VIỆN HÀN LÂM KHOA HỌC VÀ CÔNG NGHỆ VIỆT NAM
VIETNAM ACADEMY OF SCIENCE AND TECHNOLOGY

TẠP CHÍ HÓA HỌC

ISSN 0866-7144

2015

SYNTHESIS OF SOME NEW HYDRAZONES CONTAINING FUROXAN RING FROM EUGENOL

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Received 15 December 2014; Accepted for Publication 18 May 2015

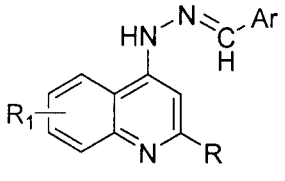
Abstract

Hydrazones have been shown to have wide range of biological activities such as anti cancer, anti fungus... In this paper, several new hydrazones containing furoxan ring were synthesized from eugenol (l-hydroxy-2-methoxy-4-allylbenzene) that is the main constituent of *Ocimum sanctum L.* oil. Reduction of diazonium salt **4** gave aryl hydrazine derivative **5** containing furoxan ring. The condensation of the hydrazine with ketones or aldehydes such as cinnamaldehyde, 2,4- dihydroxybenzaldehyde, 4-pyridinecarboxaldehyde, 2-(5-formyl-6-hydroxy-3-sulfoquinolin-7-yloxy)acetic acid, cyclohexanone, cycloheptanone, butanone, and acetyl acetone in acidic catalysis gave hydrazones **6-13** in moderate to high yield. Especially, the three component reaction of hydrazine **5**, formaldehyde, and diazonium salt **4** gave hydrazone **14**. These hydrazone structures were proved by IR, NMR spectra data. Molecular weight of hydrazone **6**, **9** and **14** were proved by MS spectra as well.

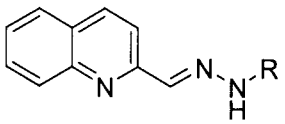
Keywords. hydrazone, furoxan, *Ocimum sanctum L*, eugenol.

1. INTRODUCTION

Hydrazones, a condensed product of hydrazine derivatives and aldehydes or ketones, have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflam matory, antiplatelet, antitubercular and antitumoral activities. Some selected examples are shown below.



I



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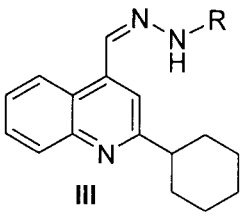
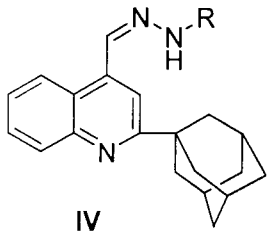


III



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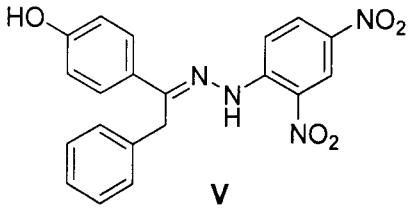
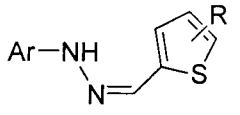


V



VI

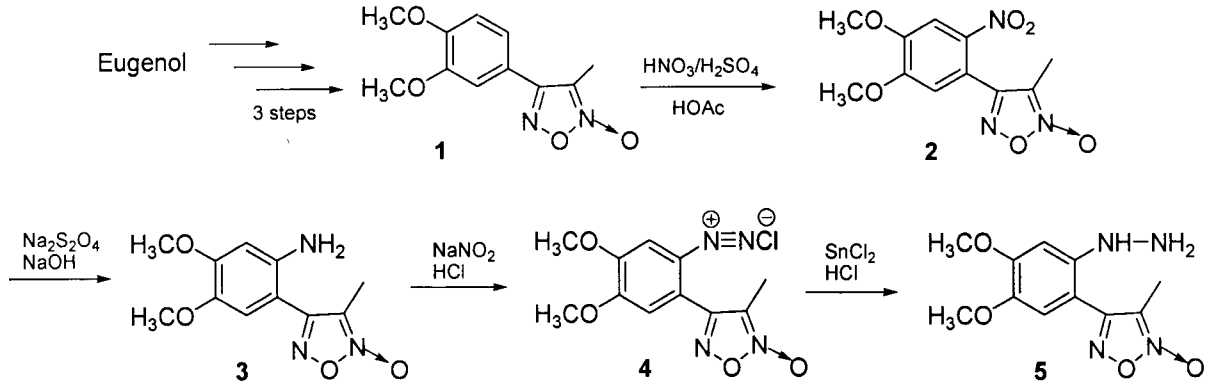
A series of 4-quinolylhydrazones **I** were synthesized and tested against *M. tuberculosis* 37Rv. Most of the derivates had antitubercular properties in which two compounds were identified with the highest activity and they were tested also against *M. avium* [1]. In 2006 Nayyar *et al.* found that the most

