

## Synthesis , Characterization and computational study of Some New Aniline oxide derivatives

Afaq A.Turki

Department of Chemistry, College of Science, University of Basrah, Basrah-Iraq

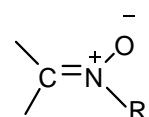
### Abstract:

The reaction of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine (1) with aldehydes (2-6) in the presence of weak acid as a catalyst afforded the corresponding aniline oxide derivatives (7-11). The structures of these products were characterized by their elemental analysis (C.H.N.),  $^1\text{H}$  NMR

**Keywords :** aniline oxide, pyrazoline derivatives, nitrone

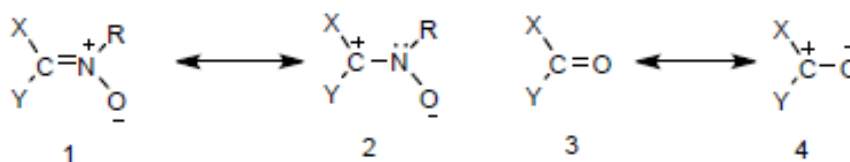
### Introduction :

The "nitrone" is an abbreviation which was suggested by Pfeiffer<sup>(1)</sup> in 1916 for compounds containing the functional group, as shown below.



R = H, alkyl, aryl ... etc.

The name emphasizes its similarity with ketone and aldehyde which were suggested to indicate a chemical relationship between nitrones and the carbonyl compounds<sup>(2)</sup>, as shown in scheme (1).



### **Scheme (1)**

The chemistry of nitrones was previously reviewed by Smith in 1938 as one of the structural systems which undergo 1,3-addition reactions<sup>(1,2)</sup>

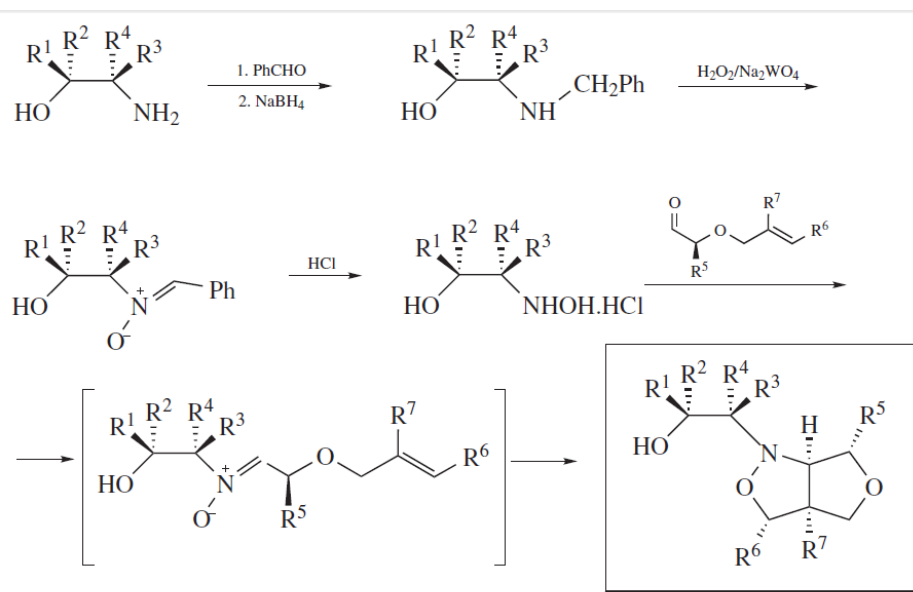
For the last 50 years many scientists have drawn special attention to nitrones due to their successful application as building blocks in the synthesis of various natural and

biologically active compounds, of stable nitroxyl radicals, and of other important products for special purposes such as spin traps for the study of radical processes including those that take place in biological systems, and they also found use as both, modifiers and regulators of molecular weight in radical polymerization.

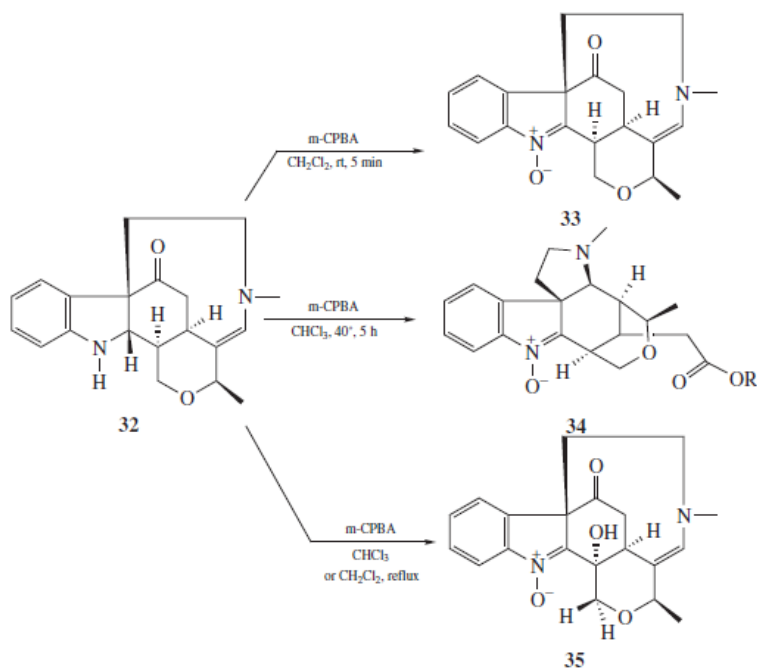
A great deal of literature <sup>(3-33)</sup> is devoted to certain aspects of nitron chemistry and its application, or to specific classes of nitrones <sup>(34,35)</sup>. However, at the present time, the reviews dealing with all or practically all aspects of nitron chemistry, except those which are well-known and widely covered in the literature <sup>(36-41)</sup>, are still lacking.

