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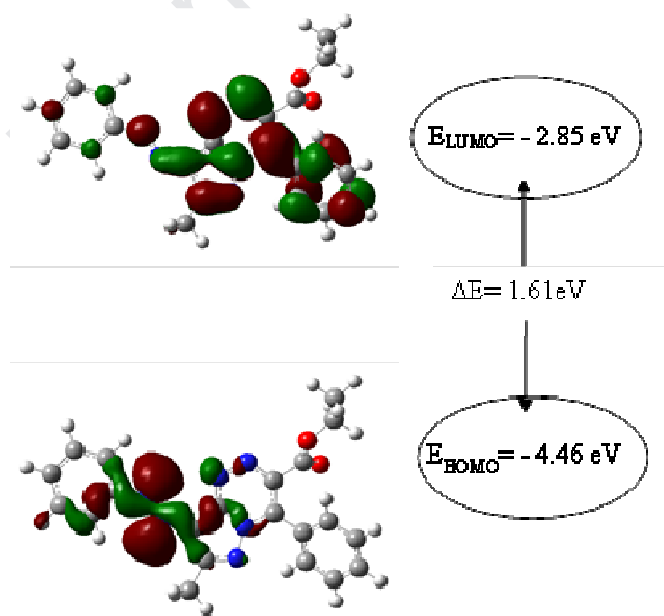
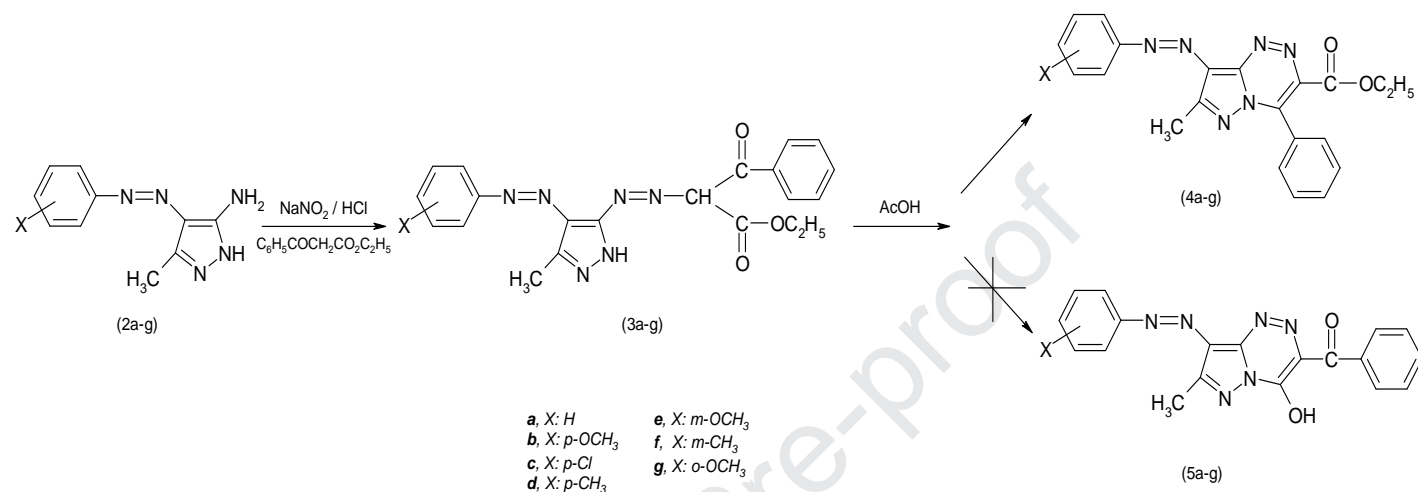
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Graphical Abstract

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Synthesis of some new pyrazolo[5,1-c][1,2,4]triazine derivatives and computational study



Synthesis of some new pyrazolo[5,1-c][1,2,4]triazine derivatives and computational study

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Abstract

In this study, the synthesis novel of seven new pyrazolo[5,1-c][1,2,4]triazin derivative disperse dyestuffs was reported. First, 2-arylhydrazone-3-ketiminobutyronitriles were synthesized and reacted with hydrazine hydrate to afford 5-amino-4-arylo-3-methyl-1H-pyrazoles. The 5-amino-4-arylo-3-methyl-1H-pyrazoles were diazotised and coupled with ethyl benzoylacetate to give ethyl pyrazolylazo benzoylacetate. The final product was heated in glacial acetic acid and seven new pyrazolo[5,1-c][1,2,4]triazine dyestuffs were synthesized. FT-IR, ¹H NMR and elemental analysis techniques were used to characterize synthesized dyestuffs. Density functional theory calculation methods were used for to determine the molecular geometries and spectroscopic properties of the new seven dyestuffs. The acquired results from calculations and experiments are conform each other.

Keywords: Ethyl benzoyl acetate, Azo dyestuff, Pyrazole, DFT, Electronic properties

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1. Introduction

Pyrazoles and their substituted derivatives exhibit wide variety of biological and pharmacological activities [1-8] and also find application in photography [9, 10] and as dyes [11,12]. Some pyrazoles were reported to have nonnucleoside HIV-1 reverse transcriptase inhibitory activity [3,7,8, 13-16].

Azolo annulated [1,2,4]triazines can be considered as isosteres of purine bases. Due to a wide and profound biological activity [17-21], this family of heterocyclic compounds causes a growing interest of researchers working in the fields of medicinal chemistry and pharmacology. Pyrazolo[5,1-c][1,2,4]triazines are similar in structure to nucleic bases, can act as metabolites and are useful as antiviral and antitumor agents [17]. In the literature, pyrazolotriazines have been reported to have cytotoxicity against cancer cells [22, 23]. Berger and coworkers reported that specific polysubstituted pyrazolo[5,1-c][1,2,4]triazines inhibit selectively B-Raf kinase activity, and are preferred for the treatment of B-Raf kinase related disorders [24]. Therefore, the development of new methods and the synthesis of newly fused 1,2,4-triazine derivatives is of great importance.

Many patents and articles in the literature identify the synthesis and dyeing characteristics of monoazo dyestuff on a heterocyclic coupling component [25-28]. There are very few studies involving monoazo dyestuff based on the pyrazolo[5,1-c][1,2,4]triazine ring. In connection with our interest in this class of compounds, our study group has reported the synthesis of some pyrazolo[5,1-c][1,2,4]triazines [29-31]. In this article, we present the synthesis of seven new monoazo dyestuff based on the pyrazolo[5,1-c] [1,2,4]triazine ring system.

In the recent years, there has been great interest to the quantum chemical calculations especially density functional theory (DFT) methods which use to determine the properties of the molecular, optical and electronic structures of the small and big sized chemical molecules at

low computational time [32–35]. In this paper, as a part of continuous studies of our research group, we synthesised new pyrazolo derivatives and characterized by elemental analyses, FT-IR, ¹H- NMR spectroscopic methods. Also, we studied on the estimated of the geometry optimization, the vibrational frequencies, the chemical shifts and the electronic properties of azo dyestuff because of their cytotoxic activity in medical and usage as a polyester/polyamide dye in industrial applications.

2. Experimental

2.1. General details

The chemicals utilized in the synthesis were supplied from Aldrich and Merck Chemical Company without any purification. Suitable spectroscopic grade solvents were used.

IR spectra were recorded via Perkin Elmer UATR Two (FT-IR) Spectrophotometer. ¹H NMR spectra were obtained on Agilent 400/55 annual refill 400 in DMSO-d₆ utilizing TMS as the internal reference and chemical shifts (δ) were reported in ppm. Melting points of dyestuffs were determined using Electrothermal 9100 melting point apparatus and not corrected.

2.2. Synthesis of 2-arylhydrazone-3-ketiminobutyronitriles (1a-g) and 5-amino-4-arylazo-3-methyl-1H-pyrazoles (2a-g)

1a-g and **2a-g** were synthesized according to the literature [36-38]. The general route for the synthesis of **1a-g** and **2a-g** is outlined in **Scheme 1**.

Scheme 1 here about

2.3. Synthesis of pyrazolo[5,1-c][1,2,4]triazine derivative dyestuffs (4a-g)

The synthesized **2a-g** compounds (0.01 mol) were dissolved in a mixture containing glacial CH_3COOH and concentrated HCl (20 ml, ratio 1: 1), and the solution was cooled to 0-5°C. Then NaNO_2 solution (0.69 g, 0.01 mol) prepared in 10 ml of water was added dropwise to this solution cooled at 0-5 °C with vigorous stirring for 1 h. The clear diazonium salt solution was added dropwise to a solution of ethyl benzoyl acetate (1.92 g, 0.01 mol) prepared in pyridine (10 mL) and cooled (0-5 °C). The pH of the coupling mixture was kept at 7-8 throughout the coupling by adding aqueous sodium acetate. Stirring was continued at 0-5 °C for 4 hours and diluted with cold water (50 ml). The precipitated products were filtered, washed several times with water, dried and recrystallized from $\text{DMF-H}_2\text{O}$ to give ethyl pyrazolylazo benzoylacetate (**3a**). The obtained product (**3a**) was refluxed for 4 hours in glacial CH_3COOH (30 ml). The solvent casted out and the final product was collected by filtration and dried. It was recrystallized from $\text{DMF-H}_2\text{O}$ (3:1) and orange crystals of the **4a** dyestuff were obtained. This procedure was also used to synthesis dyestuffs **4b-g** (**Scheme 2**). Elemental analyzes and melting points of the dyestuffs obtained are listed in Table 1.

Scheme 2 here about

Table 1 here about

3. Computational details

Quantum chemical calculations were performed at the B3LYP levels of theory with the Gaussian 16, Rev. B01 package [39] and GaussView 6.0.16 [40] was used for visualization of the structure. Geometries were optimized to the global minima at the *ab initio* DFT level 6-31G(d,p) basis set. The optimized structures were used for the calculations of vibrational

frequencies, NMR chemical shift, electronic absorption spectrum and Natural Bond Orbital (NBO) analysis. We have calculated the chemical shifts of them in the ground state to differentiate the basis from the experimental chemical shifts and geometric parameters by using DFT (B3LYP) method. And also, time-dependent density functional theory (TD-DFT) was used to examine the electronic absorption spectrum. These calculations are worthy for ensuring comprehend the chemical shifts and molecular parameters.

4. Results and Discussion

4.1. Molecular geometry

The geometric structures of the **4a-g** compounds obtained from B3LYP/6-31G(d,p) methods are represented in **Figure 1** along with the atom numbering schemes. The **4a** molecule has got 47 atoms and their basic vibrational modes are 138. The **4b**, **4e** and **4g** molecules have got 51 atoms and their basic vibration modes are 147. While **4d** and **4f** molecules have got 50 atom and 114 basic vibration modes, **4c** molecule has got 47 atoms and 137 basic vibration modes. The azo double bonds (N=N), the carbonyl single bond lengths (C-O) and the carbonyl double bond lengths (C=O) are computed in the range of 1.304-1.267 Å, 1.338- 1.341 Å and 1.215-1.214 Å, respectively.

Figure 1 here about

4.2. Tautomerization

¹H-NMR spectra of the dyestuffs showed CH₃ of ethoxy group peak at 0.99-1.00 ppm and -OCH₂- of ethoxy group peak at 4.17-4.18 ppm. Also, ¹H-NMR spectra of the dyestuffs did not show any the OH group peak. FT-IR spectra of the dyestuffs also did not show any the OH group peak. These suggest that these dyestuffs in the **4a-g** form and not in the **5a-g** form.

The structures of azo dyestuffs are thought to be as shown in **Scheme 2**. Furthermore, it is believed that the newly synthesized dyestuffs do not have a tautomeric structure.

4.3. Vibrational analysis

The FT –IR spectra of **4a-g** dyestuffs shows aromatic C–H bands at 3097-3051 cm^{-1} , aliphatic C–H bands at 2996-2973 cm^{-1} , azo (N=N) bands at 1579-1516 cm^{-1} , carbonyl (C = O) bands at 1728–1714 cm^{-1} and C–O bands at 1086–1014 cm^{-1} . As for corresponding B3LYP/6-31G(d,p) methods, aromatic C–H bands, aliphatic C–H bands, azo (N=N) bands, carbonyl (C = O) bands and C– O bands have been calculated as the values in the range of 3207-3178 cm^{-1} , 3059-3016 cm^{-1} , 1598-1505 cm^{-1} , 1801-1798 cm^{-1} and 1058-994 cm^{-1} , respectively. Experimental and theoretical results are tabulated in Table 2.

Table 2 here about

The correlations values (R^2) between these experimental and theoretical data for each molecule are computed and presented in **Table 2**. The compound **4e** has the most coherent correlation with the value of 0.9998 and **4b** compound has the least coherent correlation value with the value of 0.9965 which can be seen in **Figure 2**. These correlation values indicated that experimental and the theoretical data are very coherent each other.

Figure 2 here about

4.4. ^1H NMR analysis

^1H NMR spectra of **4a-g** dyestuffs showed at 7.94–7.07 ppm (aromatic H), 4.18–4.17 ppm (OCH_2), 2.74–2.69 ppm (pyrazole CH_3) and 1.00-0.99 (ethoxy CH_3), respectively. On the other hand, the theoretical ^1H NMR data (**4a-g** dyes) obtained from B3LYP/6-31G(d,p) method are collected in **Table 3** together with the experimental data.

Table 3 here about

As for corresponding B3LYP/6-31G(d,p) methods, aromatic H peaks, OCH₂ peaks, pyrazole CH₃ peaks and ethoxy CH₃ peaks have been calculated as the values of 8.84-7.17 ppm, 4.70-4.35 ppm, 2.90-2.85 and 1.75-1.38 ppm, respectively. The compound **4a** has the most coherent correlation with the value of 0.9968 and **4g** compound has the least coherent correlation value with the value of 0.9912 which can be seen in **Figure 3**. These correlation values indicated that experimental and the theoretical data are very coherent each other.

Figure 3 here about**4.5. Electronic Properties**

The electronic properties of a molecule are designated with the energy of HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbitals) molecular orbitals. Beside the electronic properties the chemical reactivity, stability, optical properties and bioactivity of a molecule also determine with these parameters [**41**, **42**]. The difference between HOMO and LUMO orbitals indicates the chemical reactivity of a molecule. If the difference is small the kinetic stability of a molecule is low so the intermolecular charge transfer is very high between the electron donor and acceptor groups. When **Table 4** is examined, the lowest energy gap belongs to dyestuff **4d** with 1.06 eV. On the other hand, the largest energy gap belongs to dyestuff **4f** with 3.35 eV.

Table 4 here about

In compound **4d**, the -CH₃ group is attached to the p-position and the compound has a more linear structure. In compound **4f**, the -CH₃ group is attached to the meta position and is closer to the azo group containing an unpaired electron pair. The binding of the CH₃ group to the phenyl ring from different corners indicates that the meta-position dye (**4f**) may be less reactive due to the steric effect and the p-position dye (**4d**) may be more reactive due to its planar

nature. The other parameters; I (ionization potential), A (electron affinity), χ (electronegativity), η (hardness), S (softness), μ (electronic chemical potential) and ω (global electrophilicity index) values of dyestuff **4a**, **4b**, **4c**, **4e**, **4f** and **4g** are nearly similar. Because of the delocalization of the conjugated π bonds, the HOMO-LUMO orbitals are located in the aromatic rings and azo groups, as seen **Figure 4 and 5**.

Figure 4 here about

Figure 5 here about

The absorption spectra were computed using the TD-DFT method in combination with the same functional, basis set in gas phase and in chloroform. The calculated maximum absorption wavelengths (λ_{\max}), and electronic transitions are shown in **Table 5**. The highest electronic absorption bands are calculated at 531.9 nm in gas phase and 517.2 nm in chloroform by using TD-DFT/B3LYP/6-31G(d,p) level for **4g** and also they can be attributed $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions. They were determined that these band caused by the transitions of HOMO-1 \rightarrow LUMO (78%), HOMO-1 \rightarrow LUMO+1(14%), HOMO \rightarrow LUMO (6%). The corresponding peaks for compounds **4a-f** in chloroform were obtained at 507.6 nm HOMO-1 \rightarrow LUMO (79%), 499.1 nm with the contribution HOMO-1 \rightarrow LUMO (84%), 504.7 nm with the contribution HOMO-1 \rightarrow LUMO (86%), 505.6 nm with the contribution HOMO-1 \rightarrow LUMO (84%), 503.2 nm with the contribution HOMO-1 \rightarrow LUMO (84%) and 507.2 nm with the contribution HOMO-1 \rightarrow LUMO (84%), respectively, as can be seen in **Table 5**. These values are also similar with the obtained from the gas phase calculations. The contribution rate of HOMO-LUMO orbitals are determined by using the GaussSum 2.2 program [43].

Table 5 here about

4.6. Natural Bond Orbital (NBO) Analysis

Additionally, the 6-31G(d,p)/B3LYP level were performed to the natural bond orbital (NBO) calculations for the complexes **4a-g**. NBO analysis provides a favorable charge transfer

or conjugation interaction in the molecular system, and also uses work on intermolecular binding and interaction between bonds [44]. The $E^{(2)}$ value computed from the NBO analysis show the energy of interaction between the electron acceptor and the electron donor and the larger value demonstrates an intense interaction between electron donors and electron acceptors [45].

As seen from the **Table 6**, the calculated $E^{(2)}$ values presented that the significant charge flows generally occurred from the lone pair of the carbon atoms of the pyrazole ring (C13 or C14) to the π^* bond of (N22-N23) which have stabilization energy in the range of 331.89 -338.67 kcal/mol. Also, electron densities given in the **Table 6** are another evidence of the larger electron delocalization.

Table 6 here about

5. Conclusions

Seven new pyrazolo[5,1-c][1,2,4]triazine derived azo dyestuffs have been synthesized. Characterization of these molecules was achieved by FT-IR and ^1H NMR spectrum measurements. Molecular structures of azo dyestuffs synthesized according to FT-IR and ^1H NMR results were found to be in **4a-g** form. The structures, electronic and vibration properties of novel azo dyestuffs examined by density functional methods. The vibration frequencies of some of the main peaks found with the help of experimental and theoretical studies are compatible with each other and correlation values were obtained between 0.9965 and 0.9998. The ^1H NMR data obtained by experimental and theoretical studies are also compatible with each other and their correlation values ranged from 0.9968 to 0.9912.

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Figure Captions

Figure 1: The calculated optimized structure of dyestuffs **4a-g**.

Figure 2: Linear regression results obtained by theoretical and experimental infrared values of **4a-g** compounds.

Figure 3: Linear regression results obtained by theoretical and experimental ^1H NMR values of **4a-g** compounds.

Figure 4: HOMO-LUMO orbitals diagram of the dyestuffs **4a-g**.

Figure 5: Atomic composition of dyestuff **4d**.

Tables

Table 1. Elemental analysis of dyestuffs **4a-g**.

Table 2. FT-IR data for dyestuffs **4a-g**.

Table 3. ^1H NMR data for dyestuffs **4a-g**.

Table 4. Electronic parameters of dyestuffs **4a-g**.

Table 5. Calculated absorption wavelengths, energies and oscillator strengths of **4a-g** using the TD-DFT method at the B3LYP/6-31G(d,p) level.

Table 6. Remarkable stabilization interactions in the **4a-g**.

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Highlights

- Seven new azo dyestuffs have been synthesized.
- Dyestuffs have been characterized by FT-IR and ^1H NMR.
- Theoretical studies have been done with DFT calculation method.
- Theoretical and experimental results are consistent.
- Natural Bond Orbital (NBO) Analysis.

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Author Contribution Statement

Fati Yıldırım: Methodology, Experimental studies, Reviewing, Analysis interpretation

Aykut Demirçalı: Writing, Experimental studies, Analysis interpretation, Data Curation

Aslı Öztürk Kiraz: Theoretical studies, Data curation

Fikret Karcı: Review, Consultancy

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: