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SÍNTESE, CARACTERIZAÇÃO, ATIVIDADE ANTIFÚNGICA E RELACIONAMENTO ESTRUTURA-ATIVIDADE: ESTUDO DE ALGUMAS BASES MONO E DI-SCHIFF

SYNTHESIS, CHARACTERIZATION, ANTIFUNGAL ACTIVITY AND STRUCTURE – ACTIVITY RELATIONSHIPS: STUDY OF SOME MONO- AND DI-SCHIFF BASES

JASIM, Ekhlas Q.[1]; DHAIF, Hawraa K.[2]; MUHAMMAD-ALI, Munther A.[3]*

[1,3]Basrah University, College of Pharmacy, Pharmaceutical Chemistry Department. Iraq

[2]Basrah University, College of Education for Pure Science, Department of Chemistry. Iraq

*Corresponding author
e-mail: muntheralamery@yahoo.com

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RESUMO

As bases de Schiff (SB) são tipos importantes de compostos orgânicos e possuem ampla gama de atividades biológicas devido ao uso comercial e farmacêutico. As diferentes atividades desses compostos chamaram a atenção de pesquisadores e os induziram a sintetizar e estudar novos tipos desses compostos. Duas séries de derivados da base Schiff foram sintetizadas pelas reações de condensação de aldeídos salicilaldeído substituído, 4- (N, N-dimetilamino) benzaldeído ou 2,4-dimetoxibenzaldeído com ácido 2-amino-5-iodobenzóico (1:1) ou com 3 Ácido 5-diamenobenzóico (1:2) em etanol absoluto como solvente. Diferentes técnicas analíticas caracterizaram a estrutura das bases de Schiff sintetizadas como, por exemplo, Transformada de Fourrier por Infravermelho (FT-IR), e Ressonância Magnética Nuclear de Próton ^{1}H-NMR. A pureza dos compostos sintetizados foi testada por microanálise elementar (CHN) e cromatografia em camada delagada (TLC). As propriedades estruturais das moléculas estudadas foram investigadas teoricamente através da realização da teoria funcional da densidade (DFT) usando o software HyperChem. A lipofilicidade dos compostos testados mostrou que os compostos 2c, 2b, 2a e 1c apresentam valores de logP inferiores a (5), 2,90, 3,78, 3,82 e 4,57, respectivamente, enquanto 1b e 1a possuem valores de logP superiores a (5), 5,01 e 5,03, respectivamente. A distribuição de carga de Mulliken mostrou que o átomo de oxigênio carbonílico do grupo carboxílico é mais negativo (~ -0,4) em comparação com outros átomos de oxigênio (~ -0,3) em todos os compostos selecionados. O diagrama de energia dos orbitais moleculares de fronteira e seu intervalo de banda forneceram indicações sobre a reatividade química e a estabilidade cinética das moléculas. Os compostos sintetizados foram testados quanto a efeitos antifúngicos contra *Aspergillus niger* e *Candida albicans*, o que indicou que os compostos apresentavam boa atividade antifúngica.

Palavras-chave: *Atividade microbiana, HOMO-LUMO, HyperChem, SAR, Schiff-Base.*

ABSTRACT

Schiff bases (SB) are an important type of organic compounds and have a wide range of biological activities due to commercial and pharmaceutical trading uses. The different activities of these compounds induced the researchers to synthesized and studied new types of these compounds. Two series of Schiff base derivatives were synthesized by the condensation reactions of substituted aldehydes salicylaldehyde, 4-(N,N-dimethylamino)benzaldehyde or 2,4-dimethoxybenzaldehyde with 2-amino-5-iodobenzoic acid (1:1) or with 3,5-diamenobenzoic acid (1:2) in ethanol absolute as a solvent. Different analytical techniques characterized the structure of the synthesized Schiff bases; for instance, Fourier transform infrared FT-IR and proton nuclear magnetic resonance ^{1}H-NMR. The purity of the synthesized compounds was tested by elemental microanalysis CHN and thin layer chromatography TLC. The structural properties of the studied molecules were investigated theoretically by performing density functional theory (DFT) using the HyperChem software. The lipophilicity of the tested compounds showed that the compounds 2c, 2b, 2a, and 1c have logP values less than (5), 2.90, 3.78, 3.82 and 4.57, respectively, whereas, 1b and 1a have logP values higher than (5), 5.01 and 5.03, respectively. The Mulliken charge distribution showed that the carbonyl oxygen atom of the carboxylic group is more negative (~ -0.4) as compared to other oxygen atoms (~ -0.3) in all selected compounds. Frontier molecular orbitals energy

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diagram and their bandgap provided indications about chemical reactivity and kinetic stability of the molecules. The synthesized compounds were tested for antifungal effects against *Aspergillus niger* and *Candida albicans*, which indicated that the compounds had good antifungal activity.

Keywords: *Microbial activity, HOMO-LUMO, HyperChem, SAR, Schiff-Base.*

1. INTRODUCTION:

The problem of microbial resistance is still the aim of the development of market antibiotics and enhance the drug companies to release a new type of medical agents to reduce the microbial infections (Al-Amiery *et al.*, 2009). It is, therefore, necessary to explore further, novel antifungal formulations to control fungal infections (Kathiravan *et al.*, 2012). The compounds called Schiff-base, imine, or azomethine function present in diverse natural compounds and non-natural derivatives are critical for their biological activities. These types of compounds were synthesized by direct condensation of primary amines with an aldehyde or ketone compounds (da Silva *et al.*, 2011).

