the carbon-carbon triple bond. The ^{1}H-NMR spectra of 3 and 4 show a high field signal due to the acetylenic hydrogen on the terminal alkyne. The acetylenic protons appear as a singlet at 2.5 ppm. Propargyl groups had also a CH_2 and it was found around 4.8 ppm. Interestingly, CH_2 was also affected by the acetylenic proton, and gave the doublet on the ^{1}H-NMR due to long-range proton-proton couplings (Figure 33). The ^{13}C-NMR signals for propargyl groups of 3 and 4 were shifted up-field between 60 ppm and 80 ppm. After isolation of desired compounds, it was observed that there was a singlet at 3 ppm for methyl's protons ($NHCH_3$), and a singlet at 7.8 ppm for hydrazone's proton (CH=N). Moreover, not only the aldehyde peaks on the ^{1}H-NMR but also the carbonyl peaks on the ^{13}C-NMR were disappeared after condensation reactions between **3** and methyl hydrazine (Figure 34).

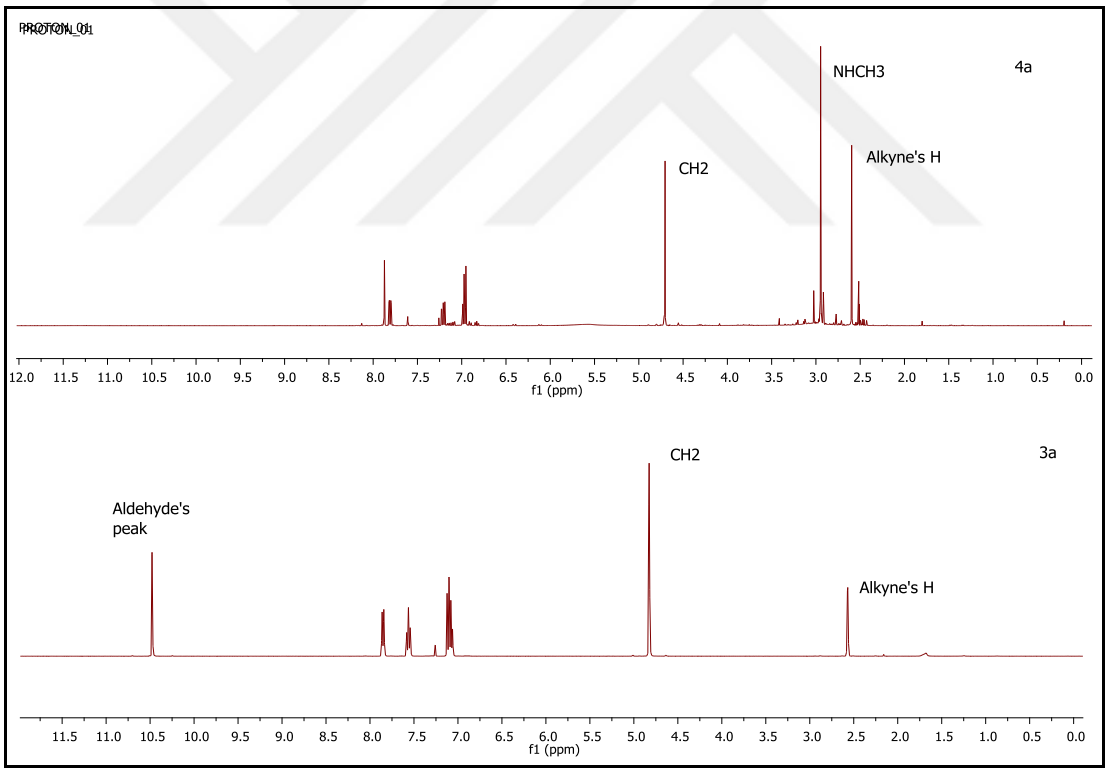

Figure 33. The comparison of ^{1}H NMR Spectra for 2-(prop-2-yn yloxy)benzaldehyde 3A and 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine 4A.