To illustrate the multifaceted chemistry of nitrones and their application in synthesis, let us consider the synthetic scheme of bicyclic and tricyclic chiral ligands as shown in Scheme (2) <sup>(42)</sup> as well as diastereo- and enantioselective syntheses of alkaloids as shown in Scheme (3) <sup>(43)</sup>.

Many successful chemical transformations based on the rich and multifaceted chemistry of nitrones underlie various synthetic strategies.

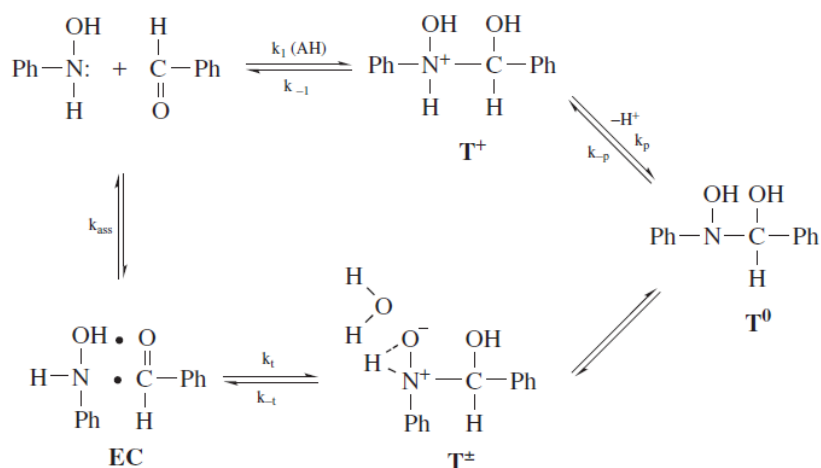


Scheme (2)



Scheme (3)

Condensation of *N*-monosubstituted hydroxylamines with carbonyl compounds is used as a direct synthesis of many acyclic nitrones. The synthesis of hydroxylamines is being carried out *in situ* via reduction of nitro compounds with zinc powder in the presence of weak acids ( $\text{NH}_4\text{Cl}$  or  $\text{AcOH}$ )<sup>(44-46)</sup>. The reaction kinetics of benzaldehyde with phenylhydroxylamine and the subsequent reaction sequence are shown in Scheme (4)<sup>(47)</sup>.



Scheme (4)

Grinding together solid anilines and solid benzaldehydes yielded various kinds of benzyldeneanilines <sup>(48)</sup>. The synthesis of primary imines by condensation of 2-hydroxylaryl ketones with ammonium iodide and piperidine under solvent free conditions <sup>(49)</sup>.

In this work we have synthesized and characterized of some new aniline oxide compounds Derived N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine. The synthesis compounds have been studied theoretically by semi-empirical molecular orbital theory at the level of PM3 of theory.

## **Experimental:**

### **General:**

Melting points were uncorrected. NMR spectra were acquired with a Bruker Ultra Shield (300 MHz). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. GC mass spectra were acquired with Shimadzu Qp5050A.

### **Synthesis of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine (1) :**

This compound was prepared as mentioned in the literature <sup>(50)</sup>. (0.467mole) of ammonium chloride, 800 ml of water and the appropriate 5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (0.406 mole) (which was prepared as mention in the literature) <sup>(51)</sup> were placed in a three-neck round bottom flask. This mixture was stirred with a mechanical stirrer; and 59 g of zinc powder was added during (15-20) minutes. As the reduction proceeded, the temperature rised to (60-65)°C, stirring was continued for 15minutes in which all the zinc powder was added, at the end of which the reaction was complete, as indicated by the lowering of the temperature of the reaction mixture. Then, the solution was filtered by suction while still hot to remove zinc oxide. The solid was washed with 100 ml of warmed water. The filtrate was saturated with NaCl salt and cooled in ice path for 1 hour. The N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine which crystallized out was filtered by suction and purified by using mixed solvent (benzene and petroleum ether (40-60)°C). These crystals after being dried in vacuum desiccator, were amounted to (34% yield) with m.p..(100-102°C). The CHN analysis for C<sub>13</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> ; C 64.19; H

5.39; N 17.27 Found C 64.15; H 5.37; N 17.27, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3500-3520 (OH stretching), 3338 (NH stretching), 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching of pyrazoline ring), 1597 (C=C stretching of aromatic ring), 1212 (C–N stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  ( 7.259-7.269) ppm (2H,d,9,11); (7.455-7.465) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7<sup>1</sup>), 4.111 ppm (1H,s,13), 3.001 ppm (1H,s,14)

## **Synthesis of aniline Oxide derivatives**

### **General procedure**

In a 100 ml round flask, (0.01 mole) of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine<sup>(50)</sup> and 11 ml of ethanol (abs.) were stirred and warmed to 50°C. An additional 5 ml of solvent to completely dissolve the N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine. A solution of (0.01 mole) of aldehydes and (0.1 g ) of p-toluene sulphonic acid was added to the mixture. Then the mixture was refluxed for (8) hours, and cooled to 0°C and kept in this temperature for overnight, the crude aniline oxide products were filtered and dried in a vacuum.

Then , recrystallisation of the products was performed by using dry toluene and resulted in different coloured crystals which were purified by column chromatography by using ( benzene: methanol) with ratio (8:2) as eluent. Different coloured crystals with different melting points, were obtained. The purity of the synthesized compounds was determined by using Thin Layer Chromatography (T.L.C.) with eluante (benzene: methanol) ratio (8:2) respectively.

### **N-benzylidene-4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)aniline oxide (2):**

From benzaldehyde (2) yield 73% solid with m.p. 38°C. The CHN analysis for  $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_2$  ; C 72.49; H 5.17; N 12.68; Found C 72.45; H 5.15; N 12.67, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3330 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching), 1270 (N–O stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  8.376 ppm (1H,s,13) ,(7.912-7.921) ppm (2H,d,8,12); (7.727-7.742) ppm (1H,d,1); (7.518-7.581) ppm (7H,m,9,11, 14,15,16,17,18); 7.065

ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7')

**4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-N-(4-methylbenzylidene)aniline oxide (3):**

From p-methyl benzyldehyde (3) 74% yield with m.p. 34°C. The CHN analysis for  $C_{21}H_{19}N_3O_2$  ; C 73.03; H 5.54; N 12.17; Found C 73.00; H 5.50; N 12.16, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3330 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching), 1592 (C=C stretching of aromatic ring), 1213 (C–N stretching), 1273 (N–O stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  8.376 ppm (1H,s,13), (7.912-7.921) ppm (2H,d,8,12); (7.727-7.742) ppm (1H,d,1); (7.518-7.581) ppm (6H,m,9,11,14,15,17,18); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.350-3.360) ppm (2H,d,7,7'); 3.006 ppm (3H,s,16).

**4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-N-(4-methoxybenzylidene)aniline oxide (4):**

From p-methoxy benzyldehyde (4) 75% yield with m.p. 35°C. The CHN analysis for  $C_{21}H_{19}N_3O_3$  ; C 69.79; H 5.30; N 11.63 Found C 69.75; H 5.30; N 11.62, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3332 (NH stretching of pyrazoline ring), 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching), 1594 (C=C stretching of aromatic ring), 1216 (C–N stretching), 1275 (N–O stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  8.376 ppm (1H,s,13), (7.912-7.921) ppm (3H,d,1,8,12); (7.455-7.465) ppm (4H,m,9,11,14,18); (7.259-7.269) ppm (2H,d,15,17); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); 4.111 ppm (3H,s,16); (3.350-3.360) ppm (2H,d,7,7')

**N-(4-bromobenzylidene)-4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)aniline oxide (5):**

From p-bromo benzyldehyde (5) 79% yield with m.p. 37°C. The CHN analysis for  $C_{20}H_{16}BrN_3O_2$  ; C 58.55; H 3.93; N 10.24; Found C 58.54; H 3.90; N 10.23, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3334 (NH stretching of pyrazoline ring), 3023 (C–H

stretching of aromatic ring), 2884 (C–H stretching of aliphatic), 1622 (C=N stretching), 1596 (C=C stretching of aromatic ring), 1217 (C–N stretching), 1280 (N–O stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  8.376 ppm (1H,s,13), (7.912-7.921) ppm (3H,d,1,8,12); (7.709-7.719) ppm (3H,d,1,15,17); (7.402-7.412) ppm (4H,d,9,11,14,18); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7<sup>\b</sup>)

**4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)-N-(4-nitrobenzylidene)aniline oxide (6):**

From p-nitro benzyldehyde (6) 85% yield with m.p. 38°C. The CHN analysis for  $\text{C}_{20}\text{H}_{16}\text{N}_4\text{O}_4$  ; C 63.82; H 4.28; N 14.89 Found C 63.80; H 4.25; N 14.87, FT-IR spectra (KBr pellet)  $\nu(\text{cm}^{-1})$  3338 (NH stretching for pyrazoline ring), 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching), 1597 (C=C stretching of aromatic ring), 1212 (C–N stretching), 1286 (N–O stretching),  $\delta_{\text{H}}(\text{CDCl}_3)$  8.376 ppm (1H,s,13), ( 8.321-8.331) ppm (2H,d,15,17); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (2H,d,14,18); (7.709-7.719) ppm (1H,d,1); (7.402-7.412) ppm (2H,d,9,11); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7<sup>\b</sup>)

**Computational methods**

All theoretical calculations in this work were performed using the computational methods. Geometry optimization of the studied compounds was done by performing the semi-empirical molecular orbital theory at the level PM3 <sup>(52)</sup>.

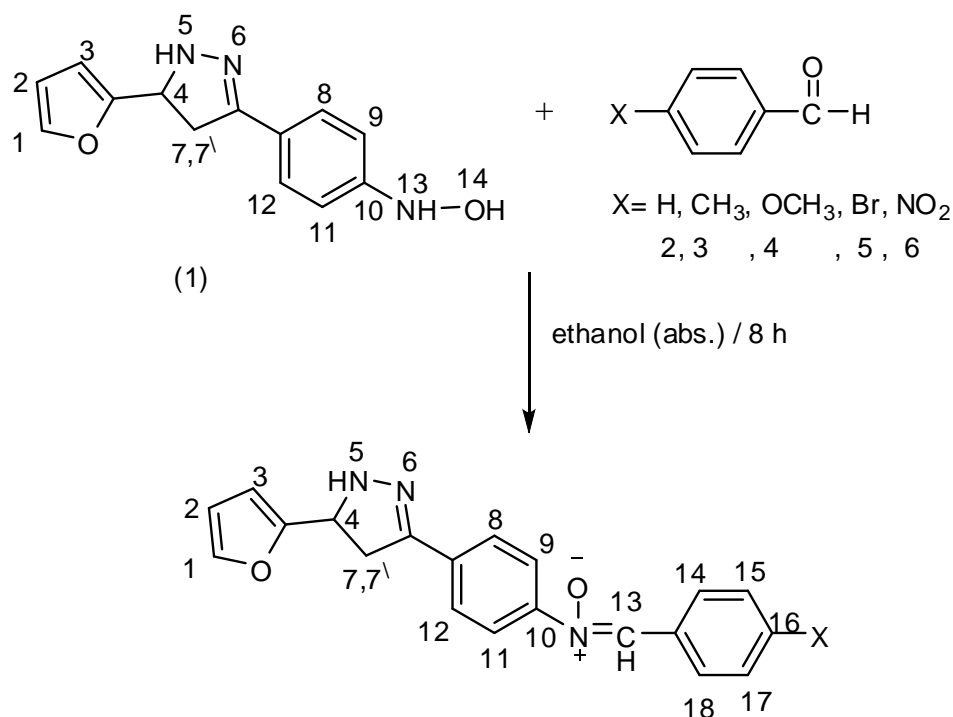
**Results and Discussion:**

Treatment of the Synthesis of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine (1) with aldehydes (2-6) in the presence of p-toluene sulphonic acid as catalyst in boiling ethanol gave, after purification from recrystallization or short column of silica gel, the pure *trans* aniline oxide derivatives (2-6) in 73-85% yield, as crystalline compounds (Scheme 5). The structures of these products were established from their elemental analysis, FT-IR, and <sup>1</sup>H NMR .

The FT-IR spectra of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine and aniline oxide compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710)  $\text{cm}^{-1}$ . These fact confirmed the correct expected chemical structure of these compounds. All the IR spectra of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine and aniline oxide derivatives showed a peak at (1614-1625)  $\text{cm}^{-1}$  which related to (C=N) stretching of aniline oxide, a peak at (1212-1219)  $\text{cm}^{-1}$  which appeared due to (C-N) stretching and a peak at 1270-1286)  $\text{cm}^{-1}$  due to  $\text{N}^+-\text{O}^-$  stretching , while a peak at (1592-1597)  $\text{cm}^{-1}$  which appeared due to (C=C stretching of aromatic ring) appeared at . While, the C-H stretching aromatic rings showed a peak within the range (3020-3022)  $\text{cm}^{-1}$  and the C-H stretching aliphatic showed a peak within the range (2880-2884)  $\text{cm}^{-1}$ . The N-H stretching showed a peak within the range (3330-3338)  $\text{cm}^{-1}$  and the O-H stretching in compound (1) showed a peak within the range (3500-3520)  $\text{cm}^{-1}$ . The  $^1\text{H}$  NMR spectra of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine and aniline oxide compounds are shown in figures (1-6). All the  $^1\text{H}$  NMR spectra of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine aniline oxide were characterized<sup>(53-55)</sup> by the presence proton (13) of nitone group (  $\text{C}=\text{N}^+-\text{O}^-$ ) showed singlet signal at 8.376 ppm in compounds (2-6) . The protons (5) of pyrazoline ring showed singlet signals within the range 7.065 ppm and showed triplet signals within the range (4.625-4.725) ppm which appeared to proton in (4) position because interaction with two protons in (7 and 7<sup>\)</sup>) position , while the two protons in (7 and 7<sup>\)</sup>) position showed doublet signals within the range (3.350-3.927) ppm because interaction with protons in (4) position. These peaks confirmed the correct expected chemical structure of N-(4-(5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl) hydroxylamine and aniline oxide compounds. The proton in the position (1) of furan ring showed doublet signals at (7.709-7.921) ppm , while the other two protons in positions (2 and 3) of furan ring showed multiplet signals within the range (6.211-6.481) ppm. The protons of aromatic rings in compound (1) showed doublet signals within the range (7.259-7.269) ppm which appeared to two protons in positions (9,11), while the other protons in positions (8,12) showed doublet signals within the range ( 7.455-7.465 ) ppm, .The protons of aromatic rings in compounds (2and 3) showed multiplet signals within the range (7.518-7.581) ppm which appeared to seven protons in positions (9,11,14,15,16,17 and 18). While the two protons in positions (8,12) showed doublet



signals within the range (7.912-7.921) ppm. While the aromatic protons in compound (4) showed doublet signals within the range (7.259-7.269) ppm which appeared to the two protons in positions (15, 17) positions. The other protons in positions (9, 11, 14 and 16) showed doublet signals within the range (7.455-7.465) ppm, and showed peak within the range (7.912-7.921) ppm due to three protons in positions (1, 8 and 12). The aromatic protons in compound (5) showed doublet signals within the range (7.402-7.412) ppm due to four protons in positions (9, 11, 14 and 16) and showed peak within the range (7.709-7.719) ppm due to three protons in positions (1, 15 and 17), while the two protons in positions (8, 12) showed doublet signals within the range (7.912-7.921) ppm. The aromatic protons in compound (6) showed doublet signals within the range (7.402-7.412) ppm due to two protons in positions (9, 11) and showed peak within the range (7.709-7.719) ppm due to protons in positions (1), while the two protons in positions (14, 18) showed doublet signals within the range (7.912-7.921) ppm and showed doublet signals within the range (8.111-8.121) ppm due to two protons in positions (8, 12), while the two protons in positions (15, 17) showed doublet signals within the range (8.321-8.331) ppm. The OCH<sub>3</sub> protons showed singlet signal for three protons at 4.111 ppm. The CH<sub>3</sub> protons showed singlet signal within the range 3.006 ppm. The NH protons showed singlet signal for two protons in the region 4.111 ppm..while the OH proton in compound (1) showed singlet signal at 3.001 ppm.