SBs are, in reality, known to have a wide range of biological properties such as antibacterial (Kangah *et al.*, 2.17; Al Momani *et al.*, 2013), anticancer (Abd-Elzaher *et al.*, 2016), antiviral (Kumar *et al.*, 2010), antifungal (Chohan and Hanif, 2013; Bharti *et al.*, 2010), antiparasitic (Al-Kahraman *et al.*, 2010) in addition to other biological performances (Abu-Dief and Mohamed, 2015). On the other hand, their structures offer a high probability of structural change, implying a high degree of molecular diversity, which remains very useful for the development of new, less toxic and potent therapeutic agents (Kangah *et al.*, 2.17).

Recently, the studies, including quantitative structure-activity relationship (QSAR), are great importance in the field of modern chemistry and biochemistry. To obtain a significant correlation, it is essential to use the appropriate descriptors, whether they are empirical, theoretical, or derived from easily obtainable experimental characteristics of structures. These descriptors refer to the molecular properties and can thus provide exact information about the physicochemical nature of the chemical systems under investigation (Thakur *et al.*, 2004).

In this paper, two series of Schiff bases were synthesized and characterized. Their antifungal activities were evaluated against *Aspergillus niger* and *Candida albicans* by the disc diffusion method. The study of structure-activity relationships (SAR) between the antifungal activity and the structural properties were also evaluated.

2. MATERIALS AND METHODS:

2.1. Materials and Reagents

All chemicals used in this study were of reagent grade (supplied either by Sigma-Aldrich or Fluka) and used without further purification.

2.2. Characterization

Uncorrected melting points were performed by one side sealed capillary tubes. Bruker model ultra-shield(Switzerland) was used to scan ^{1}H-NMR spectra using 500MHz, at Tehran University, Islamic Republic of Iran. The solvent used was deuterated DMSO, and TMS was an internal standard. Shimadzu FT-IR model 8400 Spectrophotometer was used to record the FT-IR spectra using KBr disc at the Department of Pharmaceutical Chemistry, Pharmacy College, Basrah University. The CHN analysis measurements for the synthesized compounds were performed at the analytical Laboratory of Tehran University, Iran, using the EuroVector model EA3000A (Italy).

2.3. Synthesis

2.3.1. Synthesis of Schiff-bases Series 1 (S1)

2.3.1.1. Synthesis of (E)-2-((2-hydroxybenzylidene) amino)-5-iodobenzoic acid 1a

To the mixture of 0.01mole (1.31g) 2-amino-5-iodobenzoic acid dissolved in 15ml ethanol, 0.01mole (0.53ml) salicylaldehyde in 15ml ethanol was added. The mixture was stirring at room temperature for one hour. The resulting yellow precipitate was filtered off and washed with cold methanol to remove the not reacted materials. The product was crystallized from ethanol and dried at room temperature (Scheme 1). The characterizations of the prepared compound 1a were listed in Table 1.

2.3.1.2. Synthesis of (E)-2-((4-(dimethylamino) benzylidene)amino)-5-iodobenzoic acid 1b

To the mixture of 0.01mole (1.31g) 2-amino-5-iodobenzoic acid dissolved in 15ml ethanol, 0.01mole (0.745g) 4-(N, N-dimethylamino)benzaldehyde in 15ml ethanol was added. The mixture was stirring at room temperature for one hour. The resulting red precipitate was formed after 30 min, which filtered off and washed with cold methanol to remove the not reacted materials.

The product was crystallized from ethanol and dried at room temperature (Scheme 1). The characterizations of the prepared compound 1b were listed in Table 1.

2.3.1.3. Synthesis of (E)-2-((2,4-dimethoxy benzylidene)amino)-5-iodobenzoic acid 1c

To the mixture of 0.01mole (1.31g) 2-amino-5-iodobenzoic acid dissolved in 15ml ethanol and 0.2ml of glacial acetic acid, 0.01mole (0.83g) 2,4-dimethoxybenzaldehyde in 15ml ethanol was added. The mixture was refluxed for 30min then stirred for 3h. The volume of the resulting solution was reduced, the yellow precipitate was filtered off and washed with cold methanol to remove the not reacted materials. The product was crystallized from ethanol and dried at room temperature (Scheme 1). The characterizations of the prepared compound 1c were listed in Table 1.

2.3.2. Synthesis of Schiff-bases Series 2 (S2)

2.3.2.1. Synthesis of 3-(((E)-2-hydroxybenzylidene) amino)-5-(((Z)-2-hydroxybenzylidene) amino) benzoic acid 2a

A solution of 3,5-diamenobenzoic acid 0.01mole (0.75g) in 40ml warm ethanol and 10 ml ethanol solution of salicylaldehyde 0.01mole (1.05ml) was refluxed for 1 h. A green precipitate was formed. The reaction was stirred at room temperature for farther 2 h to complete reaction. The product was filtered and recrystallized from ethanol and then dried at room temperature (Scheme 2). The characterizations of the prepared compound 2a were listed in Table 1.

2.3.2.2. Synthesis of 3,5-bis(((E)-4-(dimethylamino)benzylidene)amino)benzoic acid 2b

A solution of 3,5-diamenobenzoic acid 0.01mole (0.75g) in 40ml warm ethanol and 20 ml ethanol solution of 4-(N,N-dimethylamino)benzaldehyde 0.01mole (1.49g) with 0.5ml of glacial acetic acid was refluxed for 3 h. On cooling on ice bath the reaction mixture, the brown product was filtered and recrystallized from ethanol and then dried (Scheme 2). The characterizations of the prepared compound 2b were listed in Table 1.

2.3.2.2. Synthesis of 3,5-bis(((E)-2,4-dimethoxybenzylidene)amino)benzoic acid 2c

A solution of 3,5-diamenobenzoic acid 0.01mole (0.75g) in 40ml warm ethanol and 20 ml ethanol solution of 2,4-dimethoxybenzaldehyde 0.01mole (1.66g) with 1ml of glacial acetic acid was refluxed for 3 h. On cooling the reaction mixture to room temperature, the yellowish-green product was filtered and recrystallized from ethanol and then dried (Scheme 2). The characterizations of the prepared compound 2c were listed in Table 1.

2.4. Preliminary antifungal assay

The antifungal activity of the prepared Schiff-bases compounds was tested against the pathogenic fungus *Aspergillus niger* and *Candida albicans* at a concentration of 1000 µg/ml in dimethyl sulfoxide solvent by using the agar diffusion method. The medium used in this respect was Sabouraud dextrose agar. Fluconazole used as a standard drug.

Wells (6 mm in diameter) were cut using a stainless sterile cutting device (cork borer), and 100 µl of each compound was added to each well. Plates were incubated at 25^{o}C for 72 h, inhibition zone diameters in mm were measured (M-Ali, 2008).

3. RESULTS AND DISCUSSION:

3.1. Synthesis of compounds

The Schiff base compounds S1 were prepared from condensation of 2-amino-5-iodobenzoic acid three aldehydes, salicylaldehyde, 4-(N,N-dimethyamino)benzaldehyde or 2,4-dimethoxybenzaldehyde in ethanol, (Scheme 1). The yield of the reactions was (74-86%). The prepared compounds were soluble in ethanol, methanol, and $CHCl_3$. The second serious of Schiff base compounds S2 were prepared with good yield (68-88%) by condensation two moles of the three aldehydes above with 3,5-diamenobenzoic acid using ethanol as solvent, (Scheme 2). The products were colored compounds that were soluble in ethanol.

3.2. ^{1}H-NMR spectra

^{1}H-NMR spectra of some of the prepared compounds were performed in deuterated dimethyl sulfoxide solutions with tetramethylsaline as an internal standard. Table 2 represents the ^{1}H-NMR data spectra of the prepared compounds. All these spectra showed a signal at 2.5 ppm, which was due to the DMSO solvent and another signal at 3.33 ppm due to dissolved water in DMSO (Gottlieb *et al.*, 1997).

All compounds showed characteristic singlet signals in the range 8.156-9.657 ppm attributed to the proton of the azomethine group, which matched with the works of literature (Issa *et al.*, 2009).

For the compounds 1a and 2a, there are characteristic downfield signals referred to the intramolecular hydrogen-bonded proton of phenolic fragment –OH at 10.259 and 12.786 ppm, respectively (Jadeja *et al.*, 2016).

Two types of aliphatic signals appeared in high field range, which attributed to methyl groups attached to two types of atoms nitrogen and oxygen. Compounds 1b and 2b gave singlet signals at 3.040 and 2.955 ppm, respectively, which referred to protons of CH_3N- fragment with an integrated value of six protons. Whereas, compounds 1c and 2c showed singlet signals at 3.857 and 3.774 ppm, respectively, which referred to protons of CH_3O- groups with an integrated value of twelve protons.

All compounds didn't give signals at greater than 13 ppm attributed to protons of carboxylic acid because of DMSO solvent interactions (Abraham *et al.*, 2006).

All compounds showed multiplet signals in the range 6.420-8.526 ppm, which attributed to protons of aromatic systems.

3.3. IR spectra

FT-IR spectral data (in KBr pellets) of the compounds are given in Table 3. The IR spectra of the Schiff bases show medium or strong intensity absorption bands at 1600–1620 cm^{-1} assigned to C=N stretching mode. The presence of aromatic rings ν (C=C) has been identified by their characteristic ring vibrations at 1581–1500 cm^{-1} region. The presence of medium-strong bands particular of ν (C=O) for carboxylic acid at the range of 1728-1681 cm^{-1} confirms the proposed Schiff base framework in compounds 1b, 1c, 2b, and 2c and these bands absence in the compounds 1a and 2a.

The broad bands in the range of about 3400 cm^{-1} in the spectra of the compounds 1a and 2a demonstrates the formation of the OH···N intramolecular hydrogen bond between the salicyl part OH proton and the nitrogen atoms of azomethine groups (Bilge *et al.*, 2009).

The characteristic ν (C-H) modes of ring residues are observed at near 3050 cm^{-1}. The range about 1300 cm^{-1} in the spectra of the compounds 1b, 1c, 2b and 2c show bending vibrations bands attributed to ν (C-H) of methyl groups in the $–OCH_3$ and $–NCH_3$ fragments, whereas, weak bands referred to stretching vibration of an aliphatic C-H bond in the range about 2900 cm^{-1}.

3.4. Optimization of molecular geometries

The molecules that formed from the reaction between substituted benzaldehydes (1) and monoaminocarboxylic acid (2) or diaminocarboxylic acid (3). As shown in Scheme 1, these molecules can be classified into two series: mono- Schiff bases (4) and di- Schiff bases (5), as shown in Scheme 3. The synthesized Schiff bases compounds have been optimized to study their theoretical properties using the Hyperchem program by the PM3 method.

Three-dimensional structures and IUPAC names of mono- Schiff bases (4) and for di- Schiff bases (5) are shown in Figure 1. The calculated molecular properties of compounds are shown in Table 4.

3.5. Lipophilicity

Lipophilicity is a physicochemical property of principal importance in drug discovery and development. It affects three phases of drug activity - its pharmaceutical, pharmacokinetic, and pharmacodynamic action (Rutkowska *et al.*, 2013). log P is related to the lipophilicity of compounds and is useful to predict the absorption of drugs across the intestinal epithelium. Log P must be smaller than 5 for a good drug candidate, are based on the observation that the most orally absorbed compounds have log P < 5 (Hughes *et al.*, 2008).

