

Synthesis, Characterization And Computational Study of Some New 4,4'-(5,5'-(1,4-Phenylene)Bis(4,5-Dihydroisoxazole-5,3-Diyl))Bis(N-(4-Formylbenzylidene)Aniline Oxide) Derivatives

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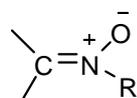
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Abstract: An efficient and practical synthesis of bis-aniline oxide ligands from 4,4'-(5,5'-(1,4-phenylene) bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-formylbenzylidene)aniline oxide with aniline derivatives in ethanol (abs.). The synthesized compounds were characterized by means of their IR- and NMR-spectral data, and elemental analysis. The structural and electronic properties of nine compounds have been investigated theoretically by performing semi-empirical molecular orbital theory at the level of PM3 of theory. The optimized structures, relative binding energies, atomic charges, position of HOMO and LUMO of the molecules are obtained.

Keyword: nitron, aniline oxide, isoxazole, heterocyclic, chalcone, di aldehyde derivatives

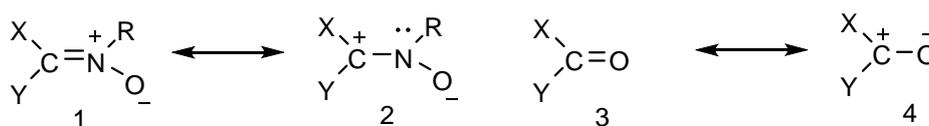
I. Introduction

Nitrones are important synthetic intermediates that have been used extensively in organic chemistry [1-7]. Some nitrones have been used for the trapping and identification of free radicals[7], particularly in biological studies [4]. Various synthetic approaches for the synthesis of nitrones have been reported by several groups[8-18]. The most general approach for the preparation of nitrones is the condensation reaction between aldehydes or ketones with N-monosubstitutedhydroxylamines[8]. The "nitron" is an abbreviation which was suggested by Pfeiffer (Pfeiffer, 1916) 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 [9], as shown in scheme (1).

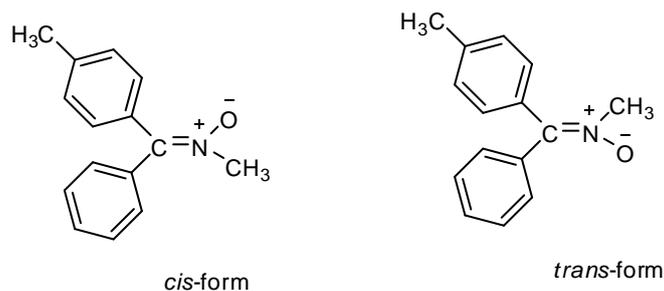


Scheme (1)

The chemistry of nitrones was previously reviewed by Smith in 1938 as one of the structural systems which undergo 1, 3-addition reactions [9,10] From their early discovery until the present time, nitrones were quite versatile intermediates in organic synthesis and have proved to be very useful tools in the construction of structurally complex molecules, usually allowing a high degree of diastereocontrol [11, 12]; for instance, they are employed in stereo selective formation of synthetically useful isoxazolidines by their 1,3-dipolar cycloaddition with alkene[13]. In addition, the alkylation of nitrones by organometallic reagents has been extensively developed and has become a reliable synthetic procedure [14, 15].

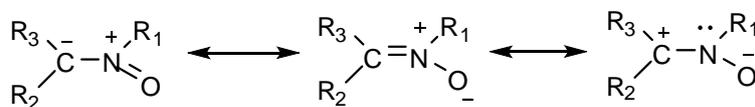
They are also used in the synthesis of many-nitrogen-containing biologically active compounds[16]. Also, some nitrones have been used for the trapping and identification of free radicals, particularly in biological studies[17-19]. There are two types of nitrones, aldonitrones and ketonitrones. Aldonitrones contain a proton on the α -carbon atom, $R_1CH=N(O)R_2$, while in the second type of nitrones, ketonitrones, the α -carbon is fully substituted by alkyl and/or aryl group, $RR_1C=N(O)R_2$. Usually for cyclic nitrones [20, 21], the names are in accordance with the parent heterocyclic structure.

Nitrones exhibit geometric isomerism because of the double bond in the nitron group[22, 23], as shown in scheme (2).



Scheme (2)

Ultraviolet spectral studies indicate that aldonitrones exist in the stable *trans* form [24]. All these azomethine-N-oxide groups are dipolar in character and the typical nitron reactions depend on this character. The polarization of the azomethine-N-oxide group is moderated by the inductive or mesomeric effect of the substituents R1, R2 and R3, as shown in scheme (3) [21].



