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Synthesis, DFT and Antimicrobial Studies of 5,6,7,8- Tetrachloro Phthalazin-1-ol and 2,3-Benzoxazin-1(2H)-one Derivatives

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2-AROYLBENZOIC acidwas allowed to react with hydrazine hydrate, hydroxylamine and methylhydrazine to afford the corresponding 5,6,7,8-tetrachloro-4-aryl-phthalazin-1-one. The antimicrobial effect of the phthalazin-1-one in the water of the swimming pool and river can be discussed. DFT based on quantum chemical computational of the new compounds were synthesized with the objective of studying their antimicrobial activity. The newly synthesized compounds were characterized on the basis of theirspectral (^{1}H-NMR, Mass spectrum, IR and Elementary analysis

Keywords: Phthalazin-1-ol, 2,3-Benzoxazin-1-one, 2-Methyl-phthalazinone, DFT Antimicrobial reagents.

Introduction

Phthalazin-1(2H)-ones are of considerable interest due to their antidiabetic[1], antiallergic[2], vasorelaxant[3], PDE4 inhibitors[4], VEGF (vascular endothelial group factor) receptor tyrosine kinases for the treatment of cancer[5,6], antiasthmatic agents with dual activities of thromboxane A2 (TXA2) synthetase inhibition and bronchodialation[7], herbicidal[8]. A number of established drug molecules like Hydralazine[9,10], Burdralazine[11,12], Azelastine[13,14], Ponalrest[15], and Zopolrest[16] are prepared from the corresponding phthlazinones. Several phthalazine derivatives have been reported to possess antitumor[17-19], antihypertensive[20,21], anticovulsant[22], antimicrobial [23], antitrypanosomal[24], and anti-inflammatory activity[25]. Most of the current nonsteroidal anti-inflammatory drugs (NSAIDs) show serious side effects including gastrointestinal disorders and kidney damage. These studies for developing safer NSAIDs lacking the gastrointestinal and renal side effects of current used ones have recently been of interest for many researches. Most of the classical NSAIDs exerts their side effects by inhibition of COX-1 enzyme since the COX-1 isoform is the constitutive one that is responsible for regulation of physiological processes, and the COX-2 isoform is discovered to be the enzyme induced by inflammatory stimuli, selective inhibition of COX-2 provides a rationale for developing anti-inflammatory and analgesic agents. Although the diaryl heterocyclic compounds are mainly studied as new class of NSAIDs without gastric side effects, many studies have also focused on a different type of compounds to develop safer NSAIDs [26]. Also in terms of this aspect, many studies have been focused on pyridazin-(3H)-ones, which are characterized to possess good analgesic and anti-inflammatory activities. Besidespyridazinones, these studies have indicated that the heterocyclic ring substitutions at the six position, and the presence of acetamide side chain when linked to the lactam nitrogen of pyridazinone ring at the two position of the pyridazinone ring, improve the analgesic and antiflammatory activity along with nil or very low ulcerogenicity[27-30]. In view of the aforementioned facts, it seemed most interesting to synthesize some [4-((3-chloro-4-methylphenyl)-2-substituted phthalazin-1(2H)-one] derivatives with the aim to obtain more precise information about the course of reactions and biological activities.

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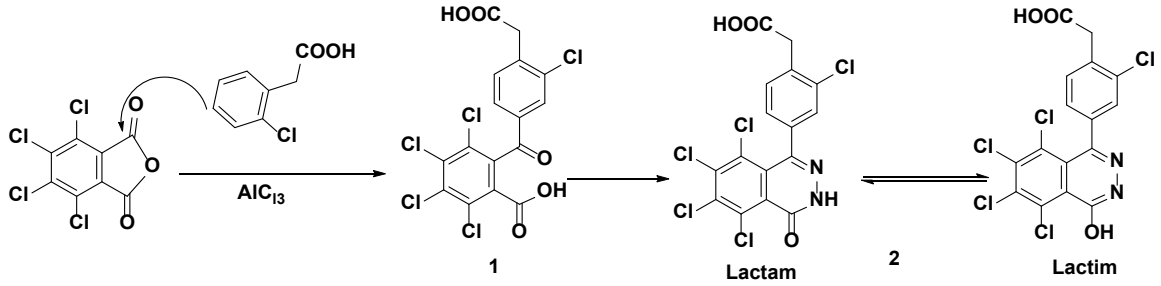
Results and Discussion

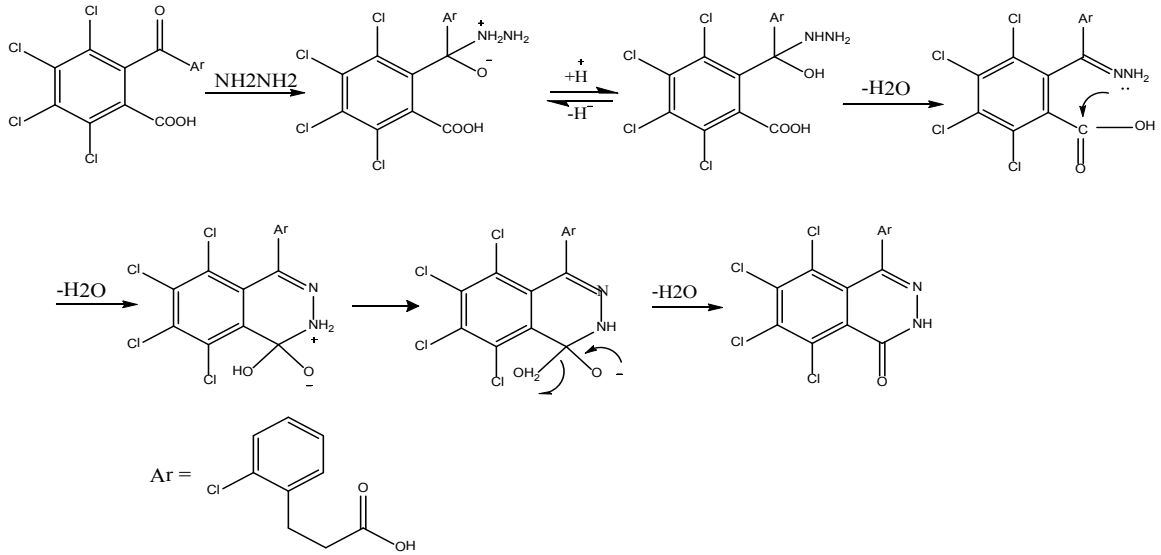
Chemistry

Aroylation of an aromatic system by reaction with phthalic anhydride under Freidel Craft's conditions[14],herein the reaction of aromatic compound with 5,6,7,8-tetrachlorophthalic anhydride in the presence of anhydrous aluminum chloride was carried out to produce 2-(aryl benzoyl) benzoic acid. Merchant et al prepared phthalazin-1-ones via the condensation of the aroyl benzoic acid with hydrazine hydrate in boiling ethanol[15]. Accordingly, our phthalazin-1-ol derivative**2** can be synthesized and its IR spectrum showed a characteristic absorption bands at ν3420 cm^{-1} corresponding to (OH). The mass spectrum shows the correct ion peak at *m/z* 449.Thus, extending the previous work[31-33], In view of the aforementioned facts, it seemed most interesting to synthesize some 2-(2-chloro-4- (5,6,7,8- tetrachloro -4-hydroxy-3,4-dihydrophthalazin-1-yl)phenoxy) acetic acid (2) with the aim to obtain more precise information about the course of reactions and biological activities.Compound 2 synthesized from the interaction of 2-chlorophenoxy acetic acid with 3,4,5,6-tetrachlorophthalic anhydride under Friedel crafts reaction conditions afforded the 2-aroyl 3,4,5,6-tetrachlorobenzoic acid that treated with hydrazine hydrate in boiling ethanol according to scheme 1.

The structural of compound**2** was inferred from: (i) correct micro analytical data (ii) Its IR spectrum exhibits strong absorption at 3420,attributable to *ν*OH.The reaction possibly proceeds according to the following mechanism (Scheme 2). The reaction takes place via hydrazone derivative followed by ring closure although carbonyl of the ketonic group was more steric than the carbonyl of the acetic acid moiety.The authors thought formation of the corresponding hydrazide via nucleophilic addition elimination reaction of hydrazine hydrate with phenoxy acetic acid through $^{2}SN_{AC}$.



Scheme 1. Outline the synthetic route of the phthalazin-1-ol2.



Scheme 2. Outline the proposal mechanism of the reaction of 5,6,7,8-tetrachloro-phthalic anhydride with 2-chloro-phenoxy-acetic acid.

Steric factor play an important role and DFT study could help the authors for explanation. The lone pair of the chlorine in meta position of the benzoic acid can repel with the electron rich of the phenoxy ring, then one of the rings turn out of plane (Fig 1) in addition to the withdrawing of 2,4-dichloro moieties causes the activation of the ketonic group. Furthermore, it well known the ketonic group is more reactive than the carboxylic group. Therefore, the reaction with ketonic group of the aroyl benzoic derivative 1 with hydrazine hydrate become easy and give the corresponding hydrazone instead of hydrazide and the reaction is followed by ring closure toafford the phthalazin-1-one derivative 2 as in Scheme 1.

Inall solvents, except petrol at high dilution, the lactim form of phthalazin-1(2H)-one is extremely unflavored in the lactam $\rightleftharpoons$ lactim dynamic equilibrium. Polar solvation effects strongly favor the amide-like structure of phthalazin-1(2H)-one tautomer in petroleum60-80^{o}C. In the absence of effective solvation and at concentration less than 10^{-5} molar to minimize dimeric hydrogen-bonded association, the lactam: lactim ratio is around 2:3 changing even further to 2:1 in the gas phase.This shows the unsolvated phthalazin-1-ol tautomer to be of approximately higher thermodynamic stability than phthalazin-1-one due to intramolecular hydrogen bond.

In this investigation the authors thought to investigate the behaviorof 2-aroyl benzoic acid derivative towards different electrophiles.The reaction of**1**was allowed to react with hydroxyl amine in boiling pyridine, it afforded the 2,3-benzoxazin-1(2H)-one **3** (Scheme 4).

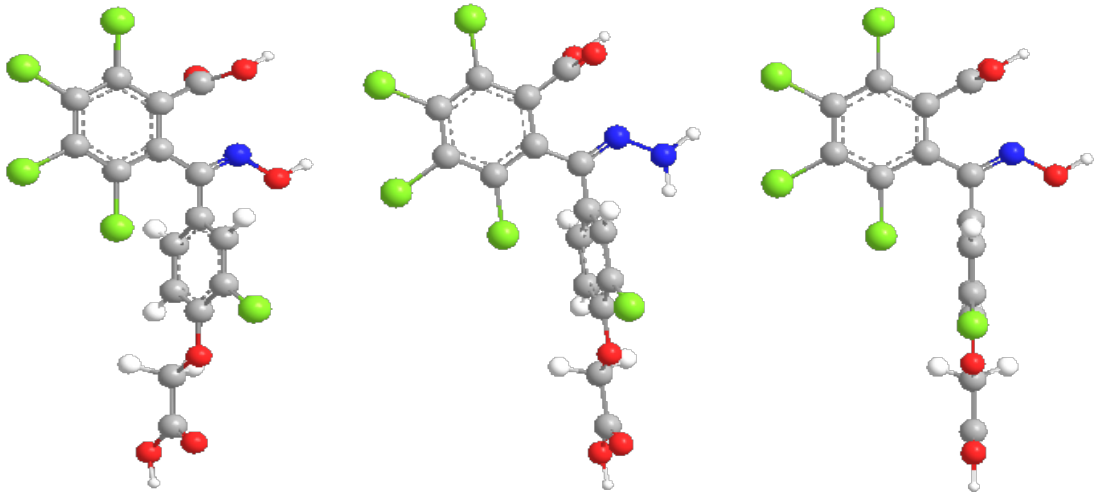
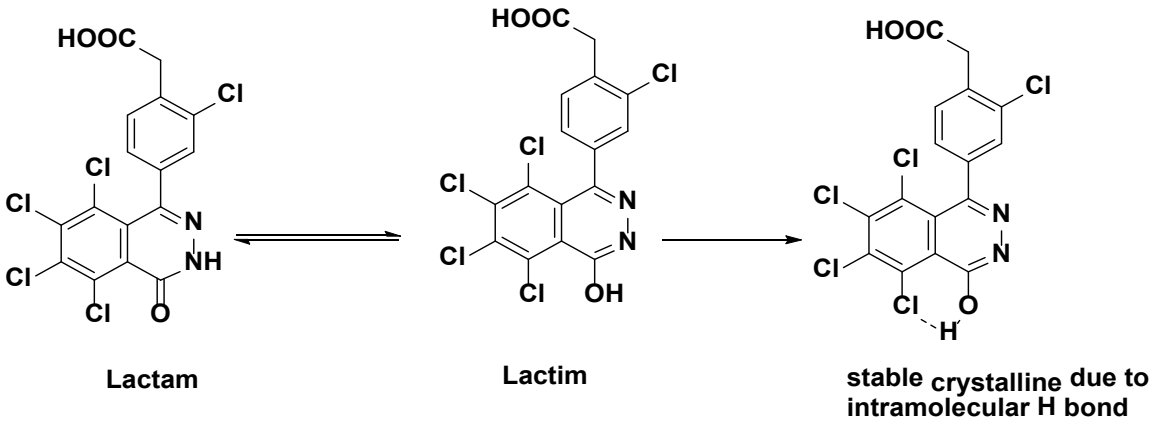
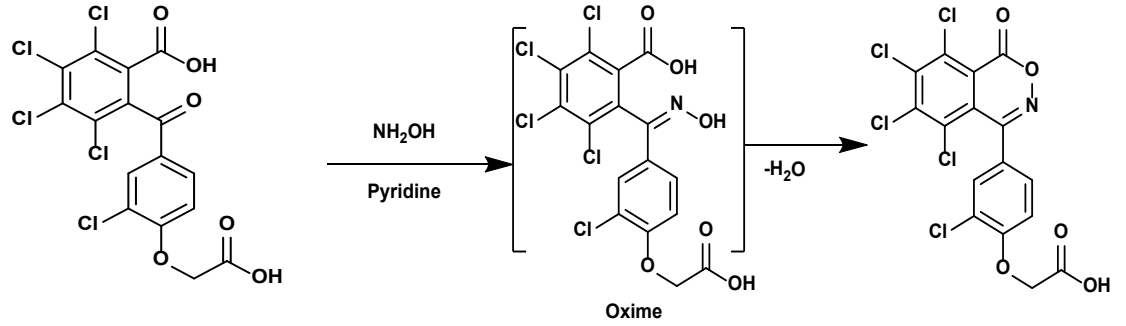


Fig. 1. DFT studyoutline the steric inhibition of resonance i.eout of plane the 2-chlorophenoxy acetic acid than other aroyl benzoic ring and formation of stable hydrazone and oxime intermediates.



Scheme 3. Outline lactam-lactim dynamic equilibrium and formation of higher lactim due to intramolecular hydrogen bond formation.



1 3

Scheme 4. outline reaction of the compound 1 with hydroxyl amine to afford the corresponding 2,3-benzoxazin-1-one 3

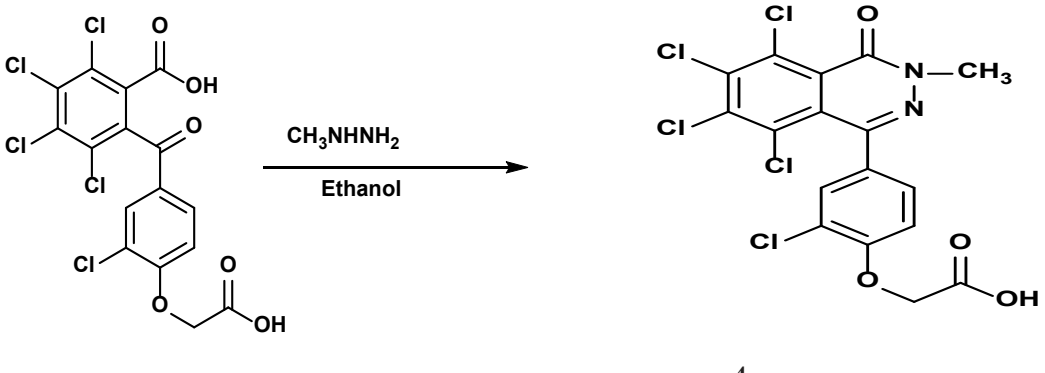
IR spectrum of the compound 3 reveals strong absorption bands in the carbonyl region at 1732 and 1708 corresponding to the carbonyl groups of both the lactone and acid precursors respectively. Similarly, theReaction of the2-aroyl benzoic acid **1** with methyl hydrazine in boiling ethanol, it afforded the methyl phthalazine-1(2H)-one **4** (Scheme 5).The structure of the compound 4 is corrected by microanalytical data. From DFT calculation, the 2-methyl-phthalazin-1-one is more stable than the corresponding hydrazone due to lowering ΔS and spontaneous ΔG of former compound **4**.

Antimicrobial studies

All the synthesized compounds were done using the agar diffusion assay. This screening was performed against the Gram-positive bacteria, Gram-negative bacteria, staphylococcus aureus atcc 06538, Escherechia coli Atcc 10536, pathogenic fungi candida albicans Atcc 1023 and Aspergills Flavus. A moderate activity was observed with compounds which proved to possess marked activity against E. coli, S. aureus and C. albicans. The strong activity was observed with the most compound of phthalazin-1-ol **2**. The inhibitory concentration was determined for each of the active compounds along with Ampicillin, Streptomycin and Nystatin as positive control. Results are shown in the following **Table 1** that outlinedthe antimicrobial activity of synthesized compounds **1**to**4**. The authors can be reported that the phthalazine derivatives(high HOMO) [34]converted to another configuration during the attacked of the bacteria and fungi, these are the one of explanation that why these compounds are weak or moderate effective as antibacterial and antifungal when the lactim form is uninvolved. Therefore, this ring was oriented towards the carbon in the microbe surface, and the adsorption is expected to take place mainly through these rings in case of the N-methyl phthalazine-1-one **4**.

Computational quantum studies:

Quantum chemical calculations were performed to evaluate the influence of the structural and electronic properties on the anti-microbial efficiency of compounds 1-4 and determine their mechanism of adsorption the phthalazine moiety on microbe surfaces.Results of the antimicrobial activities of the four phthalazine derivatives **1-4** were good agreement with the DFT calculation.



1 4

Scheme 5.Outline reaction of the 2-aroyl substituted benzoic acid with methyl hydrazine.

TABLE 1. Outline the antibacterial and antifungal activity of the synthesized compounds. Zone of Inhibition measured in mm. No activity (0.0), inhibition zone (< 7 mm), weak activity (7-10), moderate activity (11-15 mm), strong activity (> 15 mm), solvent $CDCl_3$ (6 mm).

Synthsized Compounds	*Staph.aureus*	*Escherichia coli*	*Pseud. aeruginosa*	*Candida albicans*
1	11± 0.21	12±0.12	21±0.24	16±0.22
2	19±0.24	21±0.32	21±0.26	22±0.15
3	13±0.11	14±0.15	22±0.02	16±0.07
4	10±0.13	15±0.10	21±0.11	16±0.21
Ampicillin	0.0	22±0.03	0.0	0.0
Streptomycin	20±0.02	21±0.01	0.0	0.0
Nystatin	0.0	0.0	0.0	22±0.02

The optimized phthalazine structures, HOMO/ LUMO states, total electron density surfaces mapped with the electrostatic potential (ESP), Mulliken charges and contour maps of the electrostatic potential are shown in (Figures1-4). The calculations reveal that the HOMO levels are mainly localized around one of the rings containing O and N atoms.

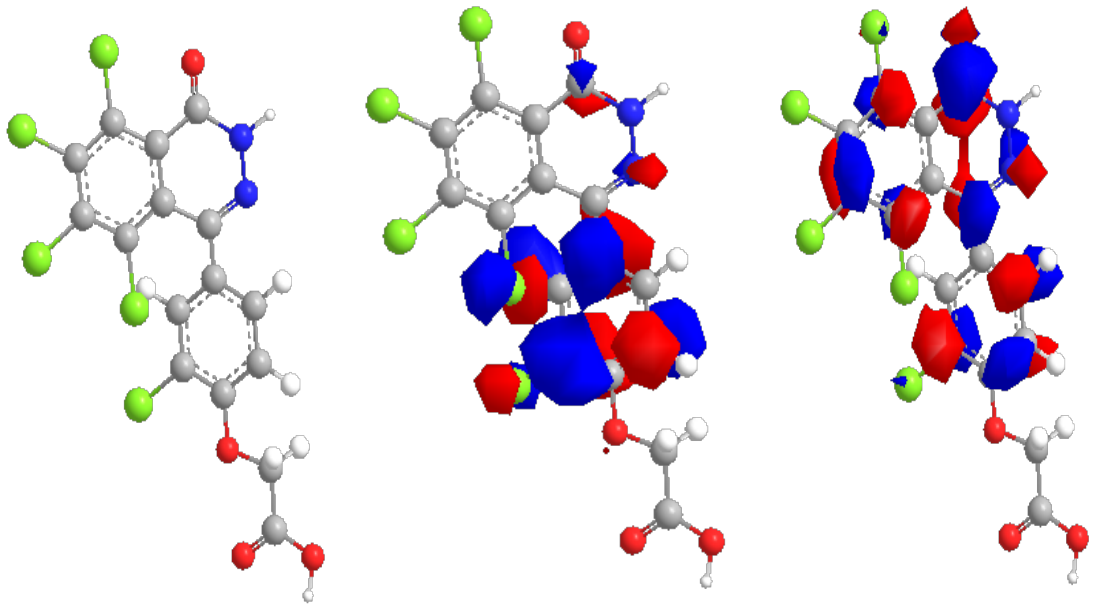


Fig. 2. Lactam form 2 HOMO LUMO

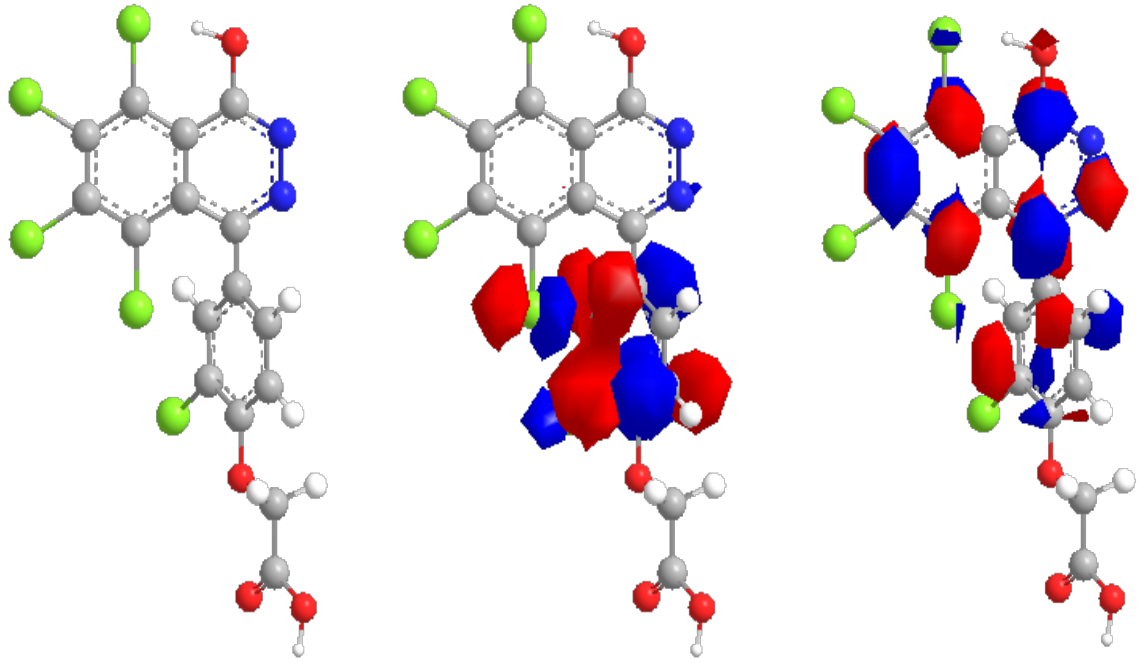


Fig. 3. Lactim form 2HOMO LUMO (More stable)

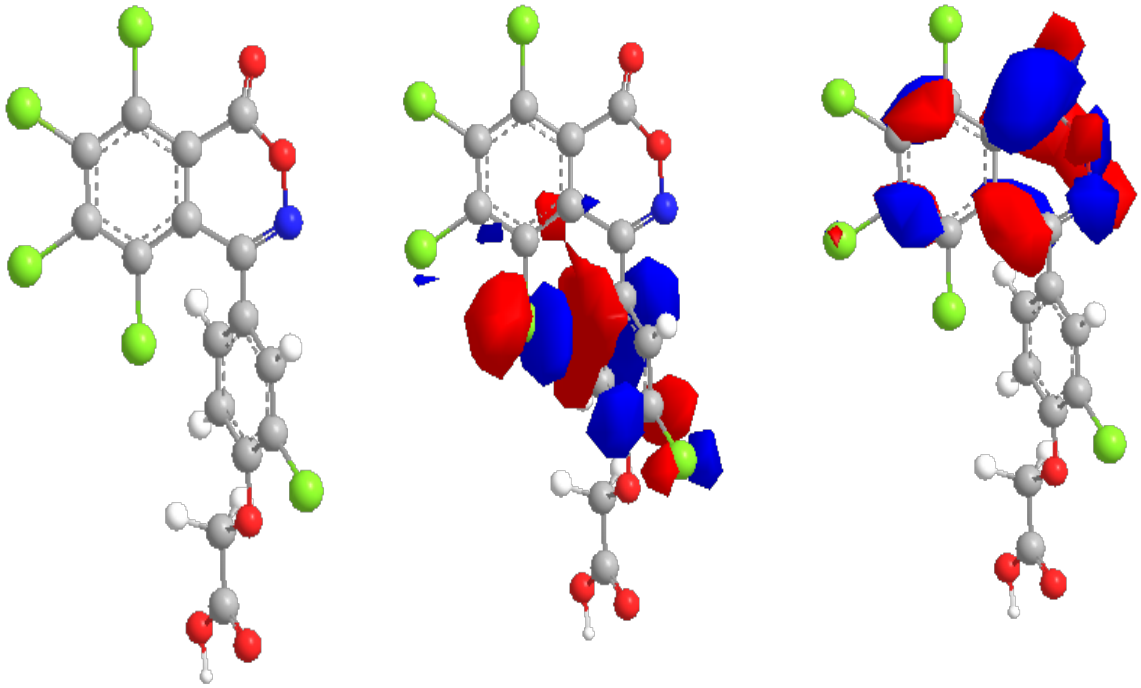


Fig. 4. Optimized Structure 3 HOMO LUMO

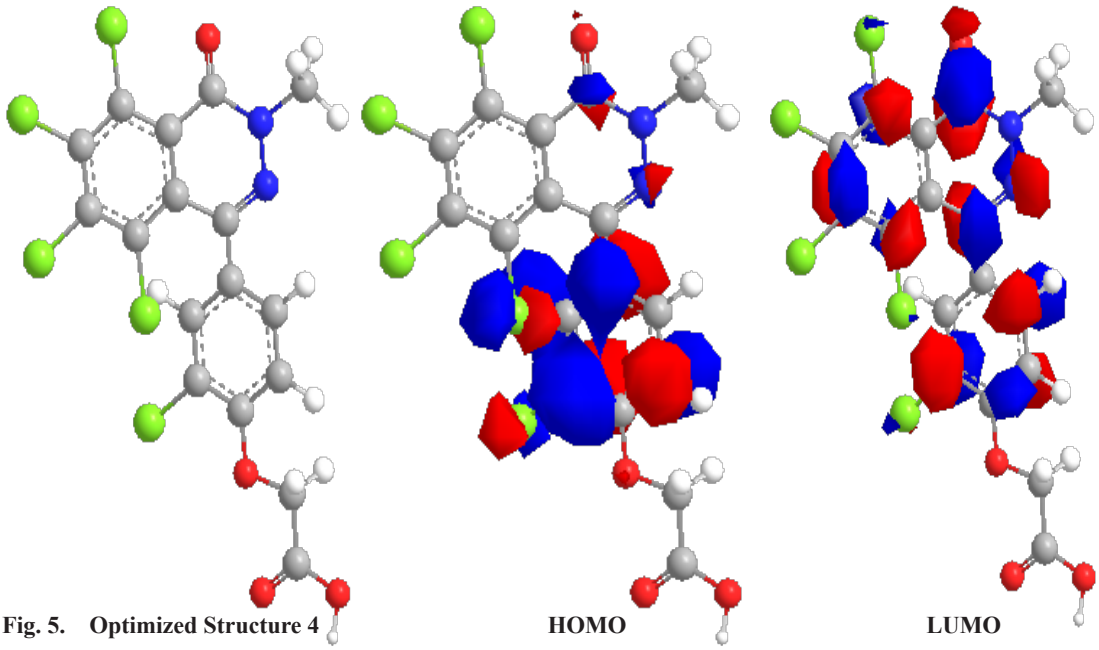


Fig. 5. Optimized Structure 4 HOMO LUMO

Experimental

Material and Method

All melting points are corrected and determined on a Stuart electric melting point apparatus (Microanalytical centre, ain shams university, Cairo, Egypt). Elemental analyses were carried out by Elementar Viro El-Microanalysis at the Micro-analytical Center, National Research Center, Egypt. IR spectra (KBr) were recorded on infrared spectrometer FT-IR 400D (New York, NY, USA) using OMNIC program and are reported frequency of absorption in terms of cm^{-1} and ^{1}H-NMR spectra recorded on a Bruker spectrophotometer (Rheinstetten, Germany) at 400 MHz using TMS as internal standard and with residual signals of the deuterated solvent δ = 7.26 ppm for $CDCl_3$ and δ 2.51 ppm for DMSO-*d6*. ^{13}C-NMR spectra were recorded on the same spectrometer (Rheinstetten, Germany) at 100 MHz and referenced to solvent signals δ = 77 ppm for $CDCl_3$ and δ 39.50 ppm for DMSO-d_6. DEPT 135 NMR spectroscopy were used where appropriate to aid the assignment of signals in the ^{1}H- and ^{13}C-NMR spectra. The mass spectra were recorded on Shimadzu GCMS-QP-1000 EX mass spectrometer (Kyoto, Japan) used the electron ionization technique at 70 e.v. Homogeneity of all synthesized compounds was checked by TLC.

2-(2-chloro-4-(5,6,7,8-tetrachloro-4-hydroxyphthalazin-1-yl)phenyl)acetic acid(2).

Hydrazine hydrate (0.015 mol) was added to a solution of 2-(4-(carboxymethyl)-3-chlorobenzoyl)-3,4,5,6-tetrachlorobenzoic acid(0.01 mol) in absolute ethanol and the reaction mixture was heated under refluxed for 3h. The solid that separated after cooling was filtered off and recrystallized from ethanol to give the phthalazinon **2**, 80% yield as colorless crystals, m.p. 220-222 ℃; The ^{1}H-NMR spectrum showed signal at 2.35 (methyl group), 7.3 – 7.7 (m , 7H , ArH) , 10.5 (s , 1H , NH , exchangeable with D_2O) . IR (KBr) *v*: 3296 (NH), 1665 (C=O) , 1605 (C=N) cm^{-1}. EIMS (70 eV) *m/z* (%): 452 (M^++3, 25%), 449 (M^+, 100), 248 (43), 220 (15), 131 (25), 105 (15).Anal cal for $C_{16}H_7N_2O_3Cl_5$: C, 42.47; H, 1.56; N 6.19; Cl 39.17; found C, 47.45; H 1.52; N 6.00; Cl, 39.00.

2-(2-chloro-4-(5,6,7,8-tetrachloro-1-oxo-1H-benzo[d][1,2]oxazin-4-yl)phenoxy)acetic acid(3).