Scheme (5)

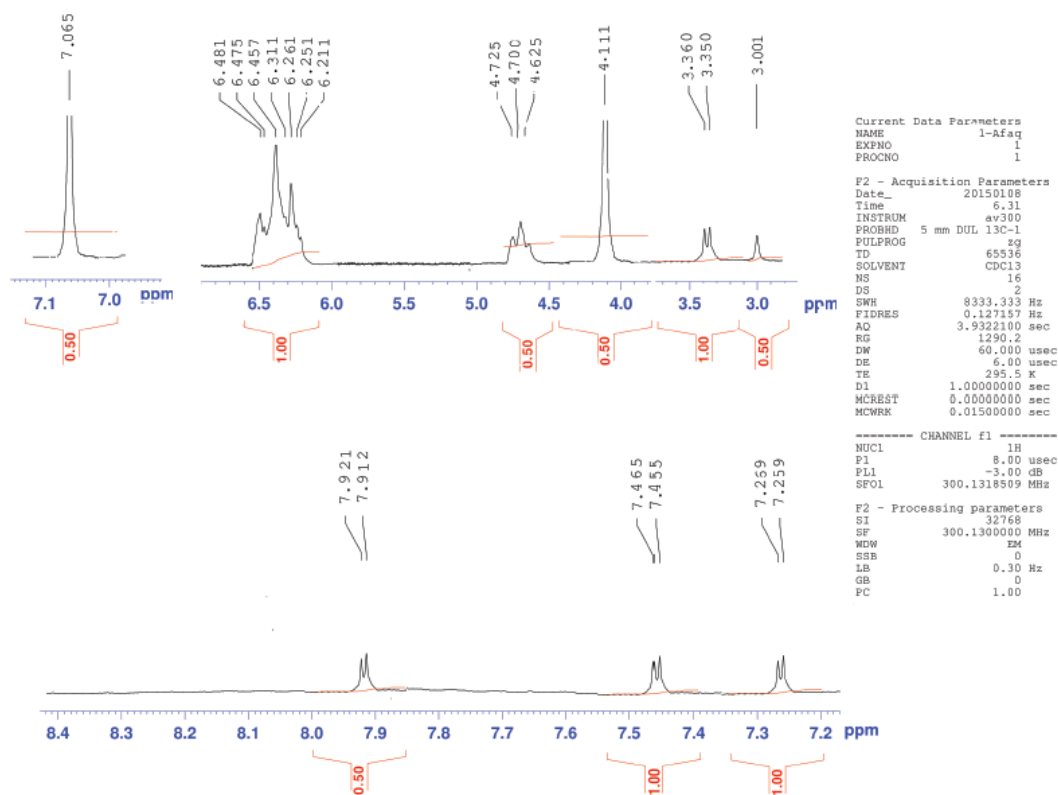


Figure (1) <sup>1</sup>H NMR spectra for compound (1)

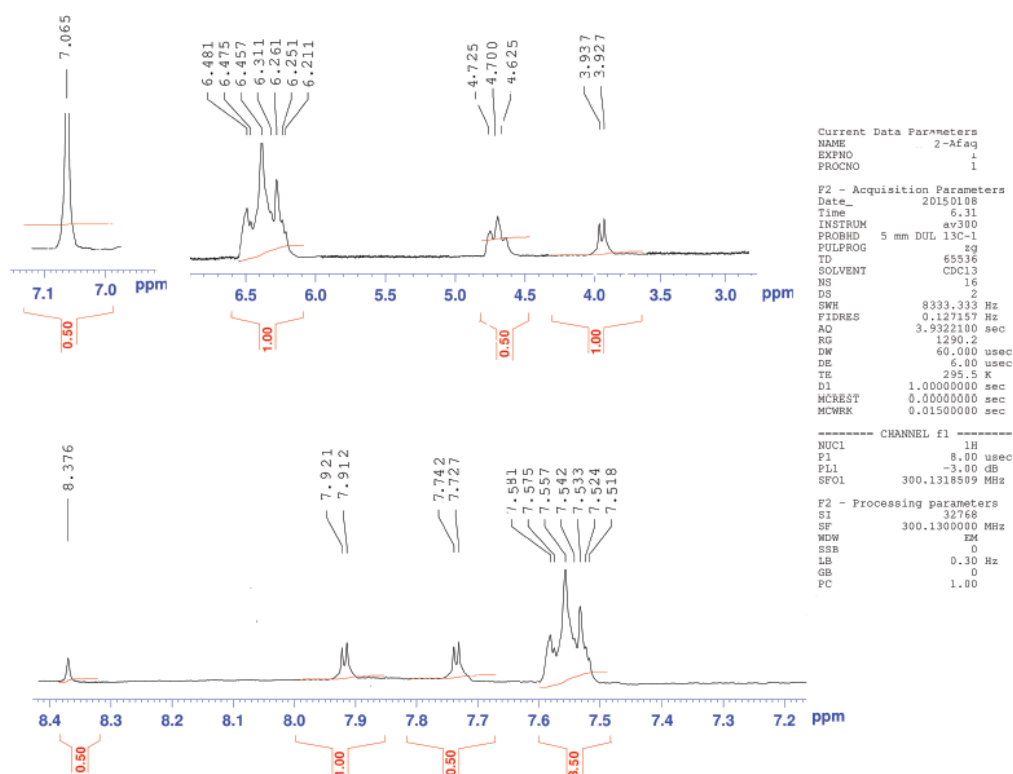


Figure (2)  $^1\text{H}$ NMR spectra for compound (2)