Scheme (3)

II. Experimental methods

General:

The uncorrected melting points of compounds were recorded by on a Gallenkamp thermal point apparatus (England). The FT-IR spectra of all synthesized compounds were recorded by using FT-IR-8400,SHIMADZU (Japan). NMR spectra were acquired with a Bruker Ultra Shield (^1H : 300 MHz) (University of AL-al-Bayt,Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analysis were performed by using Euro Vector EA3000A (University of AL-al-Bayt,Jordan).

Synthesis of N,N'-(4,4'-(5,5'-(1,4-phenylene))bis(4,5-dihydroisoxazole-5,3-diyl))bis(4,1-phenylene))bis(hydroxylamine) (1) :

This compound was prepared as mentioned in the literature [25]. (0.467mole) of ammonium chloride, 800 ml of water and the appropriate 1,4-bis(3-(4-nitrophenyl)-4,5-dihydroisoxazol-5-yl)benzene (0.406 mole) (which was prepared as mention in the literature) [25] 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 raised to (60-65) $^{\circ}\text{C}$, 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,N'-(4,4'-(5,5'-(1,4-phenylene))bis(4,5-dihydroisoxazole-5,3-diyl))bis(4,1-phenylene))bis(hydroxylamine) which crystallized out was filtered by suction and purified by using mixed solvent (benzene and petroleum ether (40-60) $^{\circ}\text{C}$). These crystals after being dried in vacuum desiccator, were amounted to (44% yield) with m.p..(150-152 $^{\circ}\text{C}$). The CHN analysis for $\text{C}_{24}\text{H}_{18}\text{N}_4\text{O}_6$ C 62.88; H 3.96; N 12.22; Found C 62.77; H 3.92; N 12.20, 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 oxazoline 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'),4.111 ppm (1H,s,13), 3.001 ppm (1H,s,14)

Synthesis of 4,4'-(5,5'-(1,4-phenylene))bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-formyl benzylidene) aniline oxide) (2) :

In a 100 ml round flask, (0.01 mole) of N,N'-(4,4'-(5,5'-(1,4-phenylene))bis(4,5-dihydroisoxazole-5,3-diyl))bis(4,1-phenylene)) bis(hydroxylamine) and 11 ml of ethanol (abs.) were stirred and warmed to 50 $^{\circ}\text{C}$. An additional 5 ml of solvent to completely dissolve the N,N'-(4,4'-(5,5'-(1,4-phenylene))bis(4,5-dihydroisoxazole-5,3-diyl))bis(4,1-phenylene)) bis(hydroxylamine) . A solution of (0.02 mole) of teraphthaldehyde and (0.1 g)

of p-toluene sulphonic acid was added to the mixture. Then the mixture was refluxed for (9) hours, and cooled to 0°C and kept in this temperature for overnight, the crude dianiline oxide products were filtered and dried in a vacuum.

Then, recrystallisation of the products was performed by using dry toluene and resulted in different yellow crystal which were purified by column chromatography by using (benzene: methanol) with ratio (8:2) as eluent. The purity of the synthesized compounds was determined by using Thin Layer Chromatography (T.L.C.) with eluante (benzene: methanol) ratio (8:2) respectively. These crystals after being dried in vacuum desiccators, were amounted to (73% yield) with m.p..(180-182°C).

Synthesis of aniline oxide derivatives:

General procedure:

(0.01mole) of 4,4'-(5, 5'-(1,4-phenylene) bis (4,5-dihydroisoxazole-5, 3-diyl)) bis (N-(4-formylbenzylidene) aniline oxide) (2) was dissolved in absolute ethanol in the presence of p-toluene sulphonic acid. Then, (0.02 mole) of aniline and its derivatives (3-9) were added and heated under reflux for (7) hrs. Then, the mixture was cooled in an ice bath for 2 hrs and yielded different colored crystal. These products treated with 5.4 ml hydrogen peroxide in 12 ml glacial acetic acid to gave dianiline oxide derivatives the residue was purified by recrystallization from benzene.

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-((oxido(phenyl)imino) methyl)benzylidene)aniline oxide) (3):

From aniline (3) yield 75% solid with m.p. 38°C. The CHN analysis for C₅₂H₄₀N₆O₆; C 73.92; H 4.77; N 9.95 Found C 73.90; H 4.75; N 9.95, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1614 (C=N stretching), 1219 (C-N stretching), 1114 (N-O stretching), 3020 (C-H stretching of aromatic ring), 2880 (C-H stretching of aliphatic), 1595 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.070-8.086) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7); (7.565-7.590) ppm (2H,t,11); (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937)ppm (4H,d,8,8').

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-((oxido(p-tolyl)imino)methyl)benzylidene)aniline oxide)(4):

From 4-methyl aniline (4) yield 73% solid with m.p. 34°C. The CHN analysis for C₅₄H₄₄N₆O₆; C 74.30; H 5.08; N 9.63; Found C 74.23; H 5.05; N 9.61, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1614 (C=N stretching), 1219 (C-N stretching), 1112 (N-O stretching), 3020 (C-H stretching of aromatic ring), 2880 (C-H stretching of aliphatic), 1595 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.070-8.086) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7); (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937)ppm (4H,d,8,8'); 3.365 ppm (6H,s,11(CH₃)).