active compounds of type **II**, **III**, and **IV** exhibited 99% inhibition at the lowest tested concentration of 3.125 μg/mL against drug-sensitive *M.tuberculosis* H37 strain [2].

The search for antitumoral drugs led to the discovery of several hydrazones. Some of diphenolic hydrazones showed maximum uterotrophic inhibition of 70 %, whereas compound **V** exhibited cytotoxicity in the range of 50-70 % against MCF-7 and ZR-75-1 human malignant breast cell lines [3]. Some recently synthesized compounds were found to possess antiproliferative properties. The most active compounds of the series were 3- and 5-methylthiophene-2-carboxaldehyde α-(*N*)-heterocyclichydrazones derivatives **VI**, which exhibited tumor growth inhibition activity against all cell lines at GI50 values between 1.63 and 26.5 μM [4].

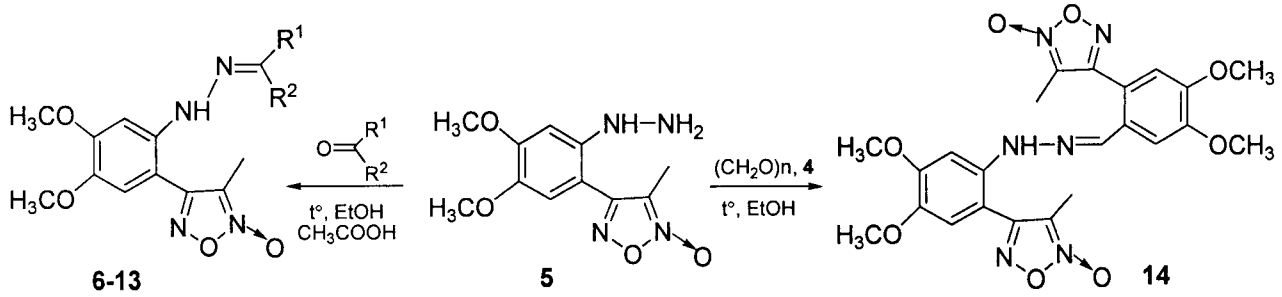
Recently, some *N*-arylidene[5-(methoxymethyl)-4-phenyl-1,2,4-triazole-3-ylsunfanyl] acetohydrazides were synthesized and found to have good activity against *E. coli* [5].

On account of the above results, together with our previous researches, an effort to obtain new hydrazones from inexpensive natural starting material prompted us to prepare the new compounds with high biological activity. The furoxan **1** was synthesized from eugenol in three steps. Nitration of compound **1** following reduction of nitro compound **2** gave an aniline derivative **3**. Peter Griess reaction converted the aniline **3** to diazonium salt **4** that was reduced with stannous chloride to give hydrazine **5** (scheme 1) [6].



Scheme 1: Synthesis of 3-methyl-4-(2-amino-4,5-dimethoxyphenyl)furoxan (**3**) [6]

The hydrazine **5** was condensed with various aldehydes and ketones to give 9 hydrazones as the following scheme 2.



Scheme 2: Synthesis of hydrazones

2. EXPERIMENTAL

Solvents and other chemicals were purchased from Sigma-Aldrich or Merck and were used as received otherwise indicated. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 500 NMR spectrometer in d_3-$CDCl_3$, d_6-DMSO. Chemical shift data for each signal were reported in ppm units with tetramethyl silane (TMS) as internal reference, where δ_{TMS} is 0. MS analyses were achieved with a Control micro-GC (Walter).

General procedure for synthesis of hydrazones

To a solution of 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (1.0 mmol) and aldehyde or ketone (1.2 mmol) in ethanol (20 mL)

was added 2-3 drops of acetic acid. The resulting solution was refluxed for 4 h. The solution was cooled down to room temperature with an ice bath. The solid was filtered and re-crystallized in associated solvents.

1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]-2-[(E)-3-phenylallylidene]hydrazine (6)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and cinnamaldehyde (0.151 mL, 1.2 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 78 % as yellow needle (0.296 g, mp. 145-6 °C) after re crystallized in EtOH/$CHCl_3$:(3/1).

1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]-2-[2,4-dihydroxylphenylidene]hydrazine (7)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and 2,4-dihydroxybenzaldehyde (0.165 g, 1.2 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 66 % as yellow needle (0.254 g, mp. 178-9 °C) after re crystallized in EtOH/$CHCl_3$:(2/1).

1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]-2-[(pyridin-4-yl)methylidene]hydrazine (8)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and 4-pyridinecarboxaldehyde (0.112 mL, 1.2 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 56 % as yellow needle (0.2 g, mp. 184-5 °C) after recrystallized in EtOH/$CHCl_3$:(2/1).

***2-[(7-carboxymethoxy-6-hydroxy-3-sulfoquinolin-5-yl)methylidene]-1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]hydrazine* (9)**

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and 2-(5-formyl-6-hydroxy-3-sulfoquinolin-7-yloxy)acetic acid (3.92 g, 1.2 mmol) in ethanol (20 mL), DMSO (3 mL) and 3 drops of HOAc. The title compound was recrystallized in DMF/water (2/1) to give red cube crystalline in 65 % (0.393 g).

2-Cyclohexylidene-1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]hydrazine (10)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and cyclohexanone (0.12 mL, 1.2 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 50 % as yellow needle (0.173 g, mp. 150-1 °C) after recrystallized in ethanol.

2-Cycloheptylidene-1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)*phenyl]hydrazine*(11)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and cycloheptanone (0.142 mL, 1.2 mmol) and 2 drops of HOAc in ethanol (20mL) to give the title compound in 50 % as yellow needle (0.180 g, mp. 150-1 °C) after recrystallized in ethanol.

2-(Butan-2-ylidene)-1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]hydrazine(12)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and butanone (0.1 mL, 1.2 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 70 % as yellow needle (0.22 g, mp. 111-2 °C) after re crystallized in ethanol.

1,1'-bis{1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]}-2,2'-(pentan-2,4-diylidene)-hydrazine (13)

This compound was prepared according to the general procedure from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and acetylacetone (0.144 g, 0.5 mmol) and 2 drops of HOAc in ethanol (20 mL) to give the title compound in 65 % as yellow needle (0.378 g, mp. 212-3 °C) after recrystallized in ethanol.

2-(-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl-2-methylidene)-1-[4,5-dimethoxy-2-(4-methylfuroxan-3-yl)phenyl]hydrazine(14)

To a solution of from 3-methyl-4-(2-hydrazino-4,5-dimethoxyphenyl)furoxan (**5**) (0.266 g, 1 mmol) and diazonium salt (**4**) (1 mmol) (3-methyl-4-(2-amino-4,5-dimethoxyphenyl)furoxan) in ethanol (20 mL) was added paraformaldehyde (36 mg, 1.2 mmol). The resulting solution was refluxed for 4 h to give the title compound in 40 % as red purple powder (0.2 g, mp. 199-200 °C) after recrystallized in ethanol.

3. RESULTS AND DISCUSSION

The condensation reaction gave 9 hydrazones in moderate to good yields with simple procedure. All

hydrazones were obtained as solid and recrystallized in the associated solvents to obtain crystals.

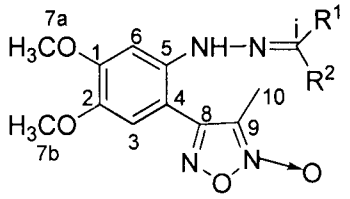
IR and MS data are shown in table 1. All hydrazones have N-H vibrations corresponding to these N-H bonds in the 3323- 3166 cm^{-1}. Compound **9** had broad bands of OH belong to acidic group at 3550- 3000 cm^{-1} and phenol functional group at 3550 cm^{-1}. Compound **7** had vibration of the phenol O-H at 3542 cm^{-1}. Similarly, these hydrazones contained C-H of aromatic rings, alkene and aliphatic C-H bonds that appeared at 3100-2820 cm^{-1}. Moreover, these hydrazone IRs showed the vibration of C=N and C=C bonds up at 1629-1521 cm^{-1}. Bands of C=N bonds were a bit stronger than vibration of C=C. The vibration of C=O (carboxylic group) of compound **9** was not so strong but only a "shoulder" band appeared at 1650 cm^{-1}. It might be a result of intrammolecular hydrogen bonding effect.