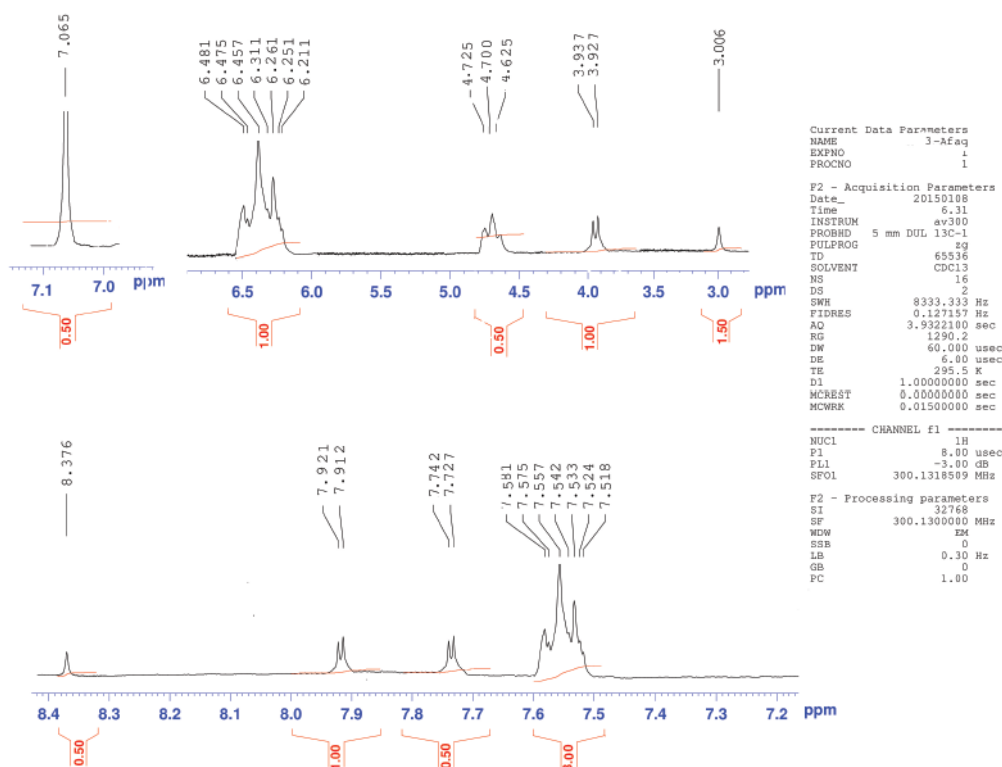


Figure (3)  $^1\text{H}$ NMR spectra for compound (3)

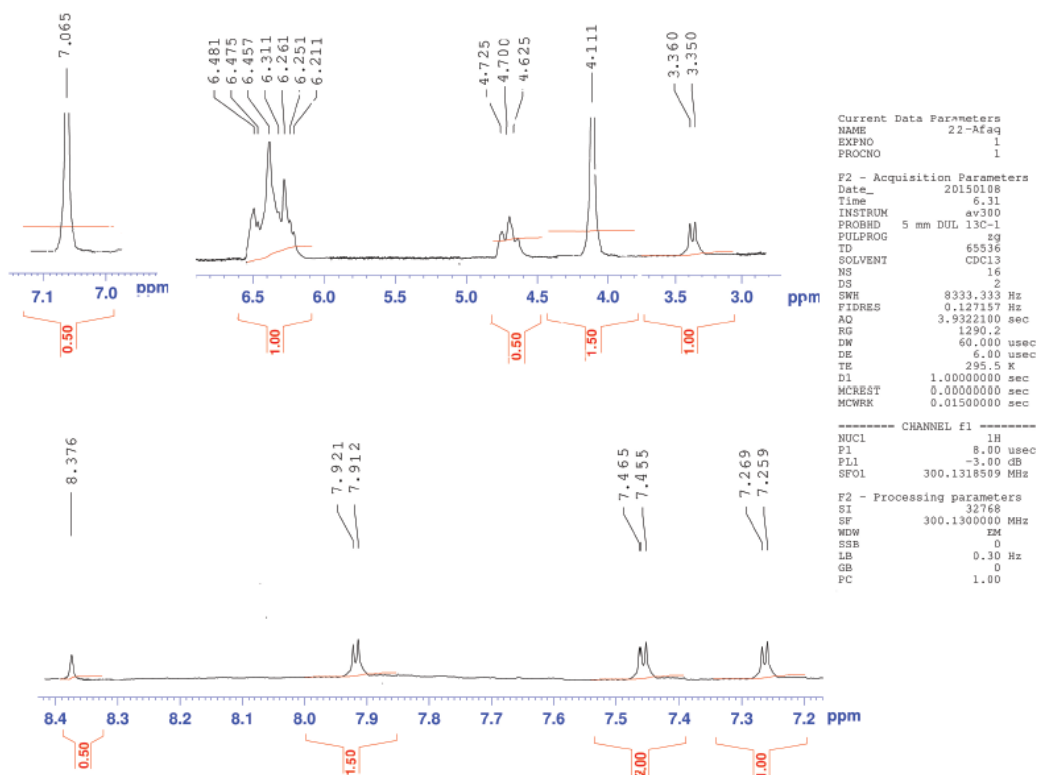


Figure (4)  $^1\text{H}$  NMR spectra for compound (4)