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-(((4-methoxy phenyl)oxidoimino)methyl)benzylidene)aniline oxide) (5) :

From 4-methoxy aniline (5) yield 68 % solid with m.p. 36°C. The CHN analysis for C₅₄H₄₄N₆O₈; C 71.67; H 4.90; N 9.29 Found C 71.63; H 4.90; N 9.27, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1612 (C=N stretching), 1218 (C-N stretching), 1110 (N-O stretching), 3020 (C-H stretching of aromatic ring), 2882 (C-H stretching of aliphatic), 1593 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.070-8.086) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7); (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937)ppm (4H,d,8,8'); 4.365 ppm (6H,s,11(OCH₃)).

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-(((4-chlorophenyl)oxidoimino)methyl)benzylidene)aniline oxide)(6):

From 4-chloro aniline (6) yield 78 % solid with m.p. 40°C. The CHN analysis for C₅₂H₃₈Cl₂N₆O₆; C 68.35; H 4.19; N 9.20; Found C 68.33; H 4.18; N 9.20, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1616 (C=N stretching), 1213 (C-N stretching), 1115 (N-O stretching), 3023 (C-H stretching of aromatic ring), 2884 (C-H stretching of aliphatic), 1591 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.180-8.192) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7); (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937)ppm (4H,d,8,8').

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-(((4-bromophenyl)oxidoimino)methyl)benzylidene)aniline oxide)(7):

From 4-bromo aniline (7) yield 77 % solid with m.p. 42°C. The CHN analysis for C₅₂H₃₈Br₂N₆O₆; C 62.29; H 3.82; N 8.38; Found C 62.26; H 3.80; N 8.36, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1615 (C=N stretching), 1218 (C-N stretching), 1114 (N-O stretching), 3025 (C-H stretching of aromatic ring), 2888 (C-H stretching of aliphatic), 1595 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.180-8.192) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7); (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937) ppm (4H,d,8,8').

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-(((4-fluorophenyl)oxidoimino)methyl)benzylidene)aniline oxide)(8) :

From 4-fluoro aniline (8) yield 79 % solid with m.p. 44°C. The CHN analysis for C₅₂H₃₈F₂N₆O₆; C 70.90; H 4.35; N 9.54; Found C 70.88; H 4.30; N 9.52, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1617 (C=N stretching), 1220 (C-N stretching), 1111 (N-O stretching), 3027 (C-H stretching of aromatic ring), 2890 (C-H stretching of aliphatic), 1597 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.180-8.192) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7) ; (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937) ppm (4H,d,8,8').

4,4'-(5,5'-(1,4-phenylene)bis(4,5-dihydroisoxazole-5,3-diyl))bis(N-(4-(((4-nitrophenyl)oxidoimino)methyl)benzylidene)aniline oxide)(9) :

From 4-nitro aniline (9) yield 83 % solid with m.p. 48°C. The CHN analysis for C₅₂H₃₈N₈O₁₀; C 66.80; H 4.10; N 11.99; Found C 66.78; H 4.10; N 11.96, FT-IR spectra (KBr pellet) $\nu(\text{cm}^{-1})$ 1620 (C=N stretching), 1224 (C-N stretching), 1118 (N-O stretching), 3029 (C-H stretching of aromatic ring), 2891 (C-H stretching of aliphatic), 1590 (C=C stretching of aromatic ring), $\delta_{\text{H}}(\text{CDCl}_3)$ 8.376 ppm (4H,s,3); (8.210-8.221) ppm (4H,d,2); (7.912-7.921) ppm (4H,d,1); (7.709-7.719) ppm (4H,d,7) ; (7.402-7.412) ppm (4H,d,6); 7.285 ppm (8H,s,4,5), 7.065 ppm (4H,s,9,10), (4.625-4.725) ppm (2H,t,12); (3.927-3.937) ppm (4H,d,8,8').

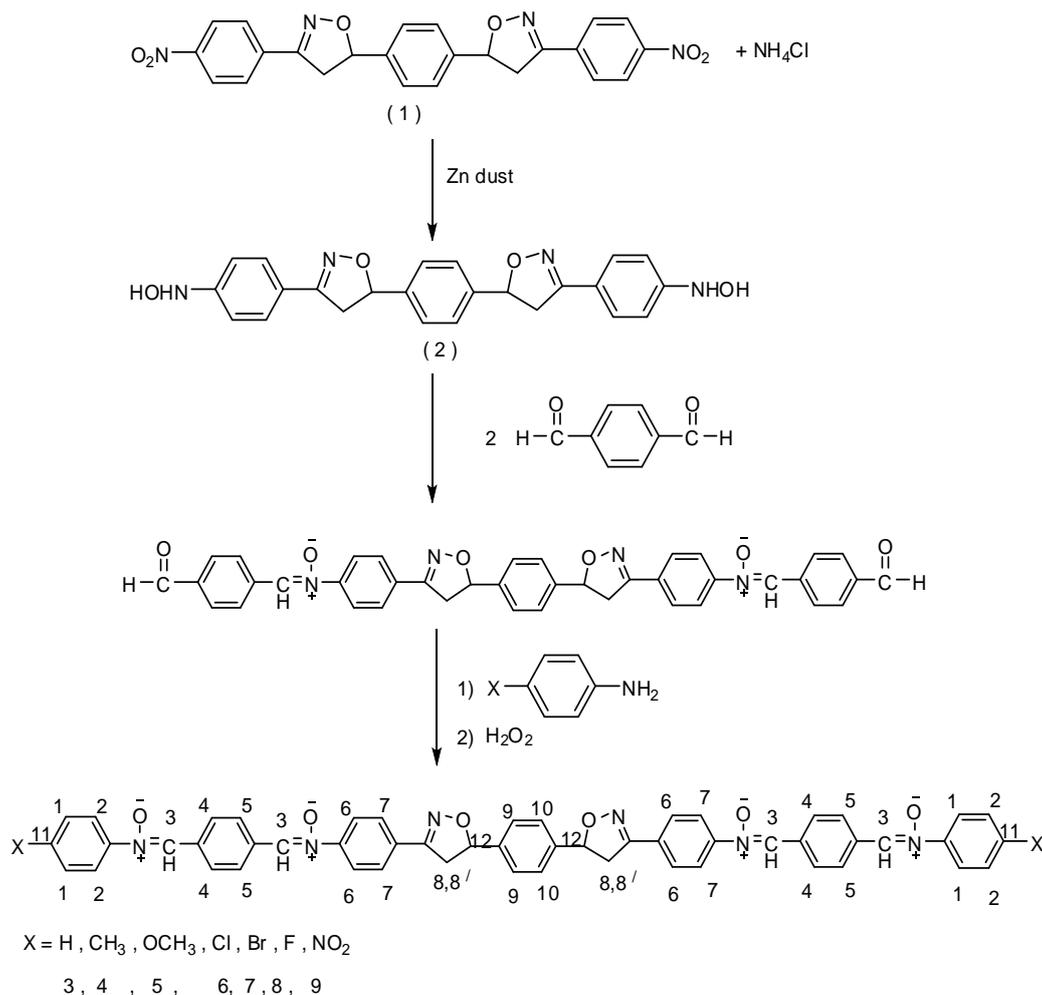
Computational methods

All theoretical calculations in this work were performed using the computational methods implemented in the Hyper chem. Version 7.5. Geometry optimization of the studied compounds was done by performing the semi-empirical molecular orbital theory at the level PM3[26].

III. Results And Discussion

Treatment of chalcones derivatives (3-9) with hydroxylamine hydrochloride in boiling ethanol gave 4,5-dihydroisoxazole derivatives compounds, after purification by recrystallization from ethanol, pure 4,5-dihydroisoxazole-5,3-diyl derivatives compounds as shown in (scheme 2) in (73-83)% yield were obtained. The structures of these products were established from their elemental analysis, FT-IR, C.H.N and ¹H NMR spectra. The FT-IR spectra of 4,5-dihydroisoxazole-3,5-diyl compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710) cm⁻¹. These fact confirmed the correct expected chemical structure of these compounds. All the IR spectra of 4,5-dihydroisoxazole-3,5-diyl derivatives showed a peak at (1612-1620) cm⁻¹ which related to (C=N) stretching of 4,5-dihydroisoxazole ring , a peak at (1213-1224) cm⁻¹ which appeared due to (C-N) stretching of 4,5-dihydroisoxazole ring and a peak at (1590-1597) cm⁻¹ which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3029) cm⁻¹ and the C-H stretching aliphatic showed a peak within the range (2880-2891) cm⁻¹. The N-O stretching showed a peak within the range (1110-1118) cm⁻¹.

All the ¹H NMR spectra of 4,5-dihydroisoxazole ring were characterized [27-29] by the presence protons (8,8') of 4,5-dihydroisoxazole ring showed doublet signals within the range (3.927-3.937) ppm because interaction with protons in position (12) and showed triplet signals within the range (4.625-4.725) ppm which appeared to protons in position (12) because interaction with two protons in (8 and 8') position , while The proton in position (3) of showed singlet signals at 8.376 ppm. The protons of aromatic rings showed doublet signal within the range (8.070-8.221) ppm ppm which appeared to four protons in (2), while the other protons in (1) position showed doublet signals within the range (7.912-7.921) ppm. The aromatic protons in position (7) showed doublet signals within the range (7.709-7.719) ppm. The other two protons in positions (6) showed doublet doublet signals within the range (7.402-7.412) ppm.while the protons in position (4,5) showed singlet signal within the range 7.285 ppm. The other protons in position (9,10) showed singlet signal within the range 7.065 ppm. The aromatic protons in compound (3) showed triplet signal within the range (7.565-7.590) ppm due to proton in position (11). The CH₃ protons showed singlet signal for six protons in the region 3.365 ppm. The OCH₃ protons showed singlet signal for six protons at 4.365 ppm.



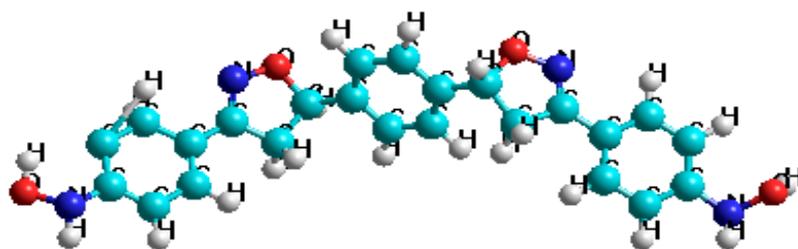
Scheme (2)

Computational Study

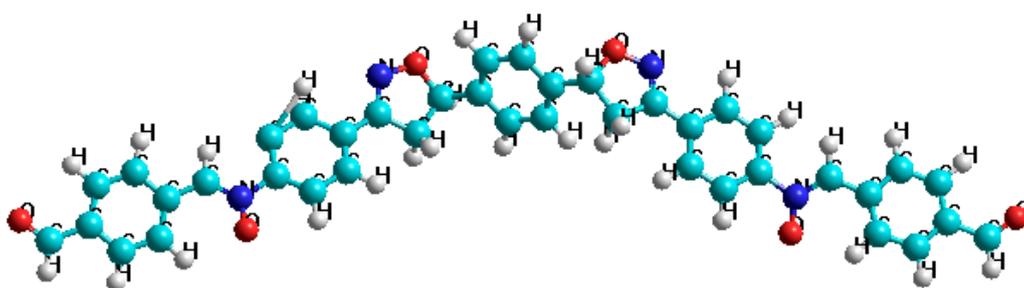
The optimized structures of the studied molecules are shown in Fig 4. The PM3 geometry optimizations yield planar structures for the synthesis compounds. The general geometries of molecule all compounds are very similar. The total energy, highest occupied and the lowest unoccupied molecular orbital (HOMO and LUMO, respectively) energies and the energy band gap (LUMO–HOMO energy difference, ΔE) and the dipole moment, μ (in Debyes) for the studied molecules are given in Table 1. The calculated dipole moment indicates that the studied molecules are pole. This means that these molecules may interact with its environmental, especially other polar molecules. The spatial distributions of HOMO LUMO are shown in Fig. 5. In general the all molecules gave similar HOMO and LUMO orbitals.

Table1. The Total energy, MO energy of the lowest, highest, HOMO, LUMO, levels, ΔE (in au) and the dipole moment, μ (in Debyes) for the studied molecules

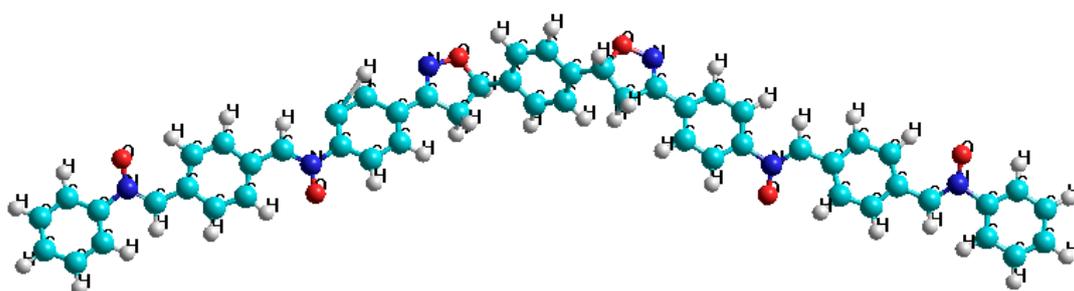
Mol.	Method	Total energy (Kcal/mol)	HOMO (ev)	LUMO (ev)	ΔE (au)	μ (D)
1	PM3	-115146.0078	-8.8763	-1.1579	-7.7184	4.967
2	PM3	-175292.7188	-8.9146	-1.6907	-7.2239	4.123
3	PM3	-218995.9844	-8.0653	-1.4164	-6.6489	9.293
4	PM3	-225902.1719	-8.0342	-1.4063	-6.6279	10.03
5	PM3	-239425.4219	-8.0090	-1.3986	-6.6104	10.46
6	PM3	-232899.7188	-8.1681	-1.4221	-6.746	9.025
7	PM3	-234512.9375	-7.9755	-2.3950	-5.5805	5.649
8	PM3	-238594.1094	-8.1731	-1.4776	-6.6955	8.04
9	PM3	-252652.6719	-8.1975	-2.4939	-5.7036	4.238