Three out of 9 hydrazones are selected to record mass spectroscopy (MS) based on ESI method. All molecular peaks match with calculated numbers (table 1).

Table 1: IR and MS data of hydrazones **6-14**

	ν_{OH} (cm^{-1})	ν_{NH} (cm^{-1})	ν_{CH} (cm^{-1})	$\nu_{C=N}$, $\nu_{C=C}$ (cm^{-1})	Mcalcd. (g/mol)	$[M+H]^+$(%)
6	-	3266	3005, 2974, 2853	1614, 1581,1524	380	381(10)
7	3542 (br)	3277	3001, 2969, 2840	1629, 1579,1523	386	-
8	-	3314	3003, 2947, 2895	1606, 1584, 1535	355	-
9	-	3166, 3550	3080, 3020, 2970, 2841	1588, 1534	575	576 (100)
10	-	3437, 3323	3070, 3000, 2946, 2860	1604, 1524	330	-
11	-	3293	3100, 3010, 2946, 2866	1589, 1521	344	-
12	-	3295	3090, 3060, 2967, 2820	1586, 1525	320	-
13	-	3300	3100, 3003, 2946, 2840	1581, 1525	596	-
14	-	3316	3090, 3010, 2935	1600, 1525	512	513 (100)

Almost all hydrazones were measured ^{1}H-NMR and ^{13}C-NMR. To make it easily, all protons, and carbons of hydrazine part are numbered as the formula below, and the carbonyl parts are labeled as shown in table 2. It is worth to know that the numeration on the structure is specifically used for NMR analysis purpose only. The assignment of protons and carbons of compound **14** was supported by HMBC, HMQC, and NOESY spectra.

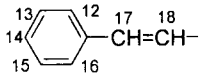
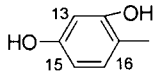
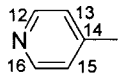
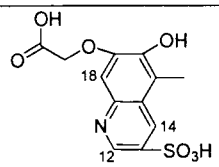
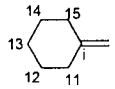
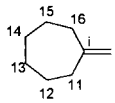
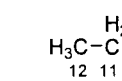
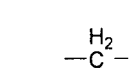
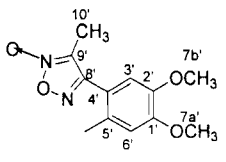


In the ^{1}H-NMR of compound **14**, all protons are singlets that are very different from the rest hydrazones since these protons are far from each other; for instant, H3, H6, H7a, H7b, H10, H3', H6', H7a', H7b' and H10' are singlets in stronger field than proton of N-H. It is important to know that chemical shifts of these protons are very constant from compound **6** to **14** (table 2). It means that the condensation reaction of hydrazine and carbonyl compound does not change core structure of hydrazine part at all. The chemical shift of proton Hi is slightly changed if the carbonyl part structures are not very different. However, chemical shift of Hi of compound **9** is 8.87 ppm (ca. 0.5-0.9ppm in difference from other hydrazones). It is explained that the quinoline ring is a strong withdrawing electron group so the Hi is moved to the weak field. Compound **6**, **7**, **8**, **9** and **14** have aromatic carbonyl parts. Their protons are at aromatic region (6.29-8.53 ppm). In contrast, compound **10**, **11**, **12**, and **13** have alphatic protons belong to the carbonyl parts. Therefore, all peaks are in strong field (1.5-2.5 ppm), and they are doublet or multiplet peaks. Compound **6** has alkene protons H17 and H18 which have coupling constant about 16 Hz, associating with *trans* conformation.

In order to prove the formation of -NH-N=CH- in hydrazone structures clearly, 2D-NMRs were analyzed carefully. HSQC spectrum of compound **14** showed a direct cross peak of Hi (7.92 ppm, s) and Ci (135.47 ppm). HMBC spectrum of compound **14** showed the correlation of Hi (7.92 ppm) with C4'

(127.56 ppm) and C6' (107.96 ppm). It also gave long tang correlation of H (NH, 9.98 s) to Ci (135.47 ppm), C4 (138.18 ppm), and C6 (98.36 ppm). That means the condensation reaction of the hydrazine and aldehyde or ketone gave hydrazone functional group as expected.