The compounds 1c, 2a, 2b, and 2c have logP values less than 5, whereas 1a and 1b have logP values greater than 5 (Table 4).

3.6. Mulliken atomic charges

The Mulliken atomic charges for the compounds calculated by the PM3 method are presented in Figure 2 and Table 4. The Mulliken charge distribution shows that the carbonyl oxygen atom of the carboxylic group is more negative (~ -0.4) as compared to other oxygen atoms (~ -0.3) in all selected compounds. Whereas, nitrogen atoms in the azomethine group have charge distribution lower than of oxygen in carboxyl, hydroxyl or methoxy groups. It has also been observed that some C atoms are positive, and some are negative.

3.7. Electric dipole moments

The polar molecule has a feature of dipole moment, which refers to electric charge distribution, which relates to the electric field. The polarity is the individual property of the particular molecule that independent of the surrounding area. A dipole moment is largely depending on the difference in electronegativity and distance between the charge separation.

According to Tab. 4, the dipole moments values show that mono- Schiff bases (S1) (2.851-5.525 D) generally have bigger electrical moments than di-Schiff bases (S2) (2.609-3.201 D). Whereas dipole moment is a vector, in symmetrical molecules such as di- Schiff bases (S2) bond dipole moments with the same value cancel each other's. For example, dipole moments of 1a and 2a can be compared. The rank of dipole moment for S1, 1a (5.525 D) > 1c (3.678 D) > 1b (2.851D), whereas, for S2 2a (3.201D) > 2c (2.803D) > 2b (2.609D).

3.8. Global reactivity descriptors

The HOMOs and LUMOs are known as Frontier molecular orbitals (FMOs), which played an essential role in evaluating molecular chemical stability, chemical reactivity, and hardness-softness of the molecule (Tanga *et al.*, 2011).

The determination of energies of the HOMO (π donor) and LUMO (π acceptor) are essential parameters in quantum chemical calculations. The HOMO is the orbital that primarily acts as an electron donor, and the LUMO is the orbital that mainly acts as the electron acceptor.

These molecular orbitals are also called the frontier molecular orbitals (FMOs). ε_{HOMO} and ε_{LUMO} are computed by the HyperChem software using the MP3 method, as shown in Figure 3.

Other quantum chemical parameters of organic compounds are obtained from calculations such as separation energies ΔE, absolute electronegativities χ, chemical potentials Pi, absolute hardness η, global electrophilicity ω, absolute softness σ, global softness S and additional electronic charge (ΔN_{max}) according to the following equations (Yousef *et al.*, 2012; Porchelvi and Muthu, 2015). All quantum chemical parameters of the prepared compounds are listed in Table 5.

$$\Delta E = \varepsilon_{LUMO} - \varepsilon_{HOMO}$$

$$\chi = -1/2\ (\varepsilon_{LUMO} + \varepsilon_{HOMO})$$

$$Pi = -\chi$$

$$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})/2$$

$$\omega = \chi^2/2\eta \qquad \sigma = 1/\eta$$

$$\Delta N_{max} = -Pi/\eta \qquad S = 1/2\eta$$

The ε_{HOMO} and ε_{LUMO} and their neighboring orbitals are all negative (as listed in Table 5), which indicates that the prepared molecules are stable (Yousef *et al.*, 2012; Yousef *et al.*, 2013).

The energy gap (ΔE) represents the chemical reactivity of compounds. For a system, the lower value of ΔE makes it more reactive or less stable. As depicted in Table-4, for compounds in group S1, 1c (7.888) > 1a (7.792) > 1b (7.428). For compounds in group S2, 2a (7.9984) > 2c (7.9959) > 2b (7.6542). Therefore, compound 1c is more stable compared with 1a and 1b in the series S1. Whereas, compound 2a is more stable compared with 2b and2c.

Electrophilicity index ω is one of the most important quantum chemical descriptors in describing the activity. The electrophilicity adequately quantifies the biological activity of drug-receptor interaction. This new reactivity index measures the stabilization in energy when the system acquires an additional electronic charge from the environment. High values of electrophilicity index increase the electron-accepting abilities of the molecules (Prabhakaran and Palanivel, 2016).

Thus, the electron-accepting abilities of compounds in the series S1 are arranged in the following order: 1a (3.207) > 1c (3.118) > 1b (2.995). The same arrange for series S2 2a (2.967) > 2c (2.823) > 2b (2.777).

The importance of η and σ is to measure the molecular stability and reactivity (N'dri *et al.*, 2018). The chemical hardness (softness) value of compound 1b (η = 3.714 eV) is the lowest among studied molecules. Thus, it appears that compound 1b is more reactive than all the studied compounds in two series. Whereas, the compound 2a (η = 3.9992 eV) is more stable than all compounds in two series.

The concepts of the parameters χ and Pi are related to each other. The inverse of the global hardness is designated as the softness σ. Also, we note that compound 1a has its value of electronegativity (χ = 4.999 eV), which is higher than other compounds' value, so it is the best electron acceptor that corresponded with the value of electrophilicity index ω.

3.9. Antifungal activity

In vitro antifungal effects of the investigated compounds were tested against two fungal species (*Aspergillus niger* and *Candida albicans*). The screening results indicate that all compounds exhibited antifungal activities. As shown in Table 5 and Figure 4 These good inhibitory may be attributed to the hydrogen bond formation of the azomethine fragment with the active sites of various constituents of cell which lead to interference with normal cellular processes (Prasad *et al.*, 2011; Thangadurai and Natarajan, 2001; Dharmaraj *et al.*, 2001).

It can be noted that compounds with -OH groups in the ortho position (1a and 2a) showed the most significant inhibitory effect against two types of fungi compared to other compounds (Ragenovic *et al.*, 2001). The activity of all compounds were more significant value against *C. albicans* than *A. niger*, which may be referred to as the high resistance of *A. niger* than *C. albicans*.

The results showed (Table 6) that the activity of all compounds was less than the activity of standard drug fluconazole.

4. CONCLUSIONS:

The two series of Schiff bases compounds (S1 and S2) were synthesized with good yields and high purity. The synthesized compounds gave promising antifungal activity against the tested fungal. There is a clear relationship between the structure of compounds

and the activity depending on the values of charges of groups and moieties, lipophilicity, and electronic dipole moments.

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6. CONFLICTS OF INTEREST:

Three authors had declared no conflicts of interest.

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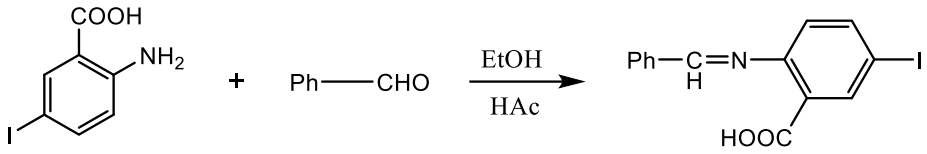

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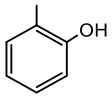
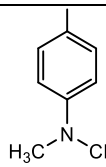
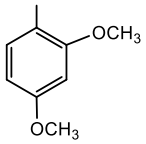
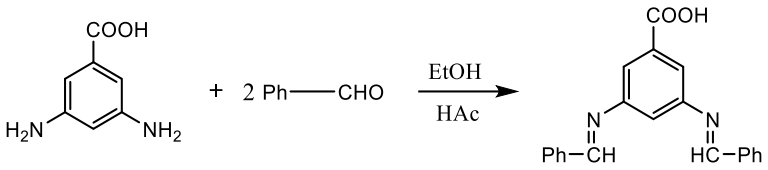
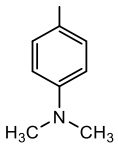
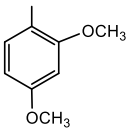
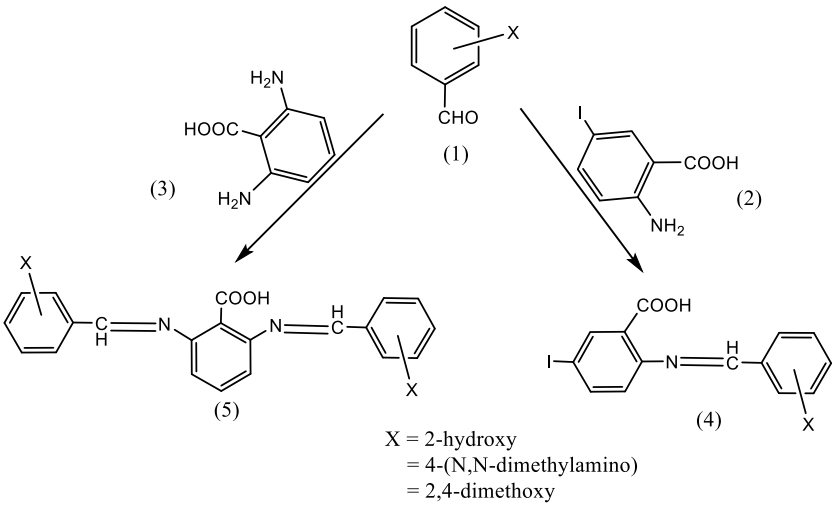
Ph =			
Name	2-[(*E*)-(2-hydroxy benzylidene)amino]-5-iodobenzoic acid	2-{(E)-[4-(dimethylamino) benzylidene]amino}-5-iodobenzoic acid	2-[(E)-(2,4-dimethoxy benzylidene)amino]-5-iodobenzoic acid

Scheme 1. *Synthesis of Schiff-bases S1*



	2a	2b	2c
Ph =			
Name	3-[(*E*)-(2-hydroxy benzylidene)amino]-5-[(*Z*)-(2-hydroxybenzylidene)amino]benzoic acid	3,5-bis(((E)-4-(dimethylamino) benzylidene)amino)benzoic acid	3,5-bis(((E)-2,4-dimethoxy benzylidene)amino)benzoic acid

Scheme 2. *Synthesis of Schiff-bases S2*



Scheme 3. *Synthesis of Schiff base S1 and S2*

Table 1. *The characterization of the prepared Schiff-base compounds*

Compd.	Molecular formula	M.Wt (g/mol)	Crystal Color	m. p. (°C)	Yield (%)	Elemental analysis Found (Calcd.)		
						C%	H%	N%
1a	$C_{14}H_{10}INO_3$	367.14	Yellow	236-238	82	45.80 (45.75)	2.75 (2.69)	3.82 (3.85)
1b	$C_{16}H_{15}IN_2O_2$	394.21	Red	210-212	86	48.75 (49.54)	3.84 (3.68)	7.11 (7.61)
1c	$C_{16}H_{14}INO_4$	411.20	Yellow	220-223	74	46.74 (47.35)	3.43 (3.34)	3.41 (3.58)
2a	$C_{21}H_{16}N_2O_4$	360.37	Pale yellow	>260	78	69.99 (70.25)	4.48 (4.31)	7.77 (7.85)
2b	$C_{25}H_{26}N_4O_2$	414.51	Red	187-190	88	72.44 (71.76)	6.32 (6.51)	13.52 (13.66)
2c	$C_{25}H_{24}N_2O_6$	448.48	Yellowish gray	113-114	68	66.95 (66.25)	5.39 (5.41)	6.25 (6.47)

Table 2. *^{1}H-NMR data of the prepared compounds*

Compd.	δ ppm				
	-OH	CH=N	$-OCH_3$	$-NCH_3$	Aromatic
1a	10.259 (s)	8.867 (s)			8.120-6.600 (m)
1b		9.664 (s)		3.040 (s)	8.245-6.597 (m)
1c		8.156 (s)	3.857 (s)		8.156-6.590 (m)
2a	12.786 (s)	9.115 (s)			7.851-6.957 (m)
2b		9.657 (s)		2.955 (s)	8.526-6.420 (m)
2c		8.785 (s)	3.774 (s)		7.997-6.579 (m)

ppm: part per million, s: singlet signal, m: multiplet signal

Table 3. *Characteristic IR spectral bands of the prepared compounds*

Compd.	υ (C-H) ar. str.	υ (C-H) alip. str.	υ(C=O)	υ (C=N)	υ (C=C)	υ(C-N)	υ(C-O)	υ (C-H) ar. bend.
1a	3055 w		1705 m	1616 s	1554 m	1184 m	1153 m	763 m
1b	3021 w	2850 w	1681 m	1604 s	1581 s 1535 s	1188 m	1165 m	817 m
1c	3018 w	2947 w 2839 w	1708 m	1600 s	1570 m 1500 m	1284 m	1207 m	825 m
2a	3074 w		1728 s	1612 s	1581 s 1504 m	1273 s	1207 m	844 m
2b	3035 w	2924 w	1685 m	1603 s	1550 s	1199 m	1168 m	821 m
2c	3055 w	2989 w	1689 s	1620 s	1589 m 1570 s	1280 m	1253 m	756 s

w: weak, m: medium, s:strong

Table 4. *Calculated molecular properties of compounds*

Comp.	MW	Volume (Å^3) /Area (Å^2)	Charge O atom	μ $(Debye)$	logP
1a	367.14	783.31/476.45	[O(18) -0.428] [O(19) -0.263] [O(16) -0.223]	5.525	5.03
1b	394.21	904.07/539.77	[O(17) -0.412] [O(18) -0.311]	2.851	5.01
1c	411.20	904.55/539.30	[O(17) -0.407] [O(18) -0.315] [O(19) -0.193] [O(21) -0.187]	3.678	4.57
2a	360.37	1029.42/618.25	[O(9) -0.409] [O(8) -0.301] [O(26) -0.233] [O(27) -0.232]	3.201	3.82
2b	414.51	1256.44/737.13	[O(9) -0.406] [O(8) -0.307]	2.609	3.78
2c	448.48	1283.59/754.12	[O(24) -0.402] [O(25) -0.312] [O(26) -0.188] [O(28) -0.189]	2.803	2.90

Table 5. *The calculated quantum chemical parameters of the prepared compounds*

Comp.	ε_{HOMO}	ε_{LUMO}	ΔE	χ	P_i	η	ω	σ	s	ΔN_{max}
1a	-8.895	-1.103	7.792	4.999	-4.994	3.896	3.207	0.256	0.128	1.281
1b	-8.431	-1.003	7.428	4.717	-4.717	3.714	2.995	0.269	0.134	1.270
1c	-8.904	-1.016	7.888	4.960	-4.960	3.9442	3.118	0.253	0.126	1.257
2a	-8.872	-0.873	7.9984	4.872	-4.872	3.9992	2.967	0.250	0.125	1.218
2b	-8.438	-0.783	7.6542	4.611	-4.611	3.8271	2.777	0.261	0.130	1.204
2c	-8.749	-0.753	7.9959	4.751	-4.751	3.9979	2.823	0.250	0.125	1.194

Table 6. *Inhibition zone of the prepared compounds and standard drug at 1000 µg/ml against Aspergillus niger and Candida albicans*

Compound	Inhibition zone (mm)	
	A. niger	*C. albicans*
1a	27	28
1b	18	22
1c	19	23
2a	23	25
2b	14	16
2c	20	23
FLC	35	38

FLC: fluconazole

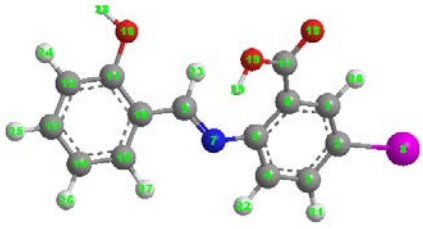
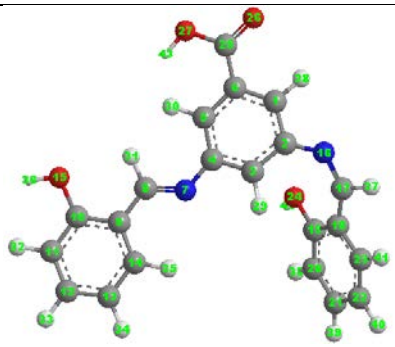
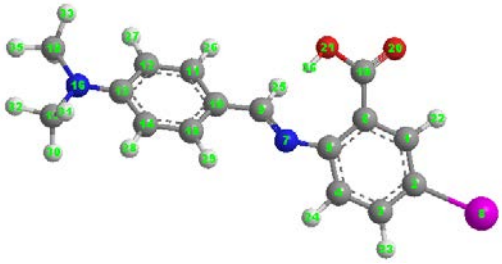
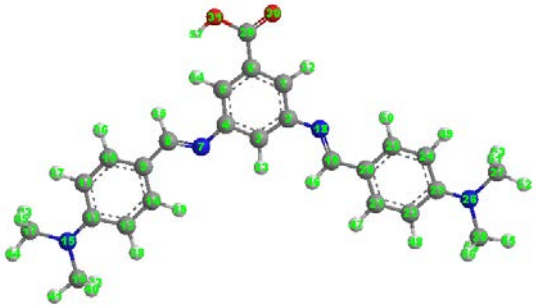
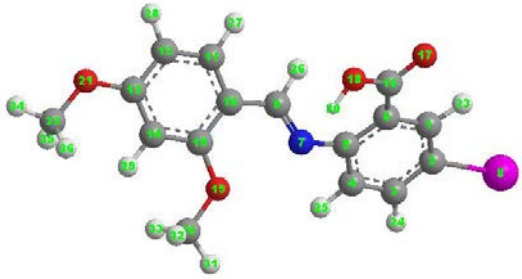
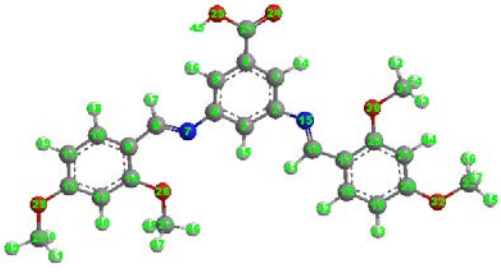
	1	2
a	 2-[(*E*)-(2-hydroxybenzylidene)amino]-5-iodobenzoic acid	 3-[(*E*)-(2-hydroxybenzylidene)amino]-5-[(*Z*)-(2-hydroxybenzylidene)amino]benzoic acid
b	 2-{(E)-[4-(dimethylamino)benzylidene]amino}-5-iodobenzoic acid	 3,5-bis(((E)-4-(dimethylamino)benzylidene)amino)benzoic acid
c	 2-[(E)-(2,4-dimethoxybenzylidene)amino]-5-iodobenzoic acid	 3,5-bis(((E)-2,4-dimethoxybenzylidene)amino)benzoic acid

Figure 1. *Three-dimensional structures and IUPAC names for mono- Schiff bases S1 and di- Schiff bases S2*

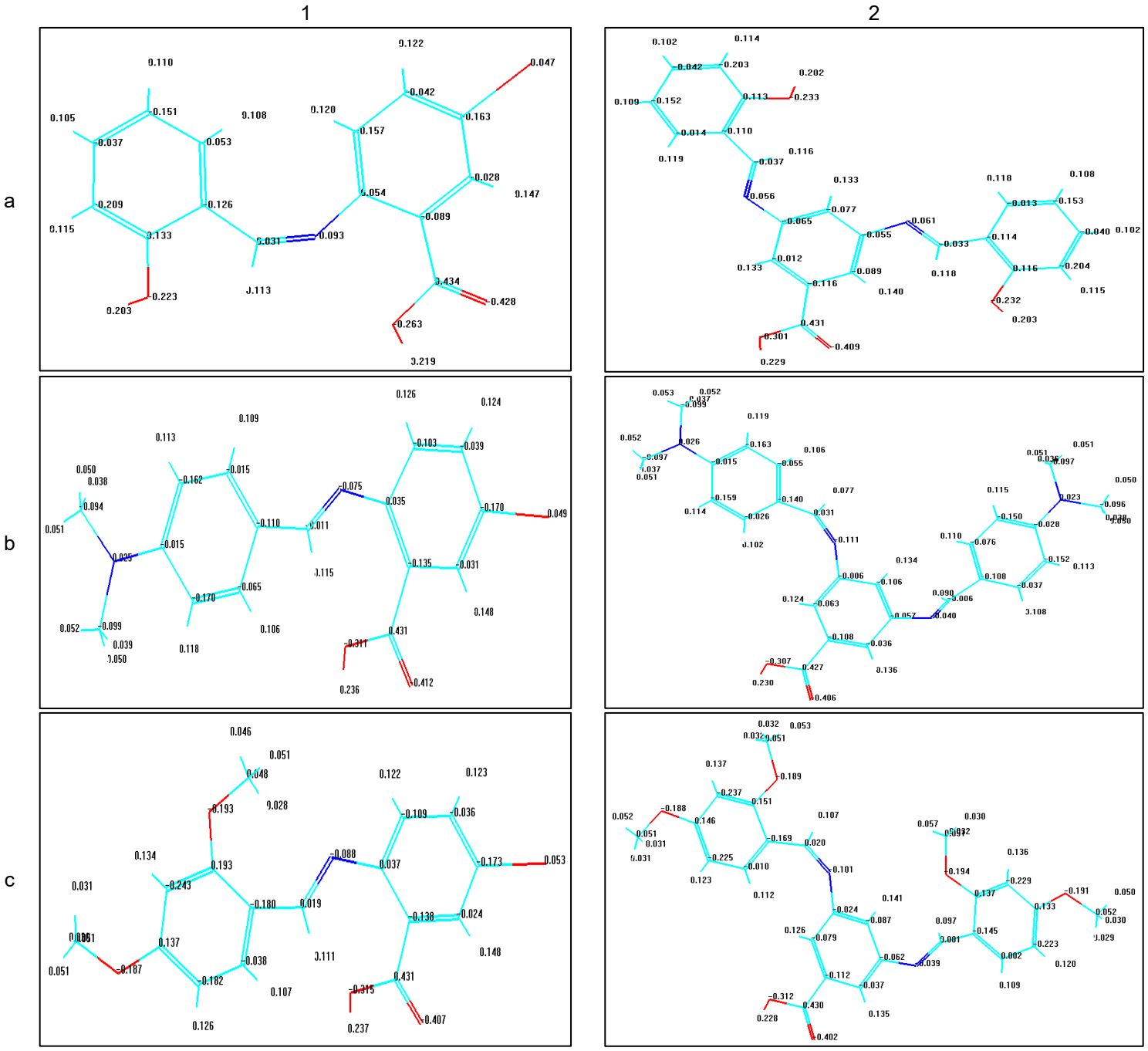


Figure 2. *Atomic charges distribution of the compounds*

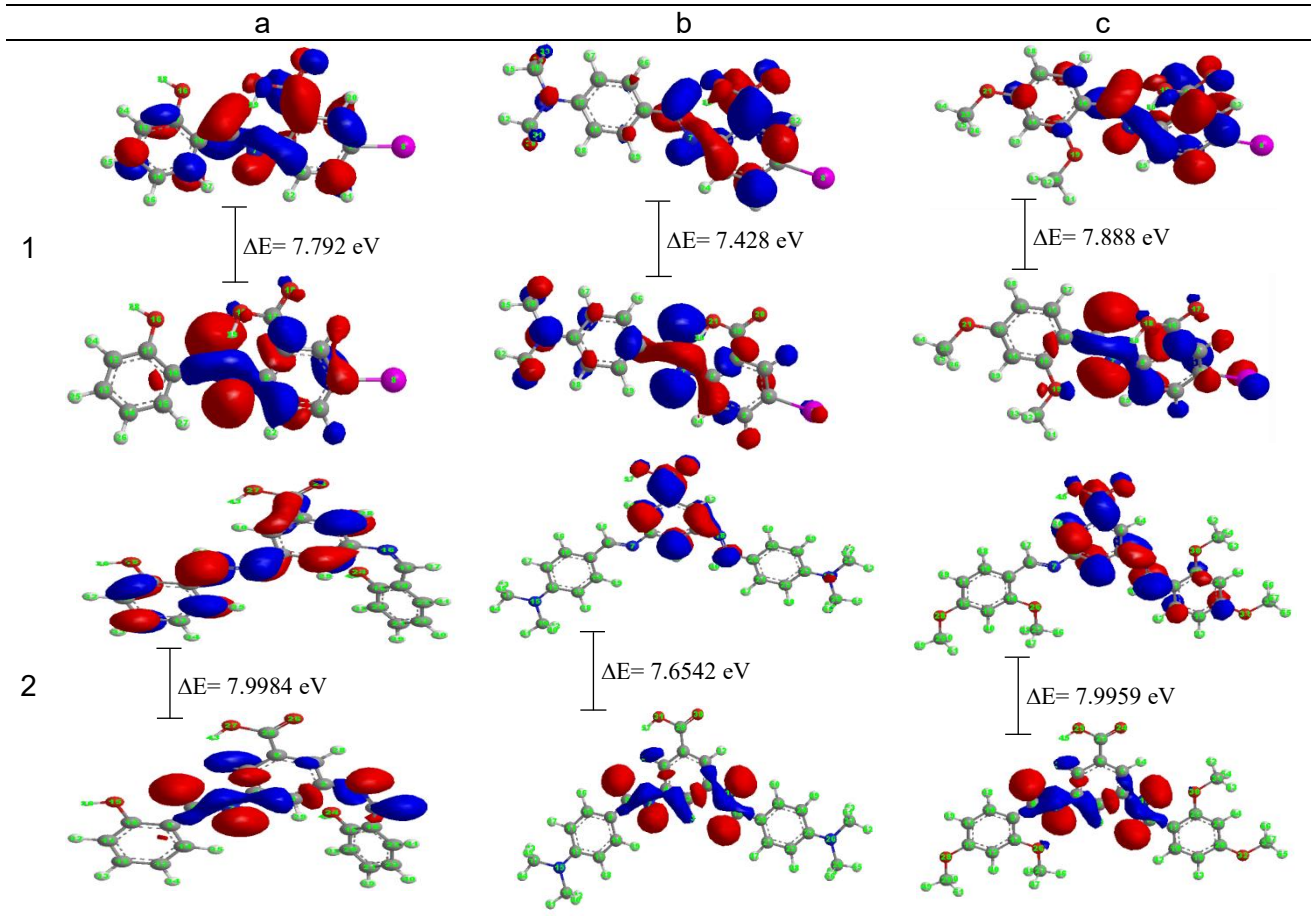