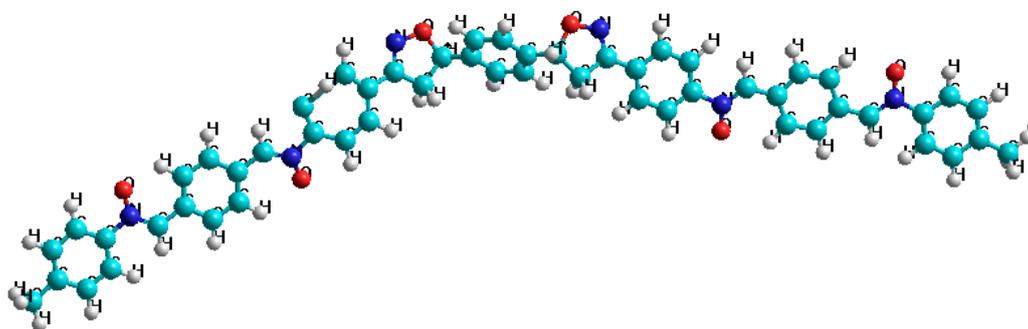
Compound (1)



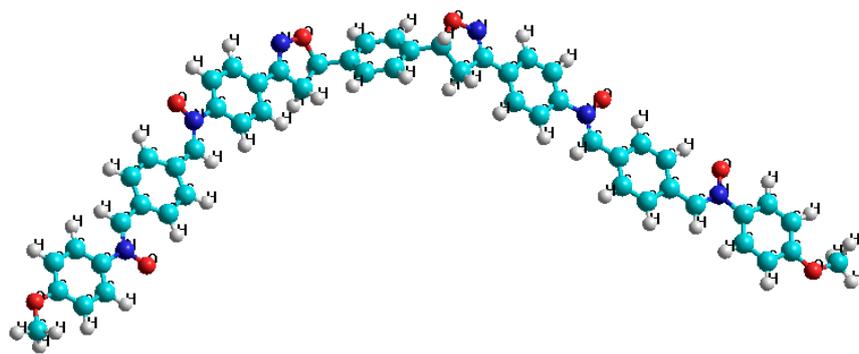
Compound (2)



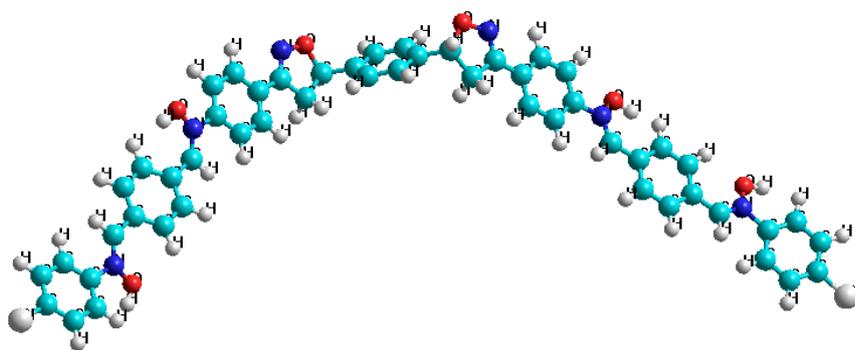
Compound (3)



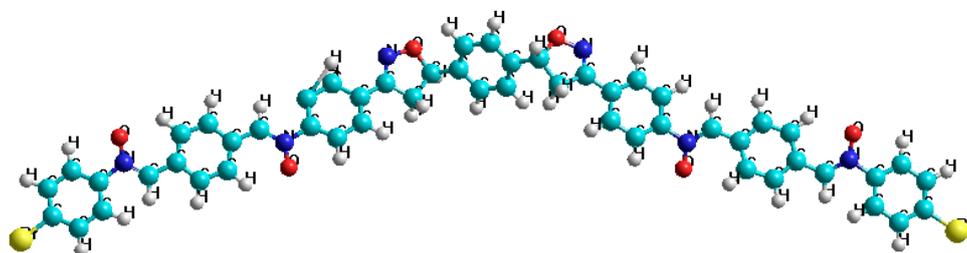
Compound (4)