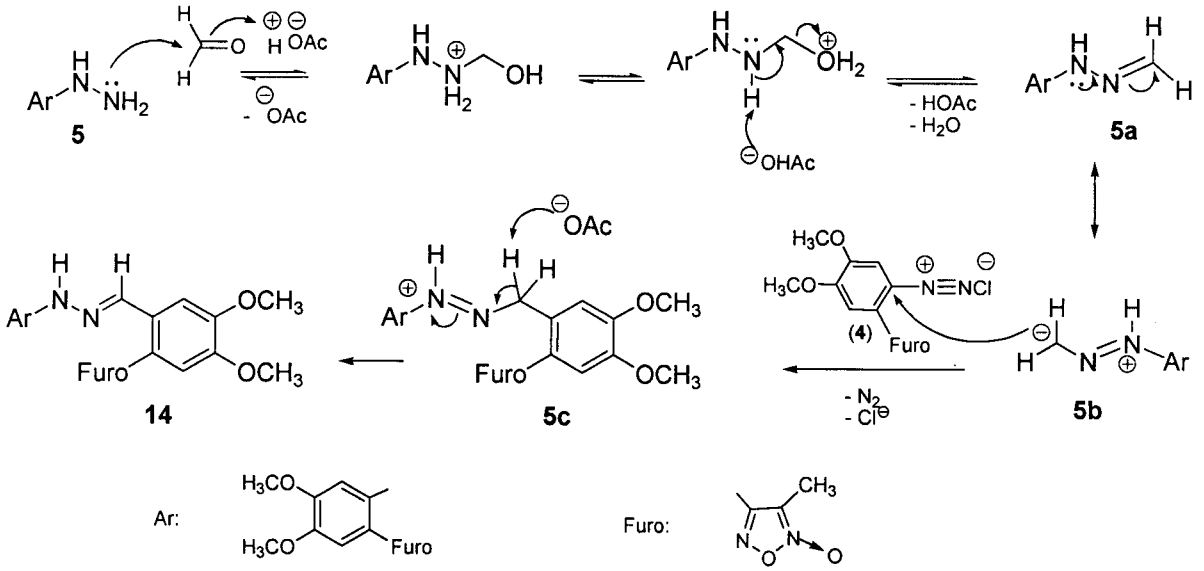
Table 2: ^{1}H-NMR data of hydrazones, δ (ppm), *J* (Hz)

Comp.	R^1	R^2	H3 H6	H7a H7b	H10 NH	H12 H16	H13 H15	H14 Hi	Other protons
6	H		6.93 s 7.10 s	3.85 s 3.72 s	2.03 9.84	7,53 d; *J* = 8 7,53 d; *J* = 8	7,35 t; *J* = 8 7,35 t; *J* = 8	7,26 t; *J* = 8 7.82 d; *J*= 9	H17: 6.78, d; *J* = 16 H18: 6.96, dd; *J* = 16; 9
7	H		6.93 s 6.96 s	3.85 s 3.72 s	2.02 s 10.28 s	- 7.27 d; *J* = 9	6.29 d; *J* = 2 6.30 d; *J* = 9	- 8.13 s	HO: 9.67, 9.66
8	H		6.97 s 7.19 s	3.90 s 3.74 s	2.02 s 10.36 s	8.53 d; *J* = 5.5, 8.53 d; *J* = 5.5	7.49 d; *J* = 5.5 7.49 d; *J* = 5.5	- 7.90 s	-
9	H		6.98 s 7.16 s	3.95 s 3.75 s	2.09 s 10.07 s	8.93 s -	- -	8.87 s -	H18: 7.31 s 4.97 s (OCH_2)
10			7.29 s 7.30 s	3.85 s 3.78 s	2.01 s 11.49 s	(11/15)e: 1.85 m (11/15)a: 1.55m 13e: 1.60 m 13a: 1.17 m		(12/14)e: 1.52 m (12/14)a: 1.37 m	
11			6.95 s 7.13 s	3.88 s 3.72 s	2.15 s 8.68 s	(11/12/15/16)e: 2.34 m (4H) (12-17)a: 1.52 m (6H)		(13/14)e: 1.69 m (2H)	
12	CH_3 k		6.98 s 7.15 s	3.85 s 3.77 s	2.15 s 8.70 s	0.98 t: *J*= 7	-	Hk: 1.86 s H11: 2.21 q, *J*= 7	
13	CH_3 k		6.96 s 7.11 s	3.79 s 3.72 s	2.14 s 8.78 s	-	-	Hk: 1.80 s H11: 3.08 s	
14	H		6.92 s 9.93 s H3': 7.10 s H6': 7.35 s	3.85 s 3.72 s H7a': 3.89 s H7b': 3.82	2.02 9.98 s H10': 2.00 s	-	-	Hi: 7.92 s	

Interestingly, compound **14** has the carbonyl part containing almost the same as hydrazine part; hence, assignment of those protons is very difficult. As shown in experimental section, compound **14** was synthesized by the condensation of the hydrazine **5** with formaldehyde in presence of diazonium salt **4**. It is wondered that CH_2 might be in the condensation product structure, but DEPT spectrum showed that the hydrazone **14** didn't contain any CH_2 group at all. On the other hand, there was a singlet peak at 7.92 ppm belonged to Hi of N=CH group. It was proved that compound **5** was reacted with diazonium salt **4** definitely.

Table 3: ^{13}C-NMR data of the hydrazones [125 MHz, δ (ppm)]

Co mp.	C1 C2	C3 C4	C5 C6	C7a C7b	C8 C9	C10 Ci	Others
6	152.21 142.38	113.90 100.50	138.27 98.23	55.51 56.21	156.58 114.12	8.43 141.21	C11: 136.57, C12: 126.49, C13: 128.77, C14: 127.95 C15: 128.77, C16: 126.49, C17: 133.95 C18: 126.21
7	152.15 142.03	114.01 100.47	139.88 97.94	55.35 56.24	156.76 144.30	8.34 138.67	C11: 128.33, C12: 157.34, C13: 102.43, C14: 159.22, C15: 107.58, C16: 112.10
8	152.60 143.50	114.35 101.73	138.15 99.31	56.04 56.60	157.25 114.55	8.76 143.01	C12: 150.44, C13: 120.22, C14: 135.75 C15: 120.22, C16: 150.44
11	154.27 141.75	113.35 100.39	139.99 98.77	56.14 55.37	157.52 113.45	9.19 151.90	C11-C16: 36.25, 30.04, 29.97, 27.67, 23.94
12	151.8 141.77	113.66 100.66	140.24 99.08	56.14 55.31	157.82 113.66	8.95 151.82	C11: 31.03, C12: 15.26, C13: 10.43
14	152.12 142.53	113.93 138.18	100.72 98.36	56.17 55.31	157.06 144.06	8.34 135.47	C1': 150.71, C2': 149.05, C3': 113.11, C4': 127.56, C5': 115.92, C6': 107.96, C7a': 55.91, C7b': 55.45, C8': 157.50, C9': 144.06, C10': 8.24



Scheme 3: Proposed mechanism of the formation of compound **14**

To explain the formation of compound **14**, a proposed mechanism is drawn in Scheme 3. The hydrazine **5** works as a nucleophile to add into the activated carbonyl electrophile (A_N), following elimination of a water molecule to form a hydrazone **5a**. The hydrazone **5a** has a resonance form **5b** that acts as nucleophile. Besides, in a reflux condition, the diazonium salt **4** is gently omitted N_2 to form a cation of benzenium type that react with the resonance form **5b** (S_N2Ar) to give an intermediate

5c that is converted to stable hydrazone **14**.

4. CONCLUSION

Condensation reaction of the hydrazine with ketones or aldehydes in acidic catalysis gave 9 hydrazones. These hydrazone structures were proved by IR, NMRs, and MS spectra. Compound **14** was recorded 2D-NMR to determine precisely associated peaks for each carbon and hydrogen atoms, especially for the formation of –NH-N=C- group. The formation of **14** is a result of nucleophile addition to carbonyl group, elimination, and nucleophile substitution of aromatic diazonium salt. Biological activity of these hydrazones is currently investigated.

Acknowledgements. *This research is funded by Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 104.01-2012.55.*

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