Figure 3. *The highest occupied and lowest unoccupied molecular orbitals of the compounds*

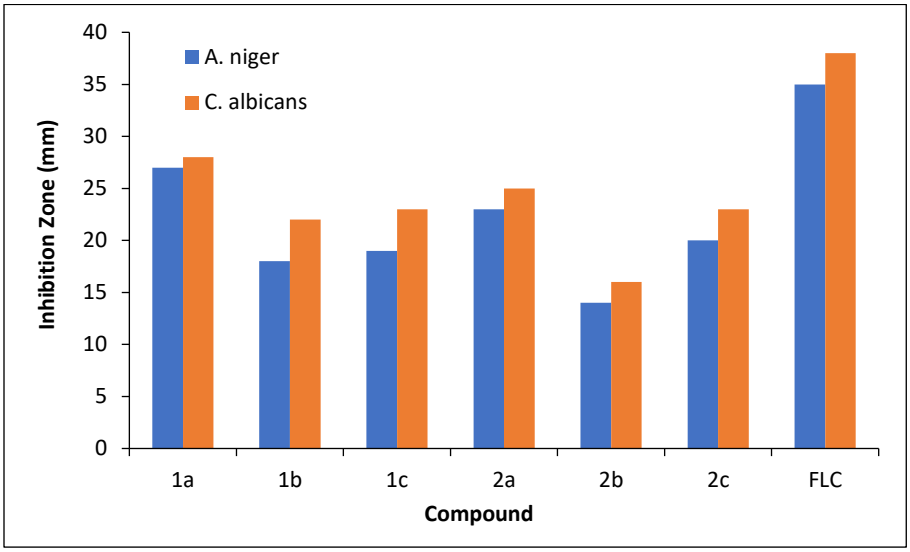


Figure 4. *The effect of the compounds toward the tested organism A. niger and C. albicans*