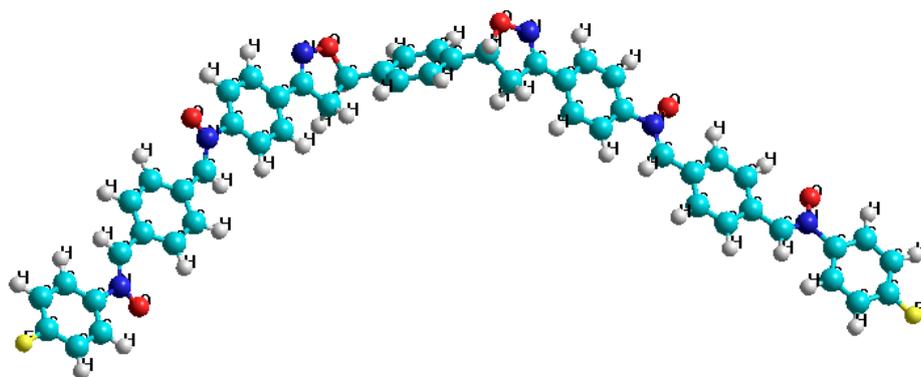
Compound (5)



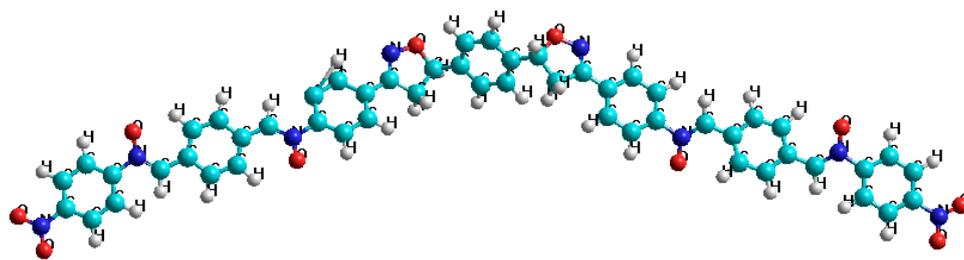
Compound (6)



Compound (7)