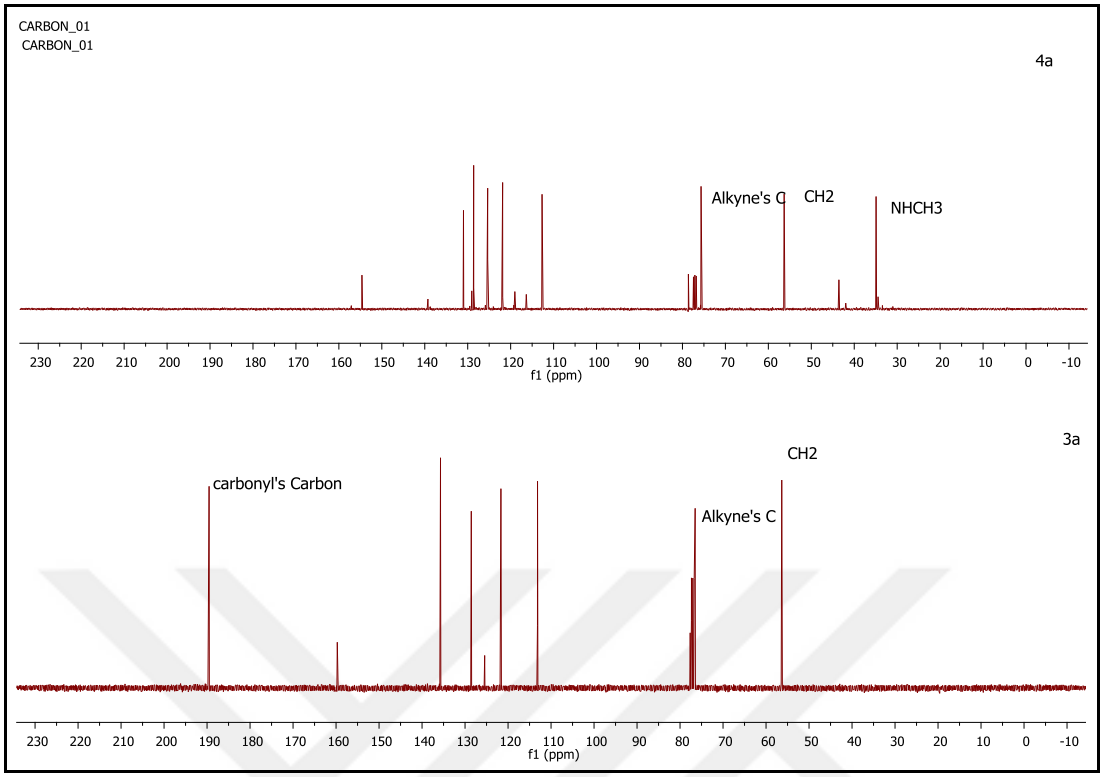

Figure 34. The comparison of ^{13}C NMR Spectra for 2-(prop-2-yn-1-yloxy)benzaldehyde 3A and 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine 4A.

4.2 Antioxidant Capacities

When synthesized structures were analyzed for their electron density, it was observed that the strong electron withdrawing groups for example nitro draws electrons away from the aromatic ring. This is known as polar effect or electronic effect in chemistry. Therefore, electrons of hydrazone's nitrogen atoms were forced to move to the aromatic ring. As a result of polar effect, N-H bond in the structure of hyrazone is weakened which increases the tendency of going under reaction with ABTS molecule. It was observed that more polar hydrazones were more amenable to go under reaction with ABTS compared to less polar ones.

The possible reaction mechanism between ABTS and 4.1 was proposed. Firstly, ABTS was allowed to react with strong oxidant potassium persulfate, its cationic radicalic

intermediates was formed. During this reaction, the colorless neutral form ABTS is converted into its blue/green ABTS radical cation. Then, radical is shifted onto nitrogen atom in-between two aromatic rings of ABTS (4.3). In the next step of the mechanism, there exists a radical type substitution reaction by an interaction of the formed intermediate 4.3 with hydrazone 4, and hereat, colorless $ABTS^{+}$ carbocation form 4.4 is generated. Meanwhile, hydrazone radical 4.5 is obtained mechanistically (Figure 35). The same mechanism pattern is applied for the other derivatives.

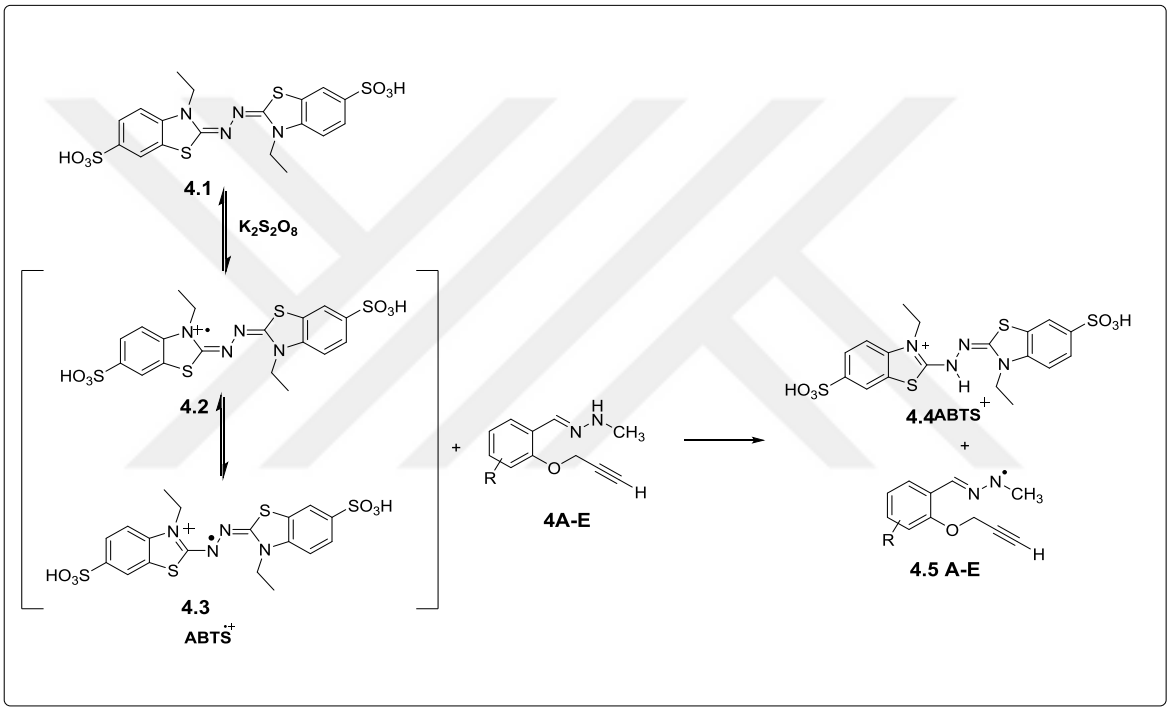

Figure 35. Proposed ABTS cation radical scavanging mechanism of hydrazone derivatives.

All synthesized hydrazone derivatives 4A-E were tested to find the antioxidant capacities. According to the experimental results of ABTS assay, calculated EC_{50} values reveal an order of 4B>4D>4E>4A>4C for all analyzed derivatives. In addition, their antioxidant capacities were found as 4C>4A>4E>4D>4B. The highest antioxidant capacity was measured for structure 4C including strong electron withdrawing nitro (NO_2) group on the aromatic ring. On the other hand, bromo substituted 4B displayed the least antioxidant capacity (Figure 36).

In ABTS assay, the measured antioxidant capacities of hydrazone derivatives were compared with trolox and they were predicated as the ratio of "µg trolox/µg derivated hydrazone". Refering the (Figure 36), while derivatives 4B and 4D could not reach the antioxidant capacity of the general standard of trolox, 4C, 4A and 4E derivatives could surpass this level in different percentages changing between %22 - %68. By exceeding the antioxidant capacity of trolox, those derivatives have a considerable potential to be used in the designing and further derivatization of more biologically active agents.