A mixture of compound **1** (0.01 mol), hydroxyl amine hydrochloride (0.03 mol), in boiling pyridine (30 mL) was heated under reflux for 2h. The reaction mixture was poured into ice/HCl and diluted with water. The solid product was obtained filtered off and crystallized from the ethanol to give **3**,70% yield , m.p. 110 ℃. EIMS (70 eV) *m/z*(%):$M^{\cdot+}$+2,466.5 (10) ; $M^{\cdot+}$, 466.5 (40) , 268 (42) .IR (KBr) *v*: 1732, 1708, 2853 and 2923 cm^{-1} attributable to C=O and CH. Anal

calfor $C_{16}H_6NO_5Cl_5$: C, 40.93 ; H, 1.29 ; N, 2.98; Cl 37.75; found C, 40.31; H, 1.08; N, 2.72, Cl, 37.49.

2-(2-chloro-4-(5,6,7,8-tetrachloro-3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)phenoxy)acetic acid(4).

A mixture of the 2-aroyl benzoic derivative **1** (0.01mol),methylhydrazine (0.015 mol)in 50 ml boiling absolute ethanol was heated under reflux for 2 h. The excess solvent was removed by distillation and the reaction mixture was diluted with water filtered off and crystallized from the ethanol to give **4** ,74 % yield , m.p. 130 ℃. ^{1}H-NMR δ: 2.35 (Methyl group), 3.8 (t , CH_2 OH) , 7.2 - 7.9 (2m , 7H , Ar-H) , 8.37(s , 1H , OH , exchangeable with D_2O) . EIMS (70 eV) *m/z* (%): $M^{\cdot+}$, 314 (2) , 302 (2.2) 290 (35) , 276 (100) , 248 (40) . IR (KBr) *v*: 1632 , 2852 , 2921 , and 3436 cm^{-1} attributable to C=O , CH and OH . Anal Cal for $C_{17}H_9N_2O_4Cl_5$: C, 42.32; H, 1.88; N, 5.81; Cl 36.73; found C, 42.12; H, 1.77; N, 5.67, Cl 36.51.

Computational details

Compounds **1-4** were modelled using the Materials Studio 7.0 (MS7.0) software from Accelrys, Inc. The VAMP module of MS7.0 was used to optimize the geometries of the compounds and calculate their electronic properties, based on semiempirical methods using the PM3 parameterisation of the neglect of diatomic differential overlap (NDDO) Hamiltonian. In particular, we calculated the electron density, dipole moment, molecular surface area and frontier molecular orbitals (i.e., the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals) of each compound. Classical MD simulations were carried out to model the adsorption of the studied molecules on the antimicrobial surface at the molecular level, using the Forcite module and the COMPASS forcefield implemented in the MS7.0 software.

Conclusion.

Three newly heterocyclic antimicrobial, phthalazine-1-ol (**2**), 2,3-benzoxazin-1-one (**3**) and 2-methylphthalazin-1-one (**4**), were synthesized via a two-stepsynthetic procedure. A comparative analysis of the overall yields and reaction times was performed using Freidel-craftsfollowed by cyclization strategies. The structures of the synthesized compounds were fully elucidated based on elemental and spectroscopic analyses. The evaluation of the antimicrobial performances of the products revealed that compound **2**had much higher activities than the other products. Preliminary structure-activity relationship via DFTcalculation indicate that the intramolecular hydrogen bond and aromaticity enhanced its potential for binding with an antimicrobial surfaceled to improved antimicrobial activities. Phthalazine-1-oland 2,3-benzoxazin-1-one derivatives generally exhibit good thermal stability and low-lying HOMO levels. The solution-processed antimicrobial phthalazine-1-ol**2**and 2,3-benzoxazin-1-one **3** bears o-chloro-phenoxy acetic acid moiety, resulting in increased the active site species that can enhance the performances of antimicrobial activity in water of river and swimming pool.

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تحضير مشتقات من 5, -8,7,6 رباعى كلورو الفيثالازينون و-2,3بنزواوكزازينون المضادة للميكروبات ودراستها بنظرية الكثافة الالكترونية

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تم السماح لحمض ارويل البنزويك (1) بالتفاعل مع الكواشف النيكلوفيلية النيتروجينية مثل هيدرات الهيدرازين ، الهيدروكسيل أمين وميثيل الهيدرازين لتحضير مشتقات جديدة من 5, -8,7,6رباعي كلورو4--أريل-فثالازين 1--ون (2) و -2,3بنزوكزازينون (3) و -2ميثيل فيثالازينون (4) على الترتيب ومناقشة تأثير هذة المشتقات المحضرة كمضادات للميكروبات في مياه حوض السباحة ومياة نهرالنيل. تم قياس DFT على أساس حسابات ميكانيكا الكم الكيميائية للمركبات الجديدة بهدف دراسة نشاطها كمضادات للميكروبات. تميزت تراكيب المركبات حديثًا على أساس طيفيها (الرنين النووى المغناطيسي، الطيف الكتلي ، الأشعة تحت الحمراء والتحليل العنصرى).