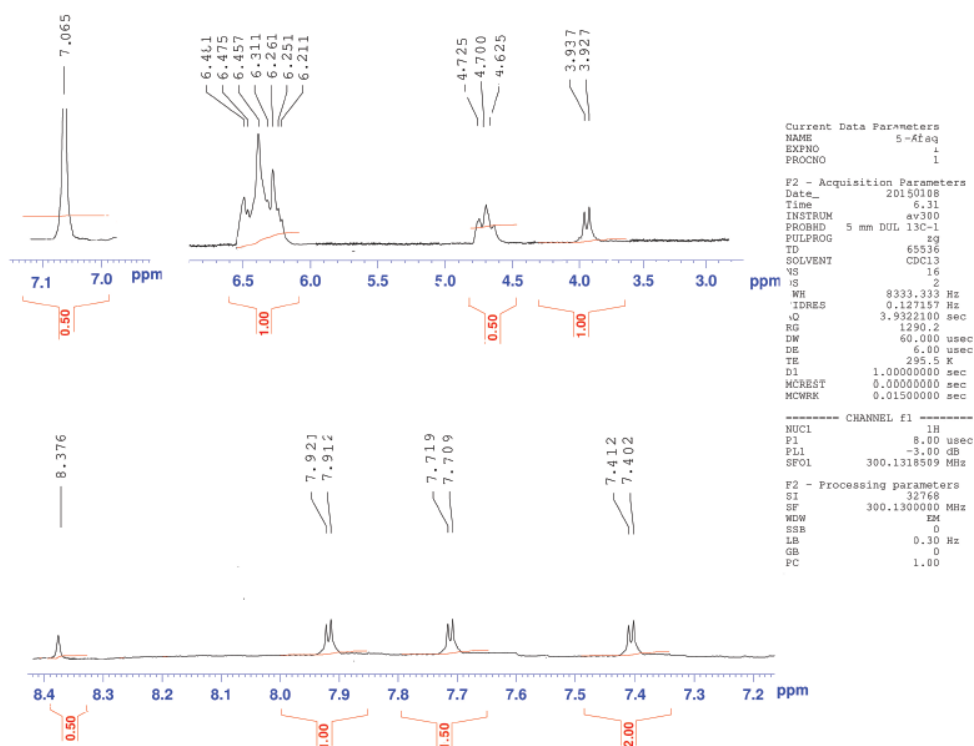
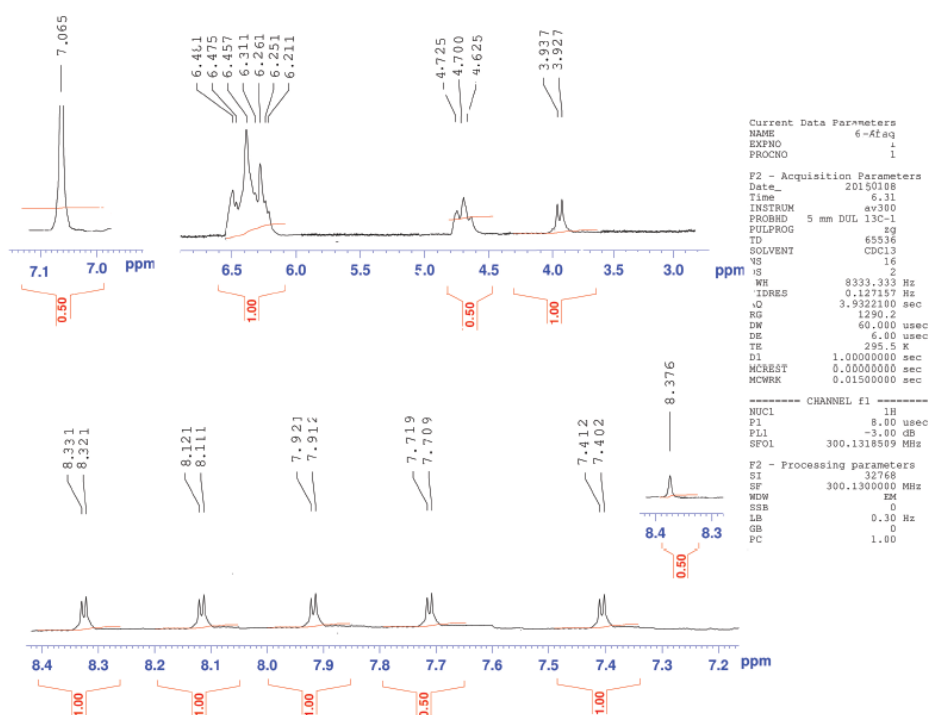


Figure (5)  $^1\text{H}$  NMR spectra for compound (5)

Figure (6)  $^1\text{H}$ NMR spectra for compound (6)

## Computational Study

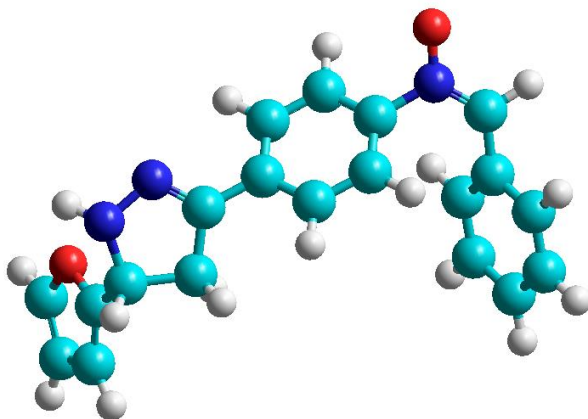
The optimized structures of the studied molecules are shown in Fig 1. The PM3 geometry optimizations yield planar structures for the synthesis compounds. The general geometries of molecule all compounds are very similar.