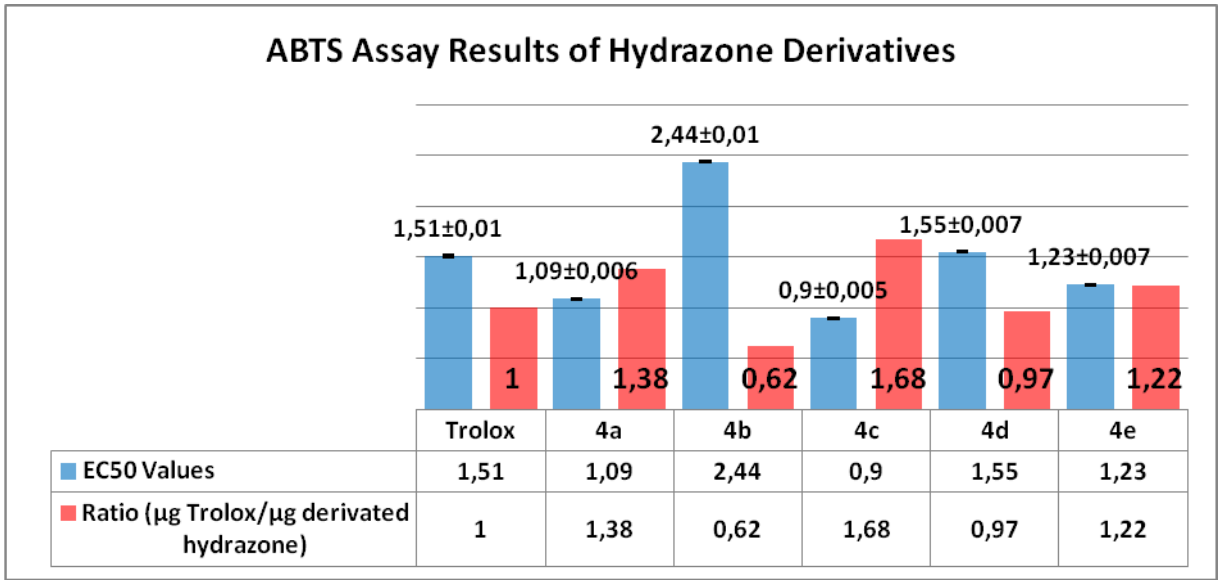

Figure 36. Antioxidant capacities of synthesized hydrazone derivatives. EC_{50} values of derivatives were calculated as the concentration (µg/ml) exhibiting 50% inhibiton of ABTS radical. Each value represents mean ± Standard Deviation (SD). All the measurements were done triplicated.

5. CONCLUSION

In the present study, a novel synthetic route to a variety of 1-Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine 4a-e by the condensation reaction of methyl hydrazine and 2-(Prop-2-yn-1-yloxy)benzaldehydes has been developed. The reaction tolerates a variety of 2-(Prop-2-yn-1-yloxy)benzaldehydes and affords the corresponding hydrazones in good to excellent yields. This methodology provides a useful new route for the synthesis of substituted Methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine, which should have displayed promising antioxidant properties. The EC_{50} values of synthesized compounds were found to increase in the order of 4B> 4D > 4E > 4A> 4C. 4A and 4C were determined as the most potent scavenger of the ABTS•+ cation radical. Such that, the compound 4C showed a considerable degree of antioxidant capacity in a way that it exceeded the level of trolox about 1.7 times higher.

Consequently, these results might help in the development of new anti-oxidative drugs with important pharmaceutical functions by giving the advantage of designing and further derivatization of more biologically active agents.

REFERENCES

Altintop, M. D., Ozdemir, A., Turan-Zitouni, G., Ilgin, S., Atli, O., Iscan, G., Kaplancikli, Z. A., 2012. Synthesis and biological evaluation of some hydrazone derivatives as new anticandidal and anticancer agents. ***European Journal of Medicinal Chemistry,*** **58**: 299-307.

Aydin, S., Kaushik-Basu, N., Arora, P., Basu, A., Nichols, B.D., Talele, T.T., . 2013. Microwave assisted synthesis of some novel flurbiprofen hydrazidehydrazones as anti-HCV NS5B and anti-cancer agents. ***Marmara Pharm J,*** **17**: 26–34.

Bhandari, S.V., Bothara, K.G., Raut, M.K., Patil, A.A., Sarkate, A.P., Mokale, V.J. Design., 2008. synthesis and evaluation of antiinflammatory, analgesic and ulcerogenicity studies of novel S-substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of diclofenac acid as nonulcerogenic derivatives. ***Bioorg Med Chem,*** **16**: 1822–31.

Bingul, M., Tan, O., Gardner, C. R., Sutton, S. K., Arndt, G. M., Marshall, G. M., Cheung, B. B., Kumar, N., Black, D. S., 2016. Synthesis, Characterization and Anti-Cancer Activity of Hydrazide Derivatives Incorporating a Quinoline Moiety. ***Molecules,*** **21** (7): 24-32.

Cano, A., Acosta, M., Arnao, M. B., 2000. A method to measure antioxidant activity in organic media: application to lipophilic vitamins. ***Redox Report,*** **5** (6)*:* 365-370.

Cere, V., Peri, F., Pollicino, S., Ricci, A., 1999. Indium-mediated allylation of the N,N-dimethyl glyoxal mono-hydrazone: One-pot synthesis of bis-homoallyl, and of homoallyl-alkyl 1,2-diols. ***Synlett,*** **10 :** 1585-1587.

Coa, J. C., Castrillon, W., Cardona, W., Carda, M., Ospina, V., Munoz, J. A., Velez, I. D., Robledo, S. M., 2015. Synthesis, leishmanicidal, trypanocidal and cytotoxic activity of quinoline-hydrazone hybrids. ***European Journal of Medicinal Chemistry,*** **101**: 746-753.

Cocco, M. T., Congiu, C., Lilliu, V., Onnis, V., 2006. Synthesis and in vitro antitumoral activity of new hydrazinopyrimidine-5-carbonitrile derivatives. ***Bioorganic & Medicinal Chemistry,*** **14** (2): 366-372.

Dandawate, P., Khan, E., Padhye, S., Gaba, H., Sinha, S., Deshpande, J., 2012. Synthesis, characterization, molecular docking and cytotoxic activity of novel plumbagin hydrazones against breast cancer cells. ***Bioorg Med Chem Lett,*** **22**: 3104–8.

Dawidowicz, A. L.; Olszowy, M., 2013. The importance of solvent type in estimating antioxidant properties of phenolic compounds by ABTS assay. ***European Food Research and Technology****,* **236** (6), 1099-1105.

Enders, D., Lochtman, R., Raabe, G., 1996. Enantioselective synthesis of 1-ferrocenylalkylamines via 1,2-addition of organolithium compounds to ferrocenecarboxaldehyde-SAMP-hydrazone**.** ***Synlett****,* **2***:* 126-128.

Enders, D., Schankat, J., Klatt, M., 1994. Enantioselective synthesis of homoallylamines and beta-amino acids via nucleophilic allylation of samp/ramp-hydrazones. ***Synlett,*** **10***:* 795-797.

Fries, S., Pytkowicz, J., Brigaud, T., 2005. Highly diastereoselective addition of organometallic reagents to a trifluoroacetaldehyde hydrazone derived from (R)-N-benzylphenylglycinol. ***Tetrahedron Letters,*** **46** (28): 4761-4764.

Gurkok, G., Altanlar, N., Suzen, S., 2009. Investigation of Antimicrobial Activities of Indole-3-Aldehyde Hydrazide/Hydrazone Derivatives. ***Chemotherapy,*** **55** (1): 15-19.

Kaplanek, R., Havlik, M., Dolensky, B., Rak, J., Dzubak, P., Konecny, P., Hajduch, M., Kralova, J., Kral, V., 2015. Synthesis and biological activity evaluation of hydrazone derivatives based on a Troger's base skeleton. ***Bioorganic & Medicinal Chemistry,*** **23** (7): 1651-1659.

Khoshkholgh, M. J., Balalaie, S., Gleiter, R., Rominger, F., 2008. Intramolecular hetero-Diels-Alder reaction of 1-oxa-1,3-butadienes with terminal acetylenes in aqueous media using CuI. ***Tetrahedron,*** **64** (48): 10924-10929.

Kivrak, A., Larock, R. C., 2010. Synthesis of Dihydrobenzisoxazoles by the 3+2 Cycloaddition of Arynes and Oxaziridines. ***Journal of Organic Chemistry,*** **75** (21)*:* 7381-7387.

Kulandasamy, R., Adhikari, A.V., Stables, J.P., 2009. A new class of anticonvulsants possessing 6 Hz activity: 3,4-dialkyloxy thiophene bishydrazones. ***Eur J Med Chem,*** **44**: 4376–84.

Lane, D. J. R., Mills, T. M., Shafie, N. H., Merlot, A. M., Moussa, R. S., Kalinowski, D. S., Kovacevic, Z., Richardson, D. R**.,** 2014. Expanding horizons in iron chelation and the treatment of cancer: Role of iron in the regulation of ER stress and the epithelial-mesenchymal transition. ***Biochimica Et Biophysica Acta-Reviews on Cancer,*** **1845** (2)*:* 166-181.

Le goff, G., Ouazzani, J., 2014. Natural hydrazine-containing compounds: Biosynthesis, isolation, biological activities and synthesis. ***Bioorganic & Medicinal Chemistry,*** **22** (23): 6529-6544.

Liu, Y. F., Teng, Q., Hu, J. F., Sun, R. F., Zhang, H., 2016. Ferrocenyl-based unsymmetrical azines as multisignaling sensors for Hg2+, Cu2+ in aqueous environment. ***Sensors and Actuators B-Chemical,*** **234***:* 680-690.

Macdonald-wicks, L. K., Wood, L. G., Garg, M. L., 2006. Methodology for the determination of biological antioxidant capacity in vitro: a review. ***Journal of the Science of Food and Agriculture,*** **86** (13): 2046-2056.

Maia, R. D., Tesch, R., Fraga, C. A. M., 2014. Acylhydrazone derivatives: a patent review. ***Expert Opinion on Therapeutic Patents,*** **24** (11): 1161-1170.

Mohanraj, M., Ayyannan, G., Raja, G., Jayabalakrishnan, C., 2016. Evaluation of DNA binding, DNA cleavage, protein binding, radical scavenging and in vitro cytotoxic activities of ruthenium(II) complexes containing 2,4-dihydroxy benzylidene ligands. Materials ***Science & Engineering C-Materials for Biological Applications,*** **69**: 1297-1306.

Montagnat, O. D., Lessene, G., Hughes, A. B., 2006. Synthesis of azide-alkyne fragments for 'click' chemical applications formation of oligomers from orthogonally protected trialkylsilyl-propargyl azides and propargyl alcohols. ***Tetrahedron Letters,*** **47**(39): 6971-6974.

Montenegro, R. C., Lotufo, L. V., de Moraes, M. O., Pessoa, C. D., Rodrigues, F. A. R., Bispo, M. D. F., Cardoso, L. N. D., Kaiser, C. R., de Souza, M. V. N., 2011. Synthesis and Antitumoral Evaluation of 7-chloro-4-quinolinylhydrazones Derivatives. ***Medicinal Chemistry,*** **7** (6): 599-604.

Narang, R., Narasimhan, B., Sharma, S., 2012. A Review on Biological Activities and Chemical Synthesis of Hydrazide Derivatives. ***Current Medicinal Chemistry,*** **19** (4): 569-612.

Navidpour, L., Shafaroodi, H., Saeedi-Motahar, G., Shafiee, A., 2014. Synthesis, anti-inflammatory and analgesic activities of arylidene-2-(3-chloroanilino)nicotinic acid hydrazides. ***Medicinal Chemistry Research,*** **23** (6): 2793-2802.

