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Dhafer S. Zinad, Ghazwan A. Salman, Ahmed Mahal, et al.

Molecular Modeling Study and Antifungal Activity of Some Synthesized Quinoline Derivatives

Dhafer S. Zinad[1,a)], Ghazwan A. Salman[2], Ahmed Mahal[3] and Fadhela M. Hussein[2]

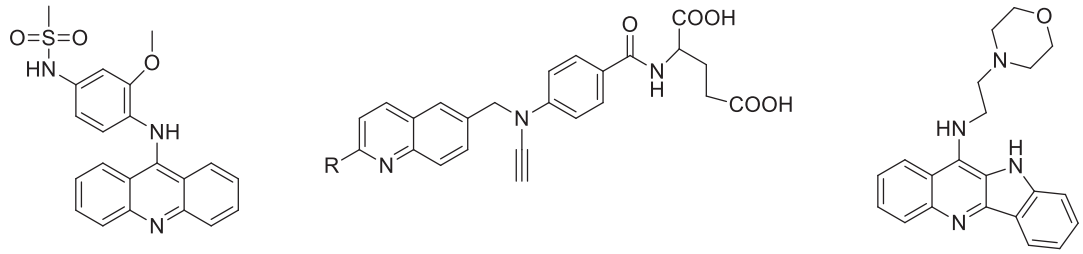
[1] *Applied Science Department, University of Technology, Baghdad 10001, Iraq.*
[2] *Department of Chemistry, College of Sciences, Mustansiriyah University, 10052, Baghdad, Iraq.*
[3] *Department of Medical Biochemical Analysis, Faculty of Health Technology, Cihan University-Erbil, Erbil, Iraq.*

[a)] *Corresponding author: 100416@uotechnology.edu.iq*

Abstract. The **c**hemical reactivity and stability of three prepared compounds (**5-7**) have been studied using molecular modelling. According to the results, compound **7** is more reactive than compounds **5** and **6**. Antifungal activity was confirmed for all the compounds and proved that the compound **6** has been shown to have a potent zone of inhibition against *Aspergillus niger* in comparison to the reference drug used of Amphotericin B, while compounds **5** and **7** showed significant activity than the positive control.

INTRODUCTION

Among the broad variety of heterocyclic nitrogen compounds that have been observed to promote pharmacologically significant compounds, quinoline scaffolds are presents in so many natural products and have played a great role in medicinal chemistry in recent decades [1-10] and exhibit significant interest, such as antibiotic, antimalarial, anti-inflammatory [11-13], anticancer [14], anti-tuberculosis [15], anti-hypertensive [16], tyrosine kinase inhibitor drugs [17], and anti-HIV [18]. A number of derivatives of quinoline serve as valuable antitumor agent (figure 1) [19].



Amsacrine

2-(4-[((2-substituted quinolin-6-yl)(ethynyl)amino) pentanedioic acid

N-(2-morpholinoethyl)-10*H*-indolo[3quinolin-11-amine

FIGURE 1. Quinoline derivatives

1,2,4-trizole, 1,3,4-thiadiazole derivatives are considered to possess significant pharmaceutical properties [20-24]. Herein and in a continuation of our recently published article [1], the chemical reactivity and stability of synthesized derivatives of quinolone containing 1,2,4-triazole [3,4-*b*][1,3,4]thiadiazine and 1,2,4-triazole [3,4-*b*][1,3,4]thiadiazole have been studied theoretically, and their antifungal activity has been investigated as well.

EXPERIMENTAL

Steps for the preparation of quinolones are illustrated in scheme 1. In ethanol, a mixture of 4-methoxy aniline with ethyl acetoacetate was refluxed (6 h) to obtain the amino ester **2** [25]. Compound **3** resulted in thermal cyclization (1 h) of compound **2** at 260ºC. Addition of chloroacetic acid to compound **3** offered compound **4** [26]. At

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a higher temperature of 170-180ºC, thiocarbohydrazide was mixed with compound **4** and produced compound **5**. The reaction of **5** with substituted benzaldehyde using *p*-TsOH, resulted in a new derivative of **6**. Furthermore, reaction of **5** with substituted 2-bromoacetophenone in ethanol gave derivative **7** with high yield. All synthesized compounds were characterized by the chemical analysis methods (^{1}H NMR, FT-IR, GC-MS).

Synthesis of derivative 5

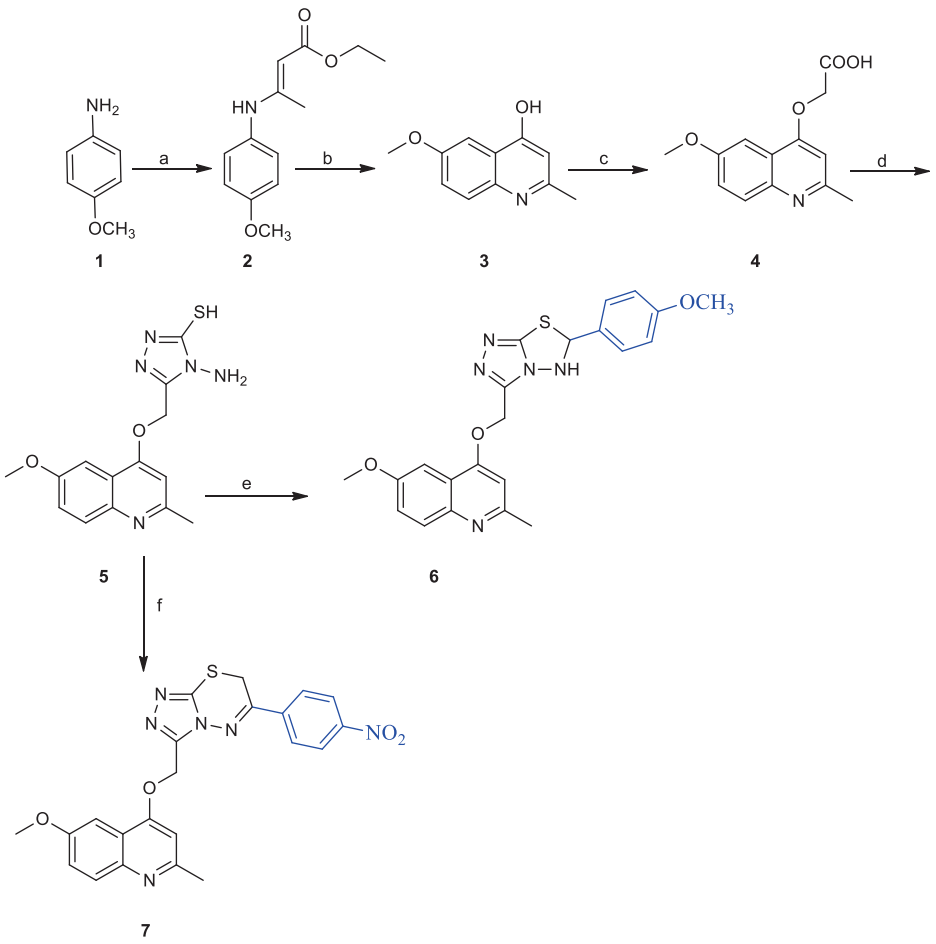
Compound 4 (0.01 mol) was mixed with thiocarbohydrazide (0.015 mol) at 170-180 ºC for half an hour. The wash of the precipitate using water and dried followed by recrystallization by using a solution of dichloromethane/ethanol yielded a yellow precipitate (74%), M.P. (232-234ºC). FT-IR (KBr) [υ, cm^{-1}]: 3280, 3269 (NH_2), 1646 (CN). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 13.34 (s, 1H, SH), 7.53-7.58 (m, 2H, ArH), 7.38 (s, 1H, ArH), 6.66 (s, 1H, ArH), 5.68 (s, 2H, NH_2), 4.59 (s, 2H, OCH_2), 3.65 (s, 3H, OMe), 2.29 (s, 3H, Me),. HRMS (ESI): $[M+H]^+$ found, 318.1022; calcd for $C_{14}H_{16}N_5O_2S$, 318.1025.

