DOI: http://dx.doi.org/10.31351/vol27iss1pp79-88

Synthesis, Characterization and Antimicrobial Evaluation with DFT Study of New Two-Amino-4-(4-Chlorophenyl) Thiazole Derivatives

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Abstract

2-amino-4-(4-chloro phenyl)-1,3-thiazole (**1**) was synthesized by refluxing thiourea with *para*-chloro phenacyl bromide in absolute methanol. The condensation of amine compound (**1**) with phenylisothiocyanate in the presence of pyridine will produce 1-(4-(4-chlorophenyl)thiazol-2-yl)-3-phenylthiourea**(2)**, which is upon treatment with 2,4 dinitrophenyl hydrazine by conventional method, afforded 1- (4 - (4 – chlorophenyl) thiazol – 2 – yl) – 3 - phenylhydrazonamide,N' - (2 , 4 - dinitrophenyl) ,(**3**).The characterization of the titled compounds were performed utilizing FTIR spectroscopy, ^{1}HNMR and CHNS elemental analysis, and by measurements of their physical properties. The synthesized compounds had been screened for their, *in vitro* preliminary antimicrobial activity against three Gram-positive bacteria: (*Staph. aureus, Micrococcus luteus* and *Bacillus subtilis*) and three Gram-negative bacteria : (*Pseud.aeruginosa, E.coli* and *Proteus mirabilis*) ,and two fungal strains(*Candida albicans* and *Candida glabrata*), using a minimum inhibitory concentration (MIC) of 100 µg\ml of test compound, by well diffusion method.

The derivatives showed moderate antibacterial activity against Gram-positive *Staphylococcus aureus* and *Bacillus subtilis* & high antifungal activity against *Candida glabrata and Candida albicans*. Computational study was performed to calculate some of thermodynamic parameters by using density functional theory (DFT)

Keywords: Antibacterial, 2-aminothiazole, sSynthesis and DFT.

تحضير والتقييم المضاد للميكروبات مع دراسة نظرية الكثافة الوظيفية لمشتقين جديدة من [٢-أمينو-٤- (٤-كلورو فينيل) ١،٣-ثيازول]

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الخلاصة

حضر المركب: [٢-أمينو-٤- (٤-كلوروفينيل) ١،٣-ثيازول] (١) من تصعيد الثيوريا مع كلورو فيناسيل البروميد باستعمال الميثانول المطلق ومن ثم مفاعلة مجموعة الامين من المركب السابق مع مع الفنيل ايسو ثايوسيانيت بوجود البيريدين لينتج المركب (٢), ثم التصعيد ثانيا للمركب (٢) مع ٢،٤- ثنائي نايتروفنيل هايدرازين بوجود الايثانول المطلق لينتج المركب النهائي (٣)

تم تشخيص المركبات المحضره باستعمال : مطياف الاشعة تحت الحمراء,والتحليل الدقيق للعناصر و كذلك قياس الخصائص الفيزيائية. للمركبات المحضره . تم تقييم النشاط الاولي المختبري المضاد للميكروبات ضد ثلاثة انواع من البكتريا الموجبه لصبغه غرام, وهي:(المكورات العنقودية الذهبية، المكورات الدقيقة،و العصوية الرقيقة)، وكذلك ضد ثلاثه انواع من البكتيريا السالبة لصبغه غرام, وهي: (الزائفة الزنجارية، الاشريكية القولونية والمتقلبة الرائعة) ونوعين من الفطريات (المبيضات البيض ، والمبيضات الجرداء) باستعمال ١٠٠مايكروغرام من المادة المحضره كأقل تركيز مثبط وذلك باستعمال طريقة الانتشار. أجريت الدراسة الحسابية لحساب بعض المعاملات الحرارية باستخدام نظريه الكثافة الوظيفية .

الكلمات المفتاحيه: مضاد للبكتريا, ٢-امينوثيازول, تحضير ,ونظريه الكثافه الوظيفيه .

Introduction

Thiazoles are significantly important heterocyclic that represent interesting properties depending on the linked groups to the thiazole[(1)]. 2-aminothiazoles are a subclass of thiazole family that are of high interest due to their broad biological activity., fungicidal[(2)], antioxidative [(3)], analgesic [(4)], bactericidal [(5)] and anti-inflammatory [(5)],anti-HIV [(6)], antitubercular [(7)], Thiazole containing N=C=S moiety have been used as antiphychotics [(8)]and antimalarial [(9)], and as herbicidal [(10)] .Thiazoles have broadly been engaged as effective γ-secretase inhibitors to hinder Alzheimer's disease [(11)] and have a lot of derivations and because of its derivations type have a lot of application in various industries, medical science, and pharmacy.In 1887, Hantzsch *et al* identified and established molecular structure of thiazoles. In 1889, the first derivation of thiazoles identified by Prop *et al* and was named 2-amino thiazole [(12)]. After that until now, many derivations identified and reported [(13, 14)]. Thiazole and related compounds are called 1 , 3 - azoles (nitrogen and one other heteroatom in a five – membered ring). They are isomeric with the 1 , 2 – bazoles , the nitrogen , and sulfur compound being called isothiazole [(15)]

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Received: 29/10/2017
Accepted: 4/3/2018

compounds from readily available reagents is one of the major challenges in organic chemistry. Therefore to meet the facile results of these tough challenges thiazole nucleus was being considered. Among the wide variety of heterocycles that have been explored for developing pharmaceutically molecules [16].Our study focuses on derivatization of new molecules starting from the parent nucleus 2-amino-4-(4-chloro phenyl) 1,3-thiazole (**1**), by treatment with phenyl isothiocyanate, to yield **(2)**, then refluxing it with to-2,4-dinitrophenyl hydrazine to produce **(3),** subsequently evaluation of the produced compounds *in vitro* for their preliminary antimicrobial activity ,also using DFT study to identify the changes in electronic structure responsible for farmacological action [17] .