Oliveira, K.N., Costa, P., Santin, J.R., Mazzamban,i L., Bürger, C., Mora, C., et al., 2011. Synthesis and antidepressant-like activity evaluation of sulphonamides and sulphonyl-hydrazones. ***Bioorg Med Chem,*** **19**: 4295–306.

Onnis, V., Demurtas, M., Deplano, A., Balboni, G., Baldisserotto, A., Manfredini, S., Pacifico, S., Liekens, S., Balzarini, J., 2016. Synthesis and Evaluation of Antiproliferative Activity of New Benzimidazolehydrazones. ***Molecules,*** **21** (5): 254-254**.**

Pathak, R. B., Chovatia, P. T., Parekh, H. H., 2012. Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlorophenyl)-4-substituted pyrazole derivatives. ***Bioorganic & Medicinal Chemistry Letters,*** **22** (15): 5129-5133.

Pinheiro, A. C., Kaiser, C. R., Nogueira, T. C. M., Carvalho, S. A., da Silva, E. F., Feitosa, L. D., Henriques, M., Candea, A. L. P., Lourenco, M. C. S., de Souza, M. V. N., 2011. Synthesis and Antitubercular Activity of New L-serinyl Hydrazone Derivatives. ***Medicinal Chemistry,*** **7** (6): 611-623.

Rahmouni, A., Souiei, S., Belkacem, M. A., Romdhane, A., Bouajila, J., Ben Jannet, H., 2016. Synthesis and biological evaluation of novel pyrazolopyrimidines derivatives as anticancer and anti-5-lipoxygenase agents. ***Bioorganic Chemistry,*** **66**: 160-168.

Rajitha, G., Saideepa, N., Praneetha, P., 2011. Synthesis and evaluation of N-(alpha-benzamido cinnamoyl) aryl hydrazone derivatives for anti-inflammatory and antioxidant activities**.** ***Indian Journal of Chemistry Section B-Organic Chemistry Including Medicinal Chemistry*****, 50** (5): 729-733.

Rea, R., Pellegrinia, N., Proteggentea, A., Pannalaa, A., Yanga, M., Rice-Evansa, C., 1999. Antioxidant activity applying an improved ABTS radical cation decolorization assay, ***Free Radical Biology and Medicine,*** **26** (9–10): 1231–1237.

Rhoda, H. M., Chanawanno, K., King, A. J., Zatsikha, Y. V., Ziegler, C. J., Nemykin, V. N., 2015. Unusually Strong Long-Distance Metal-Metal Coupling in

Bis(ferrocene)-Containing BOPHY: An Introduction to Organometallic BOPHYs. ***Chemistry-a European Journal,*** **21** (50): 18043-18046.

Rodrigo, J., Fernandez, A. P., Serrano, J., Peinado, M. A., Martinez, A., 2005. The role of free radicals in cerebral hypoxia and ischemia. ***Free Radical Biology and Medicine,*** **39** (1): 26-50.

Rollas, S., Kucukguzel, S. G., 2007. Biological activities of hydrazone derivatives. ***Molecules,*** **12** (8): 1910-1939.

Salgin-gökşen, U., Gökhan-Kelekçi, N., Yabanoglu-Çiftci, S., Yelekçi, K., Uça,r G., 2013. Synthesis, molecular modeling, and *in vitro* screening of monoamine oxidase inhibitory activities of some novel hydrazone derivatives. ***J Neural Transm,*** **120**: 883–91.

Sato, M., Bremner, I., 1993. Oxygen free-radicals and metallothionein. ***Free Radical Biology and Medicine,*** **14** (3): 325-337.

Schroder, H., Haslinger, E., 1994. Long-range proton spin-spin coupling in rigid cyclic structures by 2d nmr through-space coupling. ***Magnetic Resonance in Chemistry,*** **32** (1): 12-15.

Serafini, M., Del Rio, D., 2004. Understanding the association between dietary antioxidants, redox status and disease: is the Total Antioxidant Capacity the right tool? ***Redox Report,*** **9** (3): 145-152.

Shirinzadeh, H., Altanlar, N., Yucel, N., Ozden, S., Suzen, S., 2011. Antimicrobial Evaluation of Indole-Containing Hydrazone Derivatives. ***Zeitschrift Fur Naturforschung*** **Section C66** (7-8): 340-344.

Siddiqui, S.M., Salahuddin, A., Azam, A., 2012. Synthesis, characterization and antiamoebic activity of some hydrazone and azole derivatives bearing pyridyl moiety as a promising heterocyclic scaffold. ***Eur J Med Chem,*** **49**: 411–6.

Sonar, V. N., Crooks, P. A., 2009. Synthesis and antitubercular activity of a series of hydrazone and nitrovinyl analogs derived from heterocyclic aldehydes. ***Journal of Enzyme Inhibition and Medicinal Chemistry,*** **24** (1): 117-124.

Sondhi, S. M., Dinodia, M., Kumar, A., 2006. Synthesis, anti-inflammatory and analgesic activity evaluation of some amidine and hydrazone derivatives. ***Bioorganic & Medicinal Chemistry,*** **14** (13): 4657-4663.

Su, X., Aprahamian, I., 2014. Hydrazone-based switches, metallo-assemblies and sensors. ***Chemical Society Reviews,* 43** (6): 1963-1981.

Tatum, L. A., Su, X., Aprahamian, I., 2014. Simple Hydrazone Building Blocks for Complicated Functional Materials. ***Accounts of Chemical Research,* 47** (7): 2141-2149.

Vedachalam, S., Wong, Q. L., Maji, B., Zeng, J., Ma, J. M., Liu, X. W., 2011. N-Heterocyclic Carbene Catalyzed Intramolecular Hydroacylation of Activated Alkynes: Synthesis of Chromones. ***Advanced Synthesis & Catalysis,* 353** (2-3): 219-225.

Wang, H., Ren, S. X., He, Z. Y., Wang, D. L., Yan, X. N., Feng, J. T., Zhang, X., 2014. Synthesis, Antifungal Activities and Qualitative Structure Activity Relationship of Carabrone Hydrazone Derivatives as Potential Antifungal Agents. ***International Journal of Molecular Sciences,* 15** (3): 4257-4272.

Werengowska-ciecwierz, K., Wisniewski, M., Terzyk, A. P., Furmaniak, S., 2015. The Chemistry of Bioconjugation in Nanoparticles-Based Drug Delivery System. ***Advances in Condensed Matter Physics***.

Yang, Y., Gao, C. Y., Liu, J. L., Dong, D. W., 2016. Recent developments in rhodamine salicylidene hydrazone chemosensors. ***Analytical Methods,* 8** (14): 2863-2871.

Zora, M., Demirci, D., Kivrak, A., Kelgokmen, Y., 2016. One-pot synthesis of 4-(phenylselanyl)-substituted pyrazoles. ***Tetrahedron Letters,* 57** (9): 993-997.

Zora, M., Kivrak, A., 2011. Synthesis of Pyrazoles via Cul-Mediated Electrophilic Cyclizations of alpha,beta-Alkynic Hydrazones. ***Journal of Organic Chemistry,* 76** (22): 9379-9390.

Zora, M., Kivrak, A., Yazici, C., 2011. Synthesis of Pyrazoles via Electrophilic Cyclization. ***Journal of Organic Chemistry,* 76** (16): 6726-6742.

APPENDIX INDEX

EXTENDED TURKISH SUMMARY

(GENİŞLETİLMİŞ TÜRKÇE ÖZET)

ÖZET

2-(PROP-2-İN-1-İLOKSİ)BENZALDEHİT METİLHİDRAZON TÜREVLERİNİN SENTEZİ ve ANTİOKSİDANT KAPASİTELERİ

Bu çalışmada, 2-(prop-2-yn-1-yloxy)benzaldehyde ve metilhidrazin kondenzasyon tepkimesine sokularak 1-methyl-2-(2-(prop-2-yn-1-yloxy)benzylidene)hydrazine türevleri yüksek verimler ile sentezlenmiştir. Tepkime yapısında nitro-, halo-, metoksi, naftil gibi substituentleri bulunduran yapıların elde edilmesi içinde kullanılarak, yeni türevlerin sentezide gerçekleştirilmiştir. Elde edilen yapıların *in vitro* antioksidant kapasiteleri bulunmuştur. Bulunan sonuçlara göre 1-metil-2-(5-nitro-2-(prop-2-in-1-iloksi)benzilidin)hidrazin (4c), yapısı referans olarak alınan troloksa göre 1.7 kez daha aktivite göstermiştir.

Anahtar kelimeler: Antioksidant kapasitesi, Biyolojik özellikler, Hidrazinler, hidrazonlar.

2. MATERYAL VE YÖNTEM

2.1. Materyal

2.1.1. Deneyde kullanılan kimyasal maddeler

Deneylerde kullandığımız kimyasalların ticari olarak satılan türevleri Merck, Aldrich-Sigma, TCI ve VWR gibi şirketlerden temin edilmiştir. Ayrıca saflaştırma işlemlerinde (ekstraksiyon, kolon kromotografisi vb.) ve organik preparatların hazırlanmasında, organik kimyada çözücü olarak kullanılan çok çeşitli organik çözücüler denenmiş ve bunlardan birçoğu kullanılmıştır. Deneylerde kulllanılan cam malzemelerin tamamı aseton ile temizlenerek kurutulmuştur. Ayrıca inert gaz gerektiren deneylerimiz için Argon gazı kullanılmıştır.

2.1.2. Deneyde faydalanılan araç ve cihazlar

Tepkimeler Heidolph MR-Hei Standart marka magnetik ısıtıcılı karıştırıcılarda gerçekleştirilmiştir. Tepkime ve saflaştırma işlemleri sonunda organik çözücülerin düşük vakum altında uzaklaştırılması için IKA HB10 marka Rotary evaporatör kullanılmıştır.

Yapısal karakterizasyon için Agilent NMR (400 MHz) spektrometresinden yararlanılmıştır. Kimyasal kayma değerleri TMS referans çözücüsüne göre ppm olarak verilmiştir. Yapılardaki yarılma değerleri Hertz olarak hesaplanmış ve pikler singlet (s), doublet (d), tritlet (t), quartet (q) ve multiplet (m) olarak kısaltılmıştır. Flash kolon kromatografisi için Merck 230-400 mesh silika jel kullanılmıştır. Tepkimeler ve saflaştırma sırasında ürünlerin takip edilmesi için ticari olarak satın alınan İnce Tabaka Kromotografisi kullanılmış, kısa dalga boyunda UGVL-58 Handheld UV Lamb ile analiz edilmiştir. Infrared analizleri Yüzüncü Yıl Üniversitesi Merkezi Araştırma Laboratuvarında yapılmıştır.

2.2. Yöntem

Çalışmamızda tasarladığımız küçük moleküllerin sentezi ve antioksidant kapasiteleri aşağıdaki yöntemlere göre gerçekleştirilmiştir.

2.2.1. 2-(Prop-2-iniloksi) benzaldehit türevlerinin sentezi

2-Hidroksibenzaldehit (10 mmol) dimetilformamit içerisinde çözülür. Daha sonra üzerine 3-Bromoprop-1-in (1.5 kat) ve potasyum karbonat (1 kat) oda sıcakığında eklenir. Elde edilen karışım oda sıcaklığında ve inert gaz ortamında karıştırılır. Tepkime tamamlandıktan sonra karışım 0^0C soğutulur, oluşan ürünün kristallenmesi sağlanır ve süzülerek su ile yıkanarak istenilen ürün elde edilir.