Synthesis of compound 6

In dry DMF (20 ml) and p-TsOH, compound **5** (0.005 mol) was mixed with substituted benzaldehyde (0.2 g, 0.005 mol). The mixture was refluxed (14-15 hours) and then allowed to cool with stirring overnight. The wash of the precipitate using water and dried followed by recrystallization by using a solution of dichloromethane/dioxane yielded a yellow precipitate (74%), M.P. (217-219 ºC). FT-IR (KBr) [υ, cm^{-1}]: 3362 (NH), 1625 (CN). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 8.29 (d, 1H, *J*=7.3Hz, ArH), 8.11 (d, 1H, *J*=9.1Hz, ArH), 7.31-7.35 (m, 1H, PhH), 7.25 (dd, 1H, *J*=2.7, 9.2Hz, PhH), 7.22 (d, 1H, *J*=2.7Hz, PhH), 7.15 (d, 2H, *J*=8.6Hz, PhH), 6.72 (s, 1H, PhH), 5.77 (s, 1H, NH), 4.32 (s, 2H, OCH_2), 4.28 (s, 1H, CH), 3.74 (s, 3H OMe), 2.65 (s, 3H, Me). HRMS (ESI): $[M+H]^+$ found, 451.1186; calcd for $C_{21}H_{19}N_6O_4S$, 451.1188.

Synthesis of compound 7

2-Bromoacetophenones (0.01 mol) was mixed with compound **5** (0.005 mol) in ethanol (50 ml) and allowed for stirring under reflux (8 hours). Crushed ice was added onto the mixture followed by filtration and recrystallization using a solution of ethanol/dioxane solution yielded brown crystals (66%), M.P. (201-203 ºC). FT-IR (KBr) [υ, cm^{-1}]: 3068 (C=C), (1629 (CN), 1326, 1541 (NO_2). ^{1}HNMR (300 MHz, $CDCl_3$): δ = 8.29 (d, 1H, *J*=7.5Hz, ArH), 7.52 (d, 2H, *J*=7.3Hz, PhH), 7.31-7.39 (m, 2H, ArH), 7.07 (d, 2H, *J*=8.5Hz, ArH), 6.72 (s, 1H, ArH), 4.57 (s, 2H, OCH_2), 4.26 (s, 2H, CH_2), 3.64 (s, 3H, OMe), 2.43 (s, 3H, Me). HRMS (ESI): $[M+H]^+$ found, 463.1179; calcd for $C_{22}H_{19}N_6O_4S$, 463.1188.



SCHEME 1. Synthesis of quinolone derivatives containing different heterocyclic moieties

Conditions for synthetic reaction: (a) Ethyl acetoacetate, EtOH, 100 °C, 6 h. (b) 260 °C, 1h, (c) chloroacetic acid, K_2CO_3, stirring at 80 °C for 5 h. (d) 4, thiocarbohydrazide, 170-180 °C, 1 h. (e) aldehyde, *P*-TsOH, dry DMF, reflux, 14-15h. (f) 5, substituted 2-bromoacetophenone, EtOH, reflux, 6-8h.

MOLECULAR MODELING STUDY

In order to understand the chemical reactivity of the compound's active site during the chemical reaction, theoretical calculations are important. The energy difference between HOMO and LUMO represents the interaction of electron transfer, according to frontier molecular orbitals theory [27]. Some parameters are called chemical reactivity values including global softness (S), global hardness (η), chemical potential (μ), global electrophilicity index (ω), electronegativity (χ) and potential ionization (I) [28].

$$\chi = -\frac{(E_{LUMO} + E_{HOMO})}{2}$$

$$\mu = -\chi = \frac{(E_{LUMO} + E_{HOMO})}{2}$$

$$\eta = \frac{(E_{LUMO} - E_{HOMO})}{2}$$

$$S = \frac{1}{2\eta}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$\sigma = \frac{1}{\eta}$$

To gain structural insight into the studied compounds, DFT calculations were carried out using the B3LYP method on the 6-31G+ (d) basis set, information on bond lengths description was obtained as well. Table 1 displays the theoretical findings for bond angles bond lengths as well. The optimized molecular structures of the prepared molecules have been investigated using the software program (GAUSSIAN 03 W).

TABLE 1. Bond length for the compounds

Compound 5		**Compound 6**		**Compound 7**	
Description	Bond length (A^0)	Description	Bond length (A^0)	Bond length (A^0)	Bond length (A^0)
O_7-C_{28}	1.366	C40-H49	0.5502	N40-O48	1.2131
C1=C5	1.378	C40-O39	0.9199	C39-N40	1.4923
C5-H24	1.096	C38=039	0.7106	C39=C38	1.3987
C5-C6	1.422	C38-C36	1.3190	C36-H45	1.0978
C16=N29	1.340	C36=C34	1.2022	C17-S31	1.7435
C19-N18	1.387	C33-C31	0.7108	C17=N16	1.3470
C15=O14	1.379	C31-S19	1.7088	N16-N15	1.3404
S20-H37	1.313	C17=S19	1.3115	C14-N18	1.4153
C19-S20	1.748	C31-N32	2.3391	C14-C13	1.4786
N18-N29	1.440	N32-H12	0.9998	C13-O12	1.4330
N22-H30	0.990	N32-N18	1.4556	C11-H26	1.0961
		N18-C14	1.4217	C10-N16	1.3327
		C14=N13	1.3195	C6-N16	1.3924
		C13-O12	1.4390	C2-O1	1.3609
		C31-H28	1.0654		
		C2-O1	1.3529		
		C2=C5	0.9743		
		C6-N20	1.4460		
		C21-H25	1.0654		