Material and Methods

Chemicals used during the synthesis, supplied by hyper- chem/china. Completion of reactions and the purity of compounds were ascertained by thin-layer chromatography (TLC) , using Silica gel G_{F254} (type 60) pre-coated Aluminium sheets, Merck (Germany) exposed to UV-254nm light and the eluent used is *n*-hexane: ethyl acetate (6.0:4.0) for compound (**1**) , *n*-hexane: ethyl acetate (8.0:2.0) for compound (**2**) and *n*-hexane: ethyl acetate (4.0:6.0) for compound (**3**).Melting points were measured by using Stuart SMP3 melting point apparatus in open capillary tubes, and are uncorrected. The infrared spectra were performed in KBr disc, (υ,cm^{-1}), using FTIR Spectrophotometer (Shimadzu, WQF-520, Japan) at the University of Baghdad College of Education for Pure Sciences Ibn Al-Haitham. The CHNS elemental microanalysis of the final synthesized products was done using (Elemental Vario MICRO cube instrument, Germany) in the University of Mustansiriya-College of Pharmacy.

Chemical synthesis

General method for the Synthesis of 2-Amino-4- (4 – chlorophenyl) thiazole (1)

Method 1[18]:

A mixture of p-chloro phenacyl bromide (0.01 mol,2.3g) in 100 ml of absolute alcohol and thiourea (0.02 mol, 1.5g) were taken in a round bottom flask and refluxed for 3 h. Then the reaction mixture was cooled and precipitated with cold water. The solid separated was collected by filtration and the solvent was removed under vacuum. The residue obtained was dried, recrystallized from ethanol.

2-amino-4-(4-chlor phenyl thiazole) **(1)** Off white powder, yield 95%,m.p 167-169ºC, IR(KBr),(υ,cm^{-1}): (3438and3284) $\underline{NH_2}$ str, of *prim*.amine,3114 Ar(CH) str,1535 Ar(C=C)str,825 (C-Cl) str,669 (C-S) str; **^{1}HNMR(300 MHz,DMSO-d6 ,δ = ppm) :** 7.98 (2H , d , Cl - 2Ar –H) ; 7.41(2H,d,Cl-2Ar-H);7.08 (1H,s,H_5-Thiazol);7.06(2H,s,NH_2).

Method 2[19]

A mixture of p-chloro phenacyl bromide (0.0064 mol, 1.5 g), and thiourea (0.0064 mol, 0.489 g) in 10 ml of DMSO was stirred at room temperature until completion of the reaction. The time of the reaction was monitored by a stopwatch. The progress of the reaction was monitored by thin-layer chromatography. On completion of the reaction, the reaction mixture was poured into crushed ice. The precipitated product was filtered and dried and recrystallized from ethanol. The product was pure enough (single spot on TLC) for all practical purposes.

General method for the synthesis of 1-(4-(4-chlorophenyl) thiazol -2-yl)-3-phenylthiourea (2)[20]

A mixture of **(1)**, (0.01 mol, 2.1g) in pyridine (20 mL) was added to phenyl isothiocyanate (0.01 mol, 1.35g,) and the reaction mixture refluxed for 6 h. It was then cooled , and the solvent removed in *vacuo*. The resulting residue was triturated with water, and the solid obtained was recrystallized from ethanol .

1-(4-(4-chlorophenyl)thiazol-2-yl)-3-phenylthiourea (**2**)

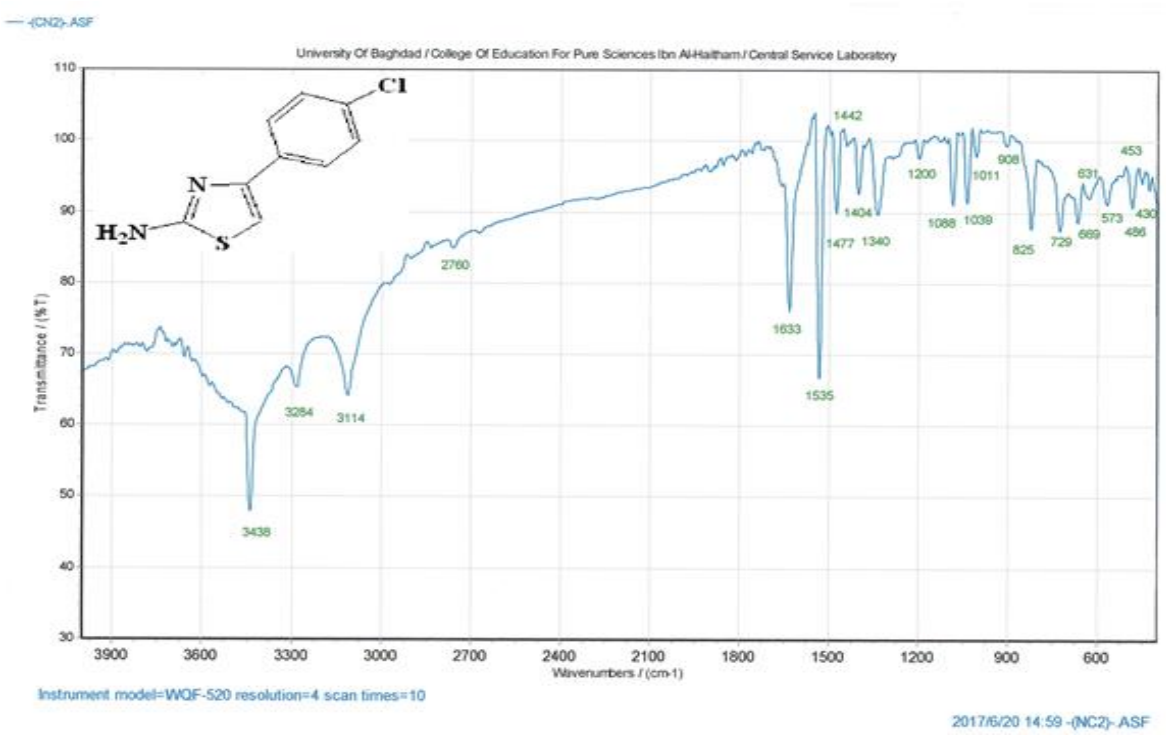
Yellow powder ,yield 92%,m.p 255-260 ºC, IR(KBr) (υ,cm^{-1}): 3159 Ar (NH)str,3113Ar(CH)str, 1576Ar(C=C) str,1196(C=S)str,658 (C-S)str; elemental micro analysis: calcd. for $C_{16}H_{12}ClN_3S_2$ C,55. 56; H,3.50; N, 12.15, S, 18.54%. Found: C,55.29; H,3.363; N, 12.08 ; S, 18.196 %.

General method for the Synthesis of 1-(4-(4-chlorophenyl)thiazol-2-yl)-3-phenylhydrazonamide N'-(2,4-dinitrophenyl) (3)[21]

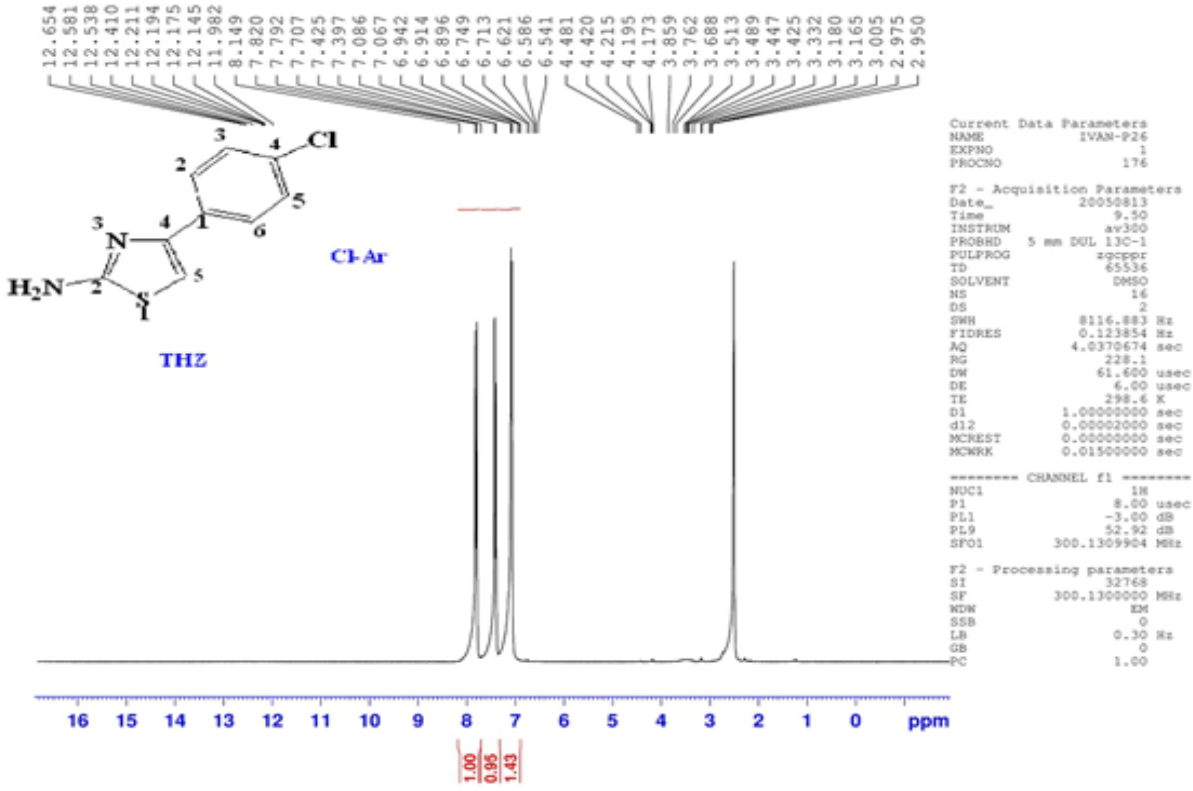
A mixture of **(2)** (0.001mol,0.345g) and 2,4 di nitro phenyl hydrazine (0.001mol 1.98g) in absolute ethanol (30 ml) was refluxed for 7h. The product separated during reflux, was filtered off and recrystallized from ethanol as brown powder.

1-(4-(4-chlorophenyl)thiazol-2-yl)-3-phenylhydrazonamide N '-(2,4-dinitrophenyl) (**3**)

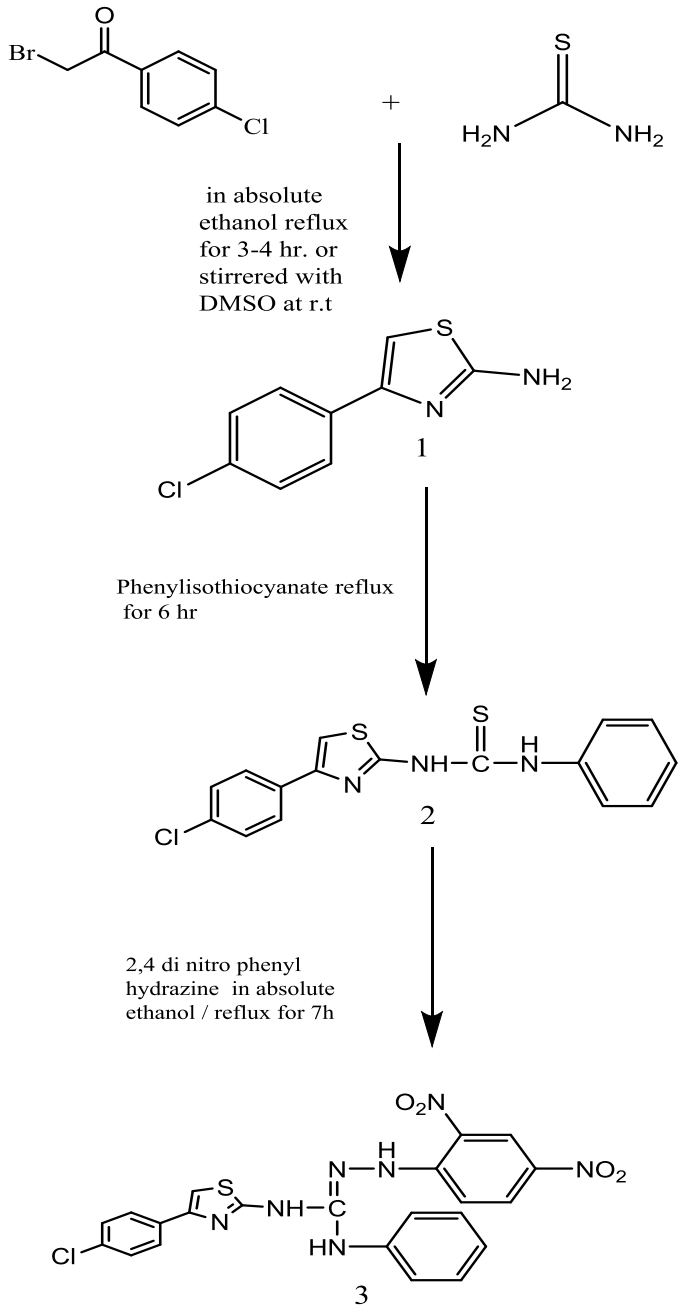
Brown powder ,yield 78%, m.p 135-137ºC, IR(KBr),(υ,cm^{-1}): 3313 (NH) str of *sec*. amine, 3026 Ar(CH)str,1614(C=N)str, 1587Ar (C=C)str, 1512 *asym*. NO_2 str,1331*sym.* NO_2 str,1196 (C-N)str.,833 (C-Cl)str,660(C-S)str., Elemental analysis: calcd. for $C_{19}H_{12}ClN_3O_2S_2$ C,51.82; H,3.16; N, 19.23; S, 6.29%. Found: C,51.050; H,3.11; N, 18.93; S, 5.98 %.



IR spectrum of compound 1



[1]HNMR of compound 1



Scheme 1. Synthesis of 2-amino thiazole derivatives (2and3)

Antimicrobial screening

The antimicrobial activities of the synthesized derivatives were measured using well diffusion technique with a comparison to cefotaxime sodium(cefot.) and sulfamethoxazole (sulf.) as standard antibacterial agents ,and miconazole as standard antifungal agent, using dimethylsulfoxide (DMSO) as solvent and as a control, and it was run in the Ministry of Health/ National Center for Drug Control and Research (NCDCR) / Baghdad , and in University of Baghdad/College of Education for Pure Sciences Ibn Al-Haitham /central service laboratory. The synthesized compounds had been screened for their in vitro preliminary antimicrobial activity against three Gram-positive bacteria: (Staph. aureus, Micrococcus luteus and Bacillus subtilis), three Gram-negative bacteria (Pseud.aeruginosa, E.coli, and Proteus mirabilis) and two fungi (Candida albicans and Candida glabrata), using a minimum inhibitory concentration (MIC) of

100 µg\ml of reference compounds (2) and (3) in DMSO as shown in table 1.

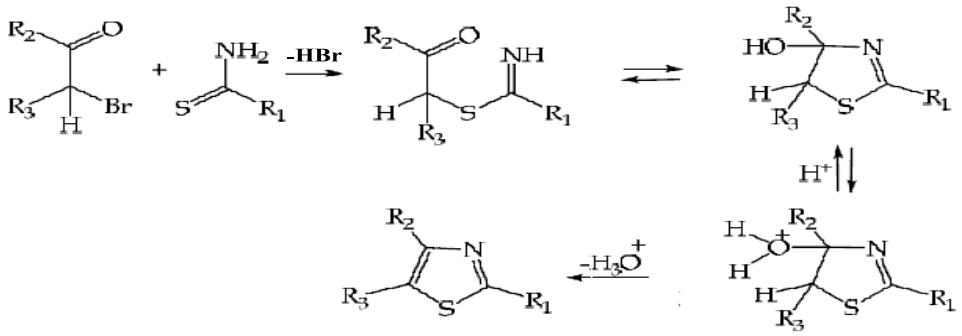
Results and Discussion

Chemistry

The 2-Amino-4-(4-chlorophenyl) thiazole (**1**) synthesis, was carried out according to Hantzsch method [22], by reaction of phenacyl bromide with thiourea in the presence of absolute methanol for 3 hours. They are characterized by FTIR, due to the appearance primary amine ($\underline{NH_2}$) stretching at 3438 and 3284 cm^{-1} and then reaction of (**1**) with phenylisothiocyanate in the presence of pyridine to produce (**2**) which was characterized by FTIR, a band of(C=S) stretching displayed at 1254cm^{-1}, and NH stretching band at 3159 cm^{-1},and finally condensation of **(2)** with, 2,4 dinitrophenyl hydrazine using absolute ethanol as a solvent. to afford (**3**) which showed the characteristic NO_2 (asymmetrical and symmetrical)stretching at 1512 and 1331 cm^{-1}, respectively, also peak attributed to(C=N) band recorded at 1614 cm^{-1}.

Synthesis of compound (1)

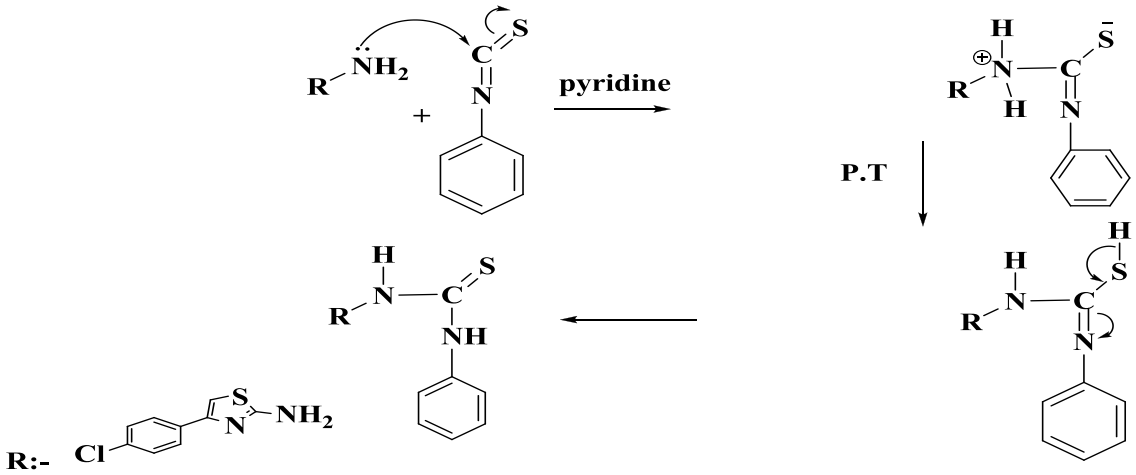
The method of parent nucleus synthesis was described by Hantzsch, in 1887 the cyclization of α-halo carbonyl compounds by a great variety of reactants containing the N-C-S fragment of the ring is still the widely used method of synthesis of thiazoles ,as shown in the following scheme (2) [22].



Scheme 2. Mechanism of synthesis of (1)

Synthesis of compound (2)

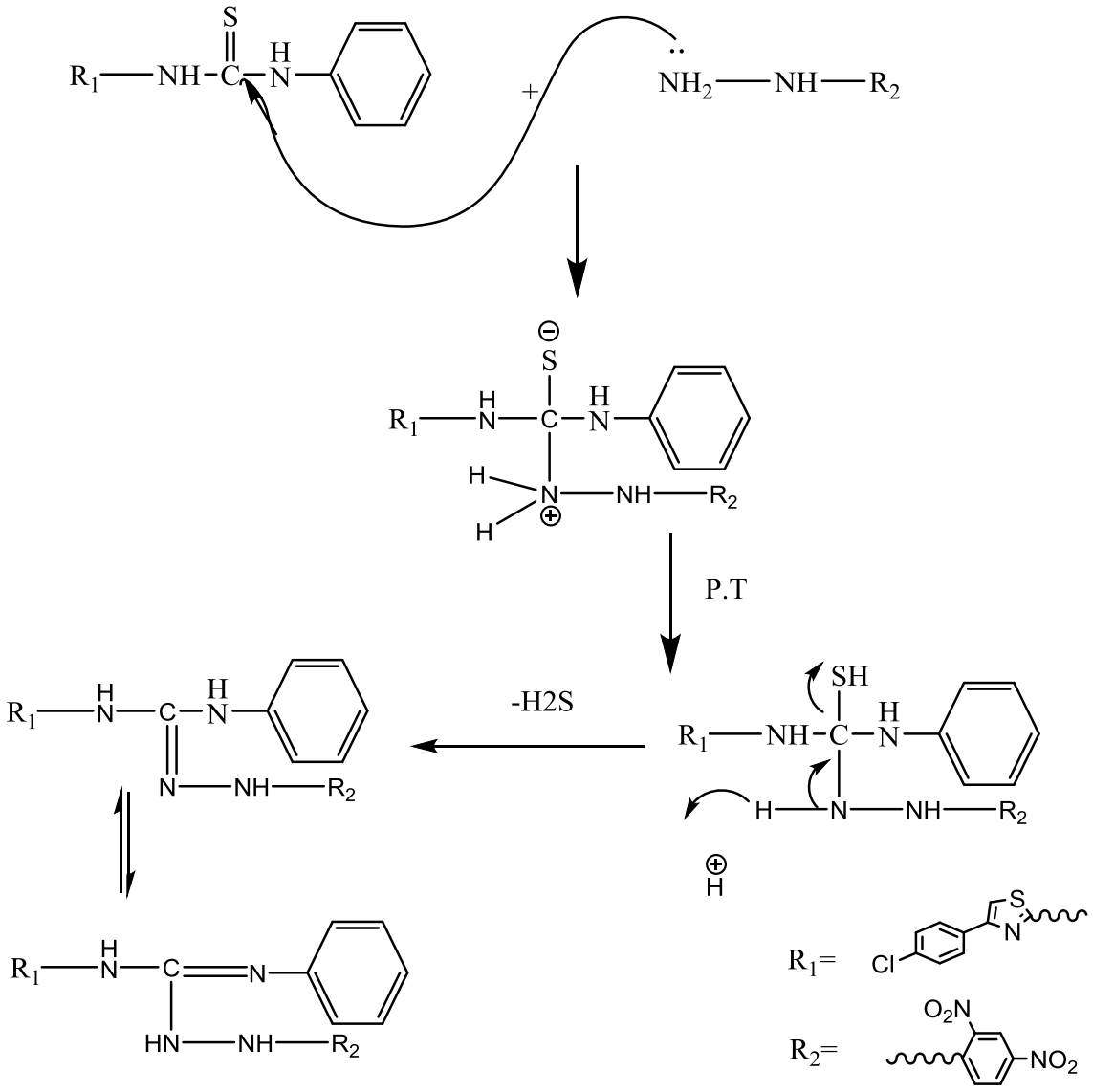
The condensation of parent nucleus (1), with phenyl isothiocyanate, afforded the corresponding 1- (4-(4- chlorophenyl)thiazol-2-yl)- 3 -phenylthiourea derivative (2), the unshared pair of electron of NH_2 of (1) would attack the carbon (C = S), of thiocarbonyl group [23] as shown in the following scheme 3.



Scheme 3. Mechanism of Synthesis of (2)

Synthesis of compound (3)

The reactivity of phenyl isothiocyanate is, determined by two active centers the nucleophilic nitrogen atom, and thiocarbonyl groups, which make them capable of participating in diverse type of addition and cyclization reactions. The unshared pair of electron of NH_2 group of 2,4-dinitro phenyl hydrazine would attack thiocarbonyl carbon(C=S) of (2) and in the presence of acidic hydrogen of ethanol, H_2S gas would be evolved, and the tatumeric structure of (3), would also formed [(24)], as shown in the scheme 4.



Scheme4. Mechanism of Synthesis of (3)

Anti microbial Activity

From the results illustrated in table1, showed that the new synthesized derivative (**2** and **3**) have moderate activity against Gram-positive bacteria *Staph. aureus* and *Bacillus subtilis* also , both compounds have no antibacterial activity against Gram-negative bacteria.It is evident that the tested compounds demonstrated the most potent antifungal activity against *Candida albicans* and *Candida glabrata*.

Table1. The antibacterial and antifungal activity of the tested compounds.

Comp. No.	*Conc. µg/ml*	*S. aureus* Conc. µg/ml (G^{+ve})	*Micrococ-cus luteus* Conc.µg/ml(G^{+ve})	*Bacillus subtilis* Conc.µg/ml (G^{+ve})	*Proteus mirabilis* Conc.µg/ml (G^{-ve})	*Pseudomonas aeruginosa*nn nConc.µg/ml (G^{-ve})	*E. coli Conc.µg/ml* (G^{-ve})	*Candida glabrata Conc. µg/ml*	*Candida albicans* Conc. µg/ml
2	100	9.3	8.0	10.15	-	-	-	17	15.5
3	100	10.4	-	10.37	-	-	-	16	18.6
Cefot.	100	44.5	34.4	36.05	33.5	35.5	56.7	-	-
sulf.	100	23	19.06	25.15	19.5	18.9	35.6	-	-
Micon azole	100	-	-	-	-	-	-	17.0	16.9
DMSO	100	-	-	-	-	-	-	-	-

(-)= No activity, (+) = slightly active (Inhibition Zone in between 5-10 mm),(++) = moderately active (Inhibition Zone in between 10-15 mm), (+++)=highly active (Inhibition Zone More Than 15 mm).

Computational Studies

Density function theory (DFT) study

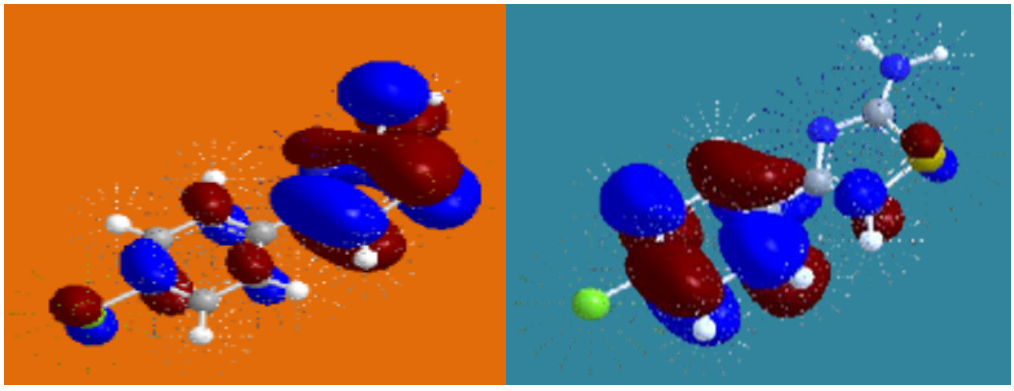
In order to explore the theoretical-experimental consistency, quantum chemical calculations were performed with complete geometry optimizations using standard Spartan 10 software. Geometry optimization was carried out by B3LYP/6-31G* level of theory. The chemical reactivity descriptors calculated using DFT are: total energy (E), log p and electronegativity (µ).

On the basis of frontier molecular orbitals, chemical hardness corresponds to the gap between the HOMO and LUMO , where ELUMO and EHOMO are the LUMO and HOMO energies. electronegativity [25] is defined as the negative of electronegativity of a molecule, Physically,(µ) describes the escaping tendency of electrons from an equilibrium system [26]. It is a measure of the stabilization in energy after a system accepts additional amount of electronic charge from the environment

Results and Discussion

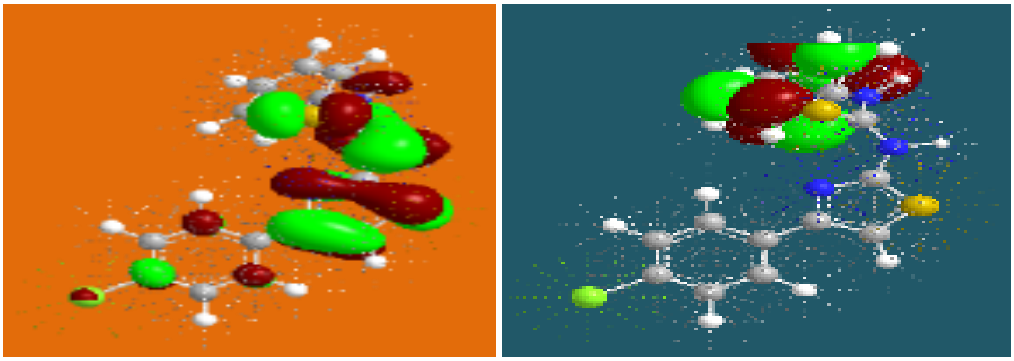
Structural and electronic properties

DFT calculations were performed for compound 1- 3. Optimized molecular structures of the most stable form are shown in Figure 1.



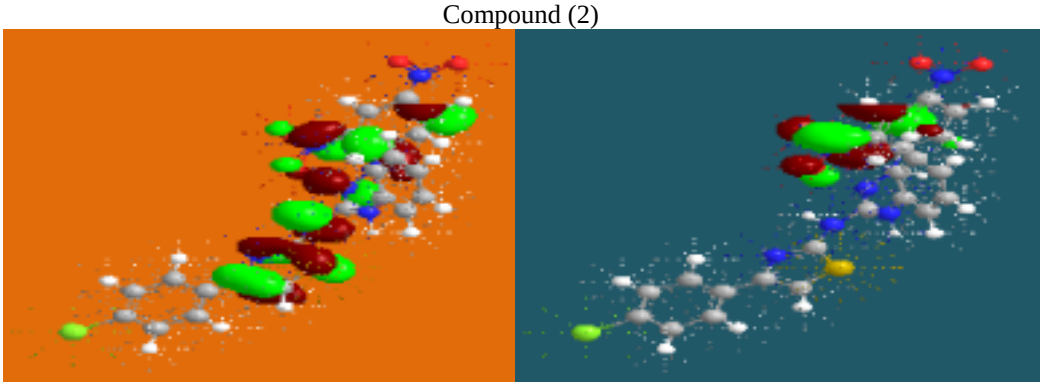
HOMO LUMO

Compound (1)



HOMO LUMO

Compound (2)



HOMO LUMO

Compound (3)

Figure 1. Highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of compounds **1**–**3**.

It can be seen that the energy gaps between HOMO and LUMO for compound **1** is 6.915, compound **2** is –5.85, compound **3** is 1.425. The lower value in the HOMO and LUMO energy gap explains the eventual charge transfer interaction taking place within the molecules. The larger the HOMO–LUMO energy gap, more stable/less reactive the molecule, for example, compound **1**. The values of (μ) for compounds 1, 2 and 3 are presented in (Table 1 row 5). The trend in electronegativity for compounds **1-3** are**: 2 > 3 >1** . The greater the electronic chemical potential, the less stable or more reactive is the compound. Therefore, compound **2** is more reactive than compounds **3** and **1,** respectively. Therefore, compound 2 is the most reactive, and 3 and 1 are the least reactive.

Electrostatic potential charges and related quantum chemical properties

The distribution of the electronic density (electrostatic potential charges), related quantum chemical parameters; HOMO/LUMO gap (Table 1, row 4), the trends in energy gap 1> 3> 2 .On the other hand log p provides a measure of a molecule's lipophilicity, where high log p-value indicates high lipophilicity, while low value suggests low lipophilicity. the partition coefficients of the compounds (log p), (Table 1, row6) were calculated for observed compounds **1-3. ,** The results indicated that compounds having the highest lipophilicity were 3 > 2 > 1 with corresponding values 6.66, 6.04 and 3.61**,**respectively. These values and properties are very useful and can be used in order to evaluate chemical properties and possibilities for interaction of compounds with biological macromolecules (receptors, enzymes) [27].

Table 1. Global chemical reactivity indices for compounds 1–3

Compound (3)	Compound (2)	Compound (1)	Parameters
Total Energy kcal/mol	1.4619	-4.2637	23.7835
HOMO ev	-8.052	-5.51	-6.283
LUMO ev	-1.137	0.34	-4.858
Energy gap eV	1.425	-5.85	6.915
Electronegative μ/ eV	-4.59	-2.59	-3.85
Log p	3.61	6.04	6.66

Conclusion

A new derivatives of 2-amino thiazole were successfully synthesized using conventional method and tested for their preliminary antimicrobial activity,using well diffusion method. The synthesized compounds displayed slight antibacterial activities against Gram-positive types, while demonstrated no antibacterial activities against Gram-negative bacteria, and high antifungal activity against tested fungal species.

The quantum chemistry calculations using the Density Function Theory (DFT) method was performed to study stability of compounds **1**-**3**. The results showed that the compound **1** is more stable than compound **3**, as was indicated via calculations of the larger the HOMO– LUMO energy gap parameter [(28)] .

References

1. Schnürch M, Waldner B, Hilber K, Mihovilovic MD. Synthesis of 5-arylated N-arylthiazole-2-amines as potential skeletal muscle cell differen tiation promoters. Bioorg. Med. Chem lett. 2011;21(7):2149-2154.

2. De Logu A, Saddi M, Cardia MC, Borgna R, Sanna C, Saddi B, Maccioni E. In vitro activity of 2-cyclohexylidenhydrazo-4-phenyl-thiazole compared with those of amphotericin B and fluconazole against clinical isolates of Candida spp. and fluconazole-resistant Candida albicans. J. Antimicrob. Chemother., 2005; 55(5):692-688.

3. Sondhi SM, Singh N, Lahoti AM, Bajaj K, Kumar A, Lozach O, Meijer L. Synthesis of acridinyl-thiazolino derivatives and their evaluation for anti-inflammatory, analgesic and kinase inhibition activities. Bioorg. Med. Chem., 2005; 13(13):4291-4299.

4. Liu HL, Lieberzeit Z, Anthonsen T. Synthesis and fungicidal activity of 2-Imino-3-(4-arylthiazol-2-yl)-thiazolidin-4-ones and their 5-arylidene derivatives. Molecules. 2000;5(9):1055-1061.

5. Holla BS, Malini KV, Rao BS, Sarojini BK, Kumari NS. Synthesis of some new 2, 4-disubstituted thiazoles as possible antibacterial and anti-inflammatory agents. Eur. J. Med. Chem., 2003; 38(3):313-318.

6. Venkatachalam TK, Sudbeck EA, Mao C, Uckun FM. Anti-HIV activity of aromatic and heterocyclic thiazolyl thiourea compounds. Bioorg. Med. Chem lett., 2001;11(4):523-528.

7. Al-Balas Q, Anthony NG, Al-Jaidi B, Alnimr A, Abbott G, Brown AK, Taylor RC, Besra GS, McHugh TD, Gillespie SH, Johnston BF. Identification of 2-aminothiazole-4-carboxylate derivatives active against Mycobacterium tuberculosis H37Rv and the β-ketoacyl-ACP synthase mtFabH. PLoS One. 2009; 4(5): 5617.

8. Pattan SR, Dighe NS, Nirmal SA, Merekar AN, Laware RB, Shinde HV, Musmade DS. Synthesis and biological evaluation of some substituted amino thiazole derivatives. Asian J.Res. Chem., 2009;2(2):196-201.

9. Karade HN, Acharya BN, Sathe M, Kaushik MP. Design, synthesis, and antimalarial evaluation of thiazole-derived amino acids. Med. Chem. Res. 2008;17(1):19-29.

10. Nüchter M, Ondruschka B, Jungnickel A, Müller U. Organic processes initiated by non-classical energy sources. J. Phys. Org. Chem. 2000;13(10):579-586.

11. Akbarzadeh A, Soleymani R, Taheri M, Karimi-Cheshmeh Ali M. Synthesis New and Novel Aryl Thiazole Derivatives Compounds. Orient J Chem., 2012;28(1):153.

12. Jain N, Singh B. An Overview of Biological and Synthetic Aspects of Thiazole Derivatives in Heterocyclic Chemistry. World j. res. rev., 2016;3(5):52-57.

13. Pattan SR, Dighe NS, Nirmal SA, Merekar AN, Laware RB, Shinde HV, Musmade DS. Synthesis and biological evaluation of some substituted amino thiazole derivatives. Asian J.Res. Chem., 2009;2(2):196-201.

14. Kottawar SS, Goswami SV, Thorat PB, Bhusare SR. L as an Efficient catalyst for synthesis of Aldimines at Ambient Temperature Condition. J Chem., 2011;8(4):1859-1863.

15. Sathe BS, Jaychandran E, Sreenivasa GM, Jagtap VA. Antimycobacterial Activity of Some Synthesized Fluorinated Benzothiazolo Imidazole Compounds. J Chem., 2011;8(2):830-834.

16. Nadeem Siddiqui*, M. Faiz Arshad, Waquar Ahsan, M. Shamsher Alam. Thiazoles: A Valuable Insight into the Recent Advances and Biological Activities, Int. J.pharm.sci. D. Res., 2009; 1(3): 136-143

17. Padmavathi P.Prabhu, Aravind Pai, Padmashree, Ramakrishna Shabaraya . Analgesic and anti-inflammatory activity Studies of some new aryl 4-thiazolidinones in experimental mice. Pharmacologyonline .2010; 1: 1132-1139

18. Dighe SN, Chaskar PK, Jain KS, Phoujdar MS, Srinivasan KV. A remarkably high-speed solution-phase combinatorial synthesis of 2-substituted-amino-4-aryl thiazoles in polar solvents in the absence of a catalyst under ambient conditions and study of their antimicrobial activities. ISRN Org Chem., 2011; 11:1-6

19. Abdel-Mohsen SA. Heterocycles derived from 5-(2-aminothiazol-4-yl)-8-hydroxyquinoline: synthesis and antimicrobial activity., J Chin Chem Soc., 2003,50(5):1085-1092.
20. Hassan MA, Sayed GH, El-Nagar AM, Hussien AM. A convenient synthesis of some diarylurea and thiourea derivatives as antimicrobial compounds. Chem Process Eng Res.,2014 ;25:1-11
21. Manisha kotadiya . "Thiazoles:- Past, present and future" Int. j. adv. eng. technol. manag. appl. sci., 2017 ; 04 (01): 24-44.
22. Karlsson I, Samuelsson K, Ponting DJ, Törnqvist M, Ilag LL, Nilsson U. Peptide reactivity of isothiocyanates–implications for skin allergy. Sci. Rep., 2016;6:1-12.
23. Bedane KG, Singh GS. Reactivity and diverse synthetic applications of acyl isothiocyanates.: J. Org. Chem., 2015;1: 206-245
24. Parr RG, Pearson RG. Absolute hardness: companion parameter to absolute electronegativity. J. Am. Chem. Soc.1983; 105(26): 7512-7516.
25. Vektariene A, Vektaris G, Svoboda J. A theoretical approach to the nucleophilic behavior of benzofused thieno [3, 2-b] furans using DFT and HF based reactivity descriptors. Arkivoc. 2009(vii):311-329.
26. R. Pearson. Chemical hardness and