2-(Prop-2-in-1-iloksi)benzaldehit (3A): (Verim: 82%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H,), 7.87 (d, *J* = 7.7 Hz; 1H), 7.57 (m, 1H), 7.11 (m, 1H), 4.83 (s, 2H, CH_2), 2.58 (s, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.5, 159.7, 135.7, 128.6, 125.4, 121.7, 113.2, 77.6, 76.5, 56.3. IR (ATR) 3268, 2873, 2116, 1679, 1581, 1480, 1456, 1329, 1286, 1220, 1006, 755, 675.

5-Bromo-2-(prop-2-in-1-iloksi)benzaldehit (3B): (Verim: 58%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 , 7.93 (d, *J* = 2.4 Hz, 1H), 7.63 (dd, *J* = 8.8 ve 2.5 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 4.81 (s, 2H, CH_2), 2.58 (t, *J* = 2.4 Hz, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.1, 158.6, 138.1, 131.1, 126.7, 115.3, 114.6, 77.3, 76.9, 56.6. IR (ATR) 3234 (asetilenik H), 2883, 2118 , 1681 , 1589, 1479, 1406, 1329, 1286, 1219, 1018, 880, 691.

5-Nitro-2-(prop-2-in-1-iloksi)benzaldehit (3C): (verim: 68%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.69 (m, 1H), 8.43 (dt, *J* = 9.2 ve 2.5 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 4.97 (s, 2H, CH_2), 2.66 (t, *J* = 2.4 Hz, 1H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 163.3, 142.1, 130.3, 125.1, 124.6, 113.7, 77.9, 76.2, 57.1. IR (ATR) 3240, 2887, 2114 ,1661 , 1575, 1480, 1412, 1315, 1286, 1219, 1018, 885, 705.

4-Metoksi-2-(prop-2-in-1-iloksi)benzaldehit (3D): (Verim: 92%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 7.45 (m, 1H), 7.16 (m, 2H), 4.87 (s, 2H, CH_2),

3.88 (s, 3H, OMe), 2.47 (s, 1H,); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 152.8, 152.6, 131.2, 124.9, 118.8, 117.6, 78.2, 76.9, 60.8, 56.0. IR (ATR) 3281, 2936, 2119, 1688, 1588, 1472, 1412, 1345, 1273, 1062, 1065, 990, 785.

2-(Etinilooksi)-1-naftilaldehit (3E): (Verim; 70%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.9 (s, 1H), 9.27 (d, *J* = 8.7 Hz, 1H), 8.07 (m, 1H), 7.80 (m, 1H), 7.63 (m, 1H), 7.44 (m, 1H), 7.37 (m, 1H), 4.94 (s, 2H, CH_2), 2.77 (t, *J* = 2.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 161.9, 137.3, 131.4, 129.9, 129.1, 128.2, 125.2, 125.1, 118.0, 113.9, 77.6, 76.7, 57.4. IR (ATR) 3258, 2966, 2123, 1696, 1495, 1363, 1177, 1227, 1062, 1001, 985, 740.

2.2.2. 1-Metil-2-(2-(prop-2-in-1-iloksi)benziliden)hidrazin türevlerinin Sentezi

2-(Prop-2-iniloksi)benzaldehit (3A) (0.5 mmol) 2 mL dioksan çözücüsü içerisinde çözülür. Daha sonra üzerine 2 mL metil hidrazin oda sıcaklığında ilave edilir. Karışım inert gaz ortamında karıştırılarak tepkimenin tamamlanması sağlanır. Tepkime bittikten sonra çözücü düşük basınç altında uzaklaştırılarak, kalan organik karışım kısa bir kolon yardımıyla saflaştırılarak tek ürün olan hidrazon elde edilir.

1-Metil-2-(2-(prop-2-in-1-iloksi)benziliden)hidrazin (4A): (Verim; 98%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H, CH=N), 7.81 (dd, *J* = 8.0 ve 1.9 Hz, 1H), 7.20 (m, 1H), 6.97 (m, 2H), 5.60 (brs, 1H, NH), 4.70 (d, *J* = 2.4 Hz, 2H, CH_2), 2.94 (s, 3H, $NHCH_3$), 2.59 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 139.2, 130.9, 128.6, 125.3, 121.8, 112.7, 78.6, 75.7, 56.3, 34.9. IR (ATR) 3284, 2960, 2866, 2793, 2116, 1600, 1483, 1463, 1223, 1098, 1021, 762.

1-(5-Bromo-2-(prop-2-in-1-iloksi)benziliden)-2-metilhidrazin (4B): (Verim; 85%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 2.5 Hz, 1H), 7.72 (s, 1H, CH=N), 7.28 (dd, *J* = 8.7 ve 2.5 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 4.70 (d, *J* = 2.4, 2H, CH_2), 2.96 (s, 3H, $NHCH_3$), 2.52 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 136.9, 130.8, 128.6, 127.8, 118.2, 114.5, 78.1, 76.0, 56.5, 34.7. IR (ATR) 3290 , 2980, 2920, 2797, 2120, 1594, 1475, 1406, 1224, 1115, 1020, 799, 633.

1-Metil-2-(5-nitro-2-(prop-2-in-1-iloksi)benziliden)hidrazin (4C): (Yield: 84%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (m, 1H), 8.07 (m, 1H), 7.68 (s, 1H, CH=N) 7.04 (m, 1H), 5.93 (brs, 1H, NH), 4.83 (s, 2H, CH_2), 3.00 (s, 3H, $NHCH_3$), 2.58 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 142.5, 126.8, 123.4, 123.0, 120.9, 111.9, 77.2, 76.8, 56.5, 34.4. IR (ATR) 3280, 2940, 2915, 2788, 2117, 1601, 1455, 1450, 1232, 1145, 1060, 787, 702.

1-(4-Methoksi-2-(prop-2-in-1-iloksi)benziliden)-2-metilhidrazin (4D) (Verim; 96%) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H, CH=N), 7.42 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.04 (td, *J* = 8.0 ve 0.5 Hz, 1H), 6.80 (dd, *J* = 8.02 ve 1.4 Hz, 1H), 4.71 (d, *J* = 2.5 Hz, 2H, CH_2), 3.84 (s, 3H), 2.98 (s, 3H, $NHCH_3$), 2.97 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 131.5, 130.9, 124.7, 116.8, 111.1, 79.4, 75.5, 60.3, 55.7, 34.7. IR (ATR) 3400, 3281, 2936, 2838, 2796, 2119, 1588, 1472, 1437, 1302, 1273, 1065, 990, 743.

1-Metil-2-((2-(prop-2-in-1-iloksi)naftalen-1-il)metilen)hidrazin (4E) (Verim; 88 %) : ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (d, *J* = 8.7 Hz, 1H), 8.28 (s, 1H, CH=N), 7.78 (m, 1H), 7.76 (m, 1H), 7.51 (m, 1H), 7.38 (m, 1H), 7.32 (d, *J* = 9 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 2H, CH_2), 3.09 (s, 3H, $NHCH_3$), 2.52 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 136.5, 133.5, 129.8, 128.1, 127.2, 126.7, 126.2, 124.3, 122.9, 114.8, 78.7, 75.8, 57.7, 35.4. IR (ATR) 3291, 2956, 2865, 2775, 2114, 1577, 1475, 1445, 1377, 1272, 1066, 995, 756.

2.2.3 Antioksidant Kapasite ölçümleri (ABTS Assay)

Absorbans için hazırlanan standart ve sentezlenen ürünler için ölçümler metanol ve ABTS içeren tüplerde gerçekleştirilmiş, ve 734 nm dalga bogunda ölçümler alınmıştır. Tüm ölçümler en az üç kez tekrarlanarak yapılmıştır. Standart olarak Troloks kullanışmıştır.

The percentage of radikal yakalama kapasite yüzdezi aşağıda verilen eşitliğe göre hesaplanmıştır. numune absorbansı

$$\text{radikal yakalama kapasitsı}\,(\%) = \frac{\text{Kontrol absorbansı} - \text{numune absorbansı}}{\text{Kontrol absorbansı}}\, x100$$

3. SONUÇ

Heteroatom içeren yeni moleküllerin tasarımı ve sentezi son yıllarda büyük önem kazanmıştır. Bu çalışmamızda, In the present study, geliştirdiğimiz yeni yöntem ile farklı 1-metil-2-(2-(prop-2-in-1-iloksi)benziliden)hidrazin 4A-E türevleri sentezlenmiştir. buna göre 2-(prop-2-iniloksi)benzaldehit ile metilhidrazin arasında kondenzasyon tepkimesi gerçekleştirilerek ürün elde edilmiştir. Tepkime yapısında farklı substitüentler bulunan türevlerin elde edilmesi içinde kullanılmış ve oldukça yüksek verimler ile istenilen ürünler sentezlenmiştir.

Sentezlenen bu yeni 1-metil-2-(2-(prop-2-in-1-iloksi)benziliden)hidrazin türevlerinin antioksidant kapasiteleri bulunmuştur. Sentezlenen EC50 değerleri kıyaslandığında 4B> 4D > 4E > 4A> 4C gibi bir sıralama elde edilmiştir. Buna göre 4A ve 4C ABTS•+ katyonic radikali ile en iyi etkileşime giren yapılardır. Bu yapılardan 4C referans maddemiz olan troloksa göre 1.7 kat daha yüksek antioksidant kapasiteye sahip hidrazon türevidir.

Sonuç olarak, elde edilen bulgular ışığında sentezlenen yapıların yeni nesil anti-oksidatif ilaç olma potansiyellerinin olduğu bulunmuştur. Buna göre gelecekte yeni türevlerinin sentezlenerek veya bu yapıların biyolojik aktivitesi bilinen yapılar ile birleştirilerek önemli biyolojik özellikler kazandırılma potasiyeline sahip olduğunuda söyleyebiliriz.

CURRICULUM VITAE

Jeger Ali OAGAZ

…….……. Personal Information

Email: Jegar.oagaz@soran.edu.iq
Phone Number: +964(0)7504952401
Address: Herir,Shaqlawa, Erbil, Iraq
Birthday: 01/12/1986
Marital Status: Single

……..…….. Educational Background

2005 – 2009
University Of Duhok
College of Education Sciences
Chemical department
(B.Sc.) Bachelor's Degree in Chemistry

UNIVERSITY OF YUZUNCU YIL
THE INSTITUTE OF NATURAL AND APPLIED SCIENCES
THESIS ORIGINALITY REPORT

Date: 31/05/2017

SYNTHESIS OF 2-(PROP-2-YN-1-YLOXY)BENZALDEHYDE METHYLHYDRAZONE DERIVATIVES AND THEIR ANTIOXIDANT CAPACITIES

The title of the mentioned thesis, above having total 49 pages with cover page, introduction, main parts and conclusions , has been checked for originality by TURNITIN computer program on the date 31/05/2017 and its detected similar rate was 11% according to the following specified filtering originality report rules:

Excluding the Cover page.
Excluding the Thanks.
Excluding the Contents.
Excluding the Symbols and Abbreviations.
Excluding the Materials and Methods.
Excluding the Bibliography.
Excluding the Citations.
Excluding the publications obtained from the thesis.
Excluding the text parts less than 7 words (Limit match size to 7 words).

I read the Thesis Originality Report Guidelines of Yuzuncu Yil University for Obtaining and Using Similarity Rate for the thesis, and I declare the accuracy of the information I have given above and my thesis does not contain any plagiarism; otherwise I accept legal responsibility for any dispute arising in situations which are likely to be detected.

Sincerely yours,

31/05/2017
Date and signature

Name and Surname:	Jeger Ali OAGAZ
Student ID:	149102335
Science:	Chemical Science
Program:	Thesis
Statute: M.Sc.	X ph.D. ☐

APPROVAL OF SUPERVISOR

SUITABLE

Assoc. Prof. Dr. Arif KIVRAK

APPROVAL OF THE INSTITUTE

SUITABLE

Prof.Dr.Sabit ŞENSOY
Enstitü Müdürü