To consider the chemical reactivity of a compound, orbital energies must be compared. The energy of the orbital HOMO is greater, and it serves as an electron donor. The orbital LUMO acts as an acceptor for the less energetic electron. The hardness value (larger difference between the energy of HOMO and LUMO) for the final products contributes to greater products stability and intermediates as shown in Table 2.

TABLE 2. Quantum chemical factors for the compounds

Parameter	**5**	**6**	**7**
E HOMO (eV)	-9.016945	-8.781372	-8.777985
ELUMO (eV)	-0.6227065	-1.321811	-2.341373
ΔE gap (eV)	8.3942385	7.459561	6.436612
IE (eV)	9.016945	8.781372	8.777985
EA (eV)	0.6227065	1.321811	2.341373
η (eV)	4.19711925	3.7297805	3.2181306
ω (eV)	2.767460117	3.41655171	4.802482314
x(eV)	4.81982575	5.0515915	5.559679
μ Debye	6.045	4.186	3.215
S (eV)	0.119129329	0.134416533	0.155369704
σ (eV)	0.238258658	0.268833066	0.310739408

Single point energy of ligand		
Compound	Energy (kcal/ mol)	Dipole moment (D)
5	-3597.022983	6.045
6	-5292.536628	4.186
7	-5309.895224	3.215

On the basis of the results mentioned in table 2, compound **7** (ΔE_{gap} = 6.436612 eV) is the compound with the lowest energy gap. This allows the molecule with the shortest distance to be the softest. Compound **5** (ΔE_{gap} = 8.3942385 eV) is the compound which has the largest energy gap. The compound with the largest HOMO energy is compound 7 (E_{HOMO} = -8.777985 eV). Its higher energy allows it to be the strongest electron donor. Furthermore, compound 7 (E_{LUMO} = -2.341373 eV) has the lowest LUMO energy, indicating that it may be the strongest electron acceptor.

Both of IE (potential ionization) and EA (electron affinity) are related to the HOMO and LUMO's electron orbital energies, respectively. The calculations of these two factors make it possible to determine the absolute electronegativity (χ) and the absolute hardness (η). Compound **7** has the lowest potential ionization value (IE = 8.777985 eV), rendering it the best donor of electrons. Also, it has the highest electron affinity value (EA = 2.341373 eV), so it would be the best acceptor of electrons.

The chemical reactivity varies with the molecules chemical structure. Compound 7 has the lowest molecular hardness (softness) value among other molecules (η= 3.2181306 eV, S= 0.155369704 eV). Thus, it is observed that compound **7** is the most reactive than other molecules. Compound **7** has the greatest electronegativity value (χ =5.559679 eV) among other compounds, thus it is the strongest acceptor of electrons. The global electrophilicity index value for compound **7** (ω= 4.802482314 eV) shows that the electrophile is the greatest other compounds. The smallest orbital energy gap (ΔE= 6.436612 eV) of **7** leads to be the greatest chemical reactivity, most polarizable and least kinetically stable "the softest molecule" form (figure 2).