In order to explain the configuration of the synthesized aniline oxide compounds, semi-empirical calculations of the two isomers of aniline oxide compounds, *trans*- and *cis*- isomers, had been performed, as shown in table (1).

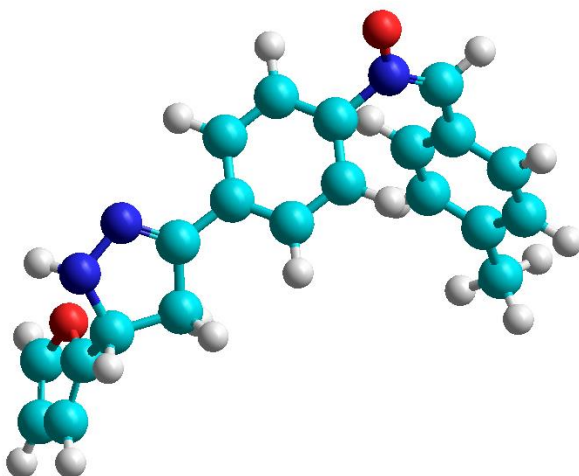
Table (1) Heat of formation of the synthesized aniline oxide compounds

Symbol	Heat of formation (kcal/mole)	
	<i>Cis</i> -form	<i>Trans</i> -form
2	105.3377439	104.2886838
3	95.1789618	94.9610496
4	186.9382921	43.0286312
5	110.4560819	89.9178555
6	121.4325626	92.9436777

The results showed that the *trans*-isomers of aniline oxide compounds, due to their lower value of heat of formation, were more stable as compared with the *cis*-isomers. The calculations suggested that the aniline oxide compounds in the form of *trans*-isomer which is the most stable. Geometries of *trans*-aniline oxide compounds are shown in figures (7-11).



**Figure (7) : Balls and cylinders model of *trans*- aniline oxide compound (2)**



**Figure (8) : Balls and cylinders model of *trans*- aniline oxide compound (3)**

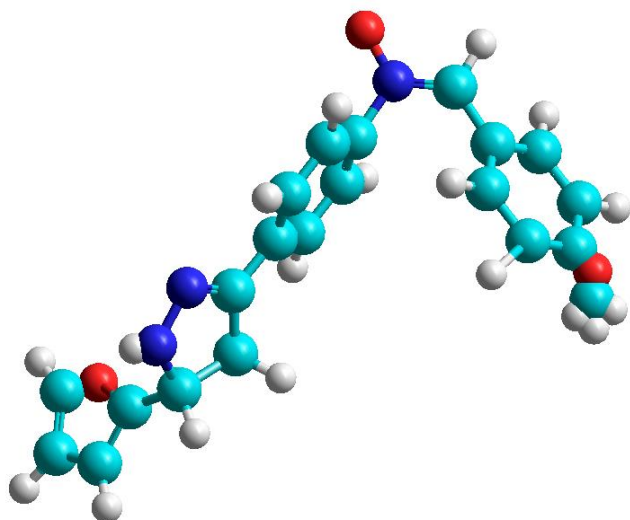


Figure (9) : Balls and cylinders model of *trans*- aniline oxide compound (4)

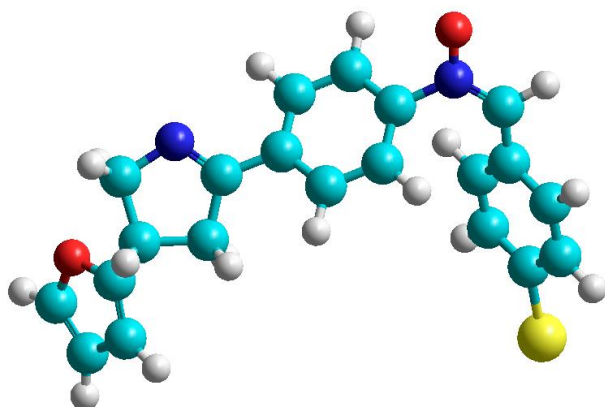


Figure (10) : Balls and cylinders model of *trans*- aniline oxide compound (5)

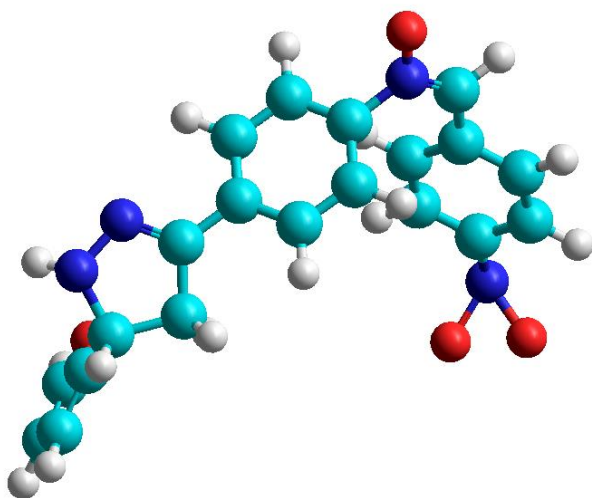


Figure (11) : Balls and cylinders model of *trans*- aniline oxide compound (6)

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