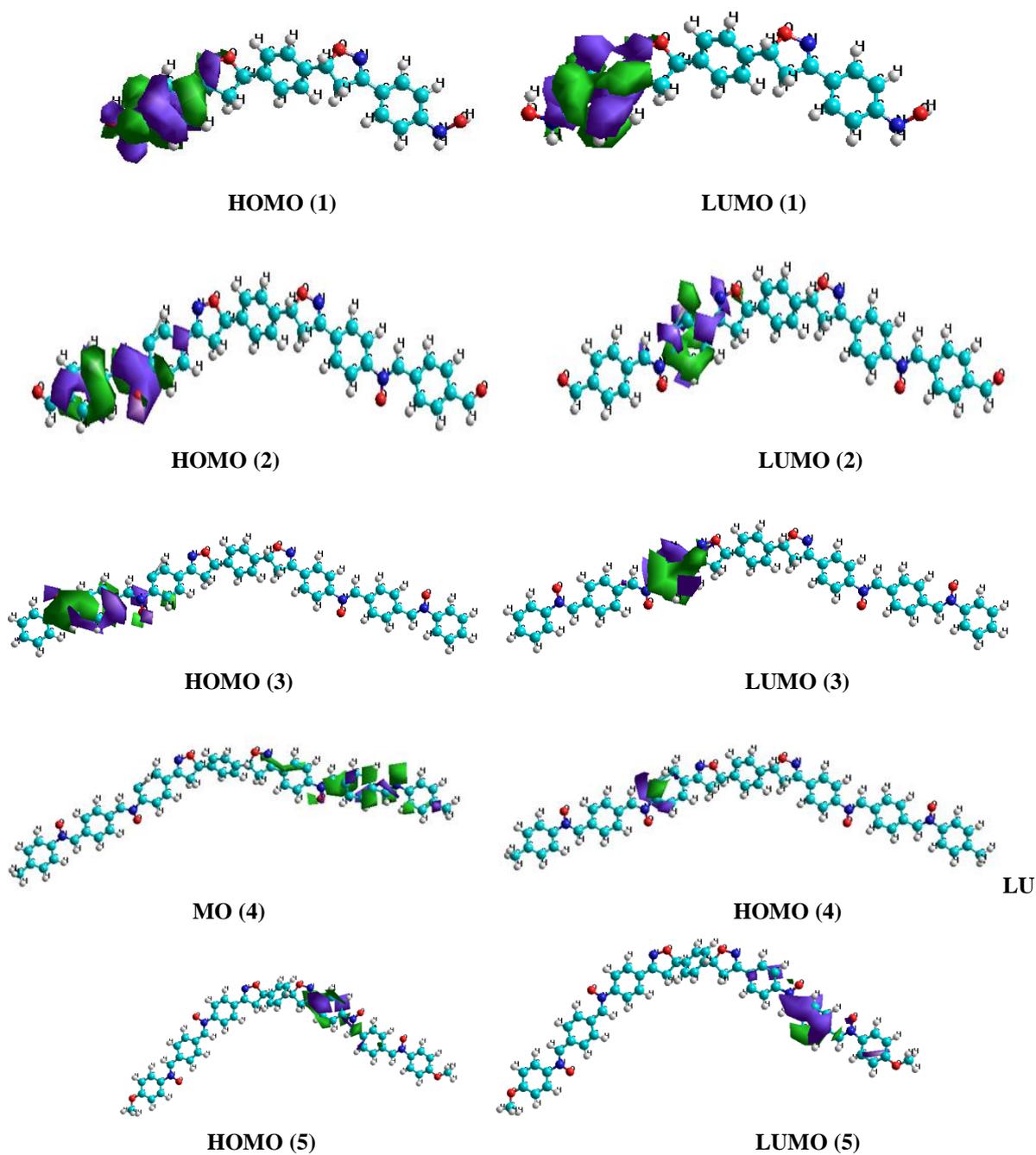


Compound (8)



Compound (9)

Fig1. The optimized structure of the studied molecules optimization has been performed by PM3 method.



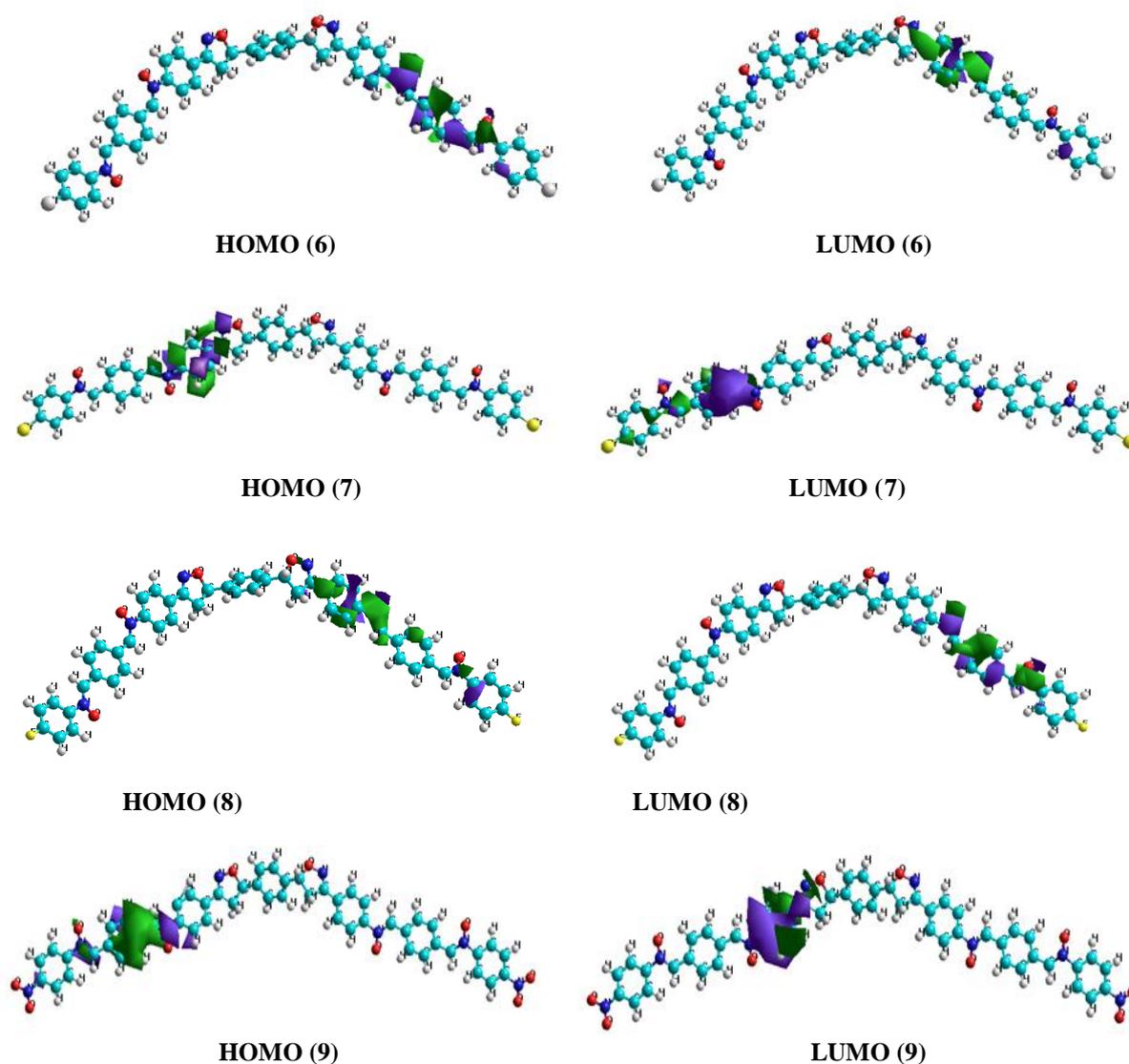


Fig 2. 3D HOMO and LUMO plots of the studied molecules

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