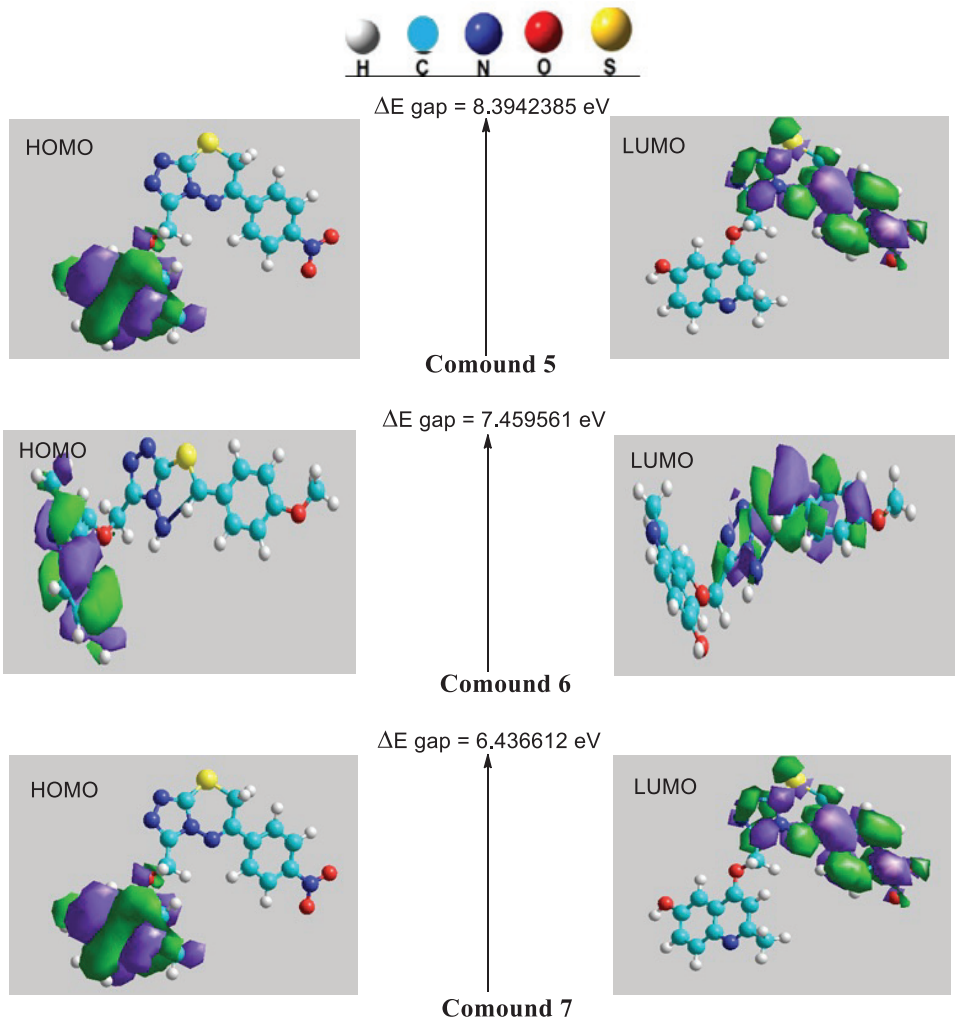


FIGURE 2. Energy gap (HOMO and LUMO) of the studied compounds

ANTIFUNGAL ACTIVITY

The antifungal activity of the prepared compound was performed using agar diffusion method by estimating the inhibition zone [29,30]. Amphotericin B (100 µg/mL) was used as positive control drug against strain of fungi (*A. niger*) in dextrose agar medium. Solidify of the sanitized agar media which was poured into in Petri-dishes was carried out followed by diffusion of the prepared compounds for 1-2 hours in the cavities. DMSO solvent was utilized as a control. These plates were incubated for 48 hours (37 °C). The results were presented in Table 3.

TABLE 3. Antifungal activity for 5, 6 and 7

Compound	Inhibition zone (cm) ± SD
5	1.39 ± 0.01
6	1.43 ± 0.05
7	1.37 ± 0.01
Amphotericin B	1.34 ± 0.06

Compared to Amphotericin B, compound **6** showed the best potent activity against *A. niger* (1.43 ± 0.05 cm). The activity of compound **6** may be due to hydrogen-bonding between the active centres of cell constituents and the nitrogen atom (NH) of thiadiazole, which interferes with the normal cell. It is worth to mention also that

incorporation of substituted 1,2,4-triazole-3-thiol ring, triazolo[3,4-b][1,3,4]thiadiazole and triazolo[3,4-b][1,3,4]thiadiazine structures on quinoline core can lead to increases the activity of the synthesized compounds as compared to the positive control.

CONCLUSION

The previously synthesized compounds have been studied for their reactivity, stability and antifungal activity. DFT study has confirmed the best reactivity of compound **7** among other compounds **5** and **6**. Antifungal study has confirmed the potent activity of compound **6** while the compounds **5** and **7** showed good activity against the tested *Aspergillus niger*. As a result of the previous discussion, theoretical simulation is most helpful in interpreting chemical reactivity, kinetic stability, polarizability, and biological properties of the molecules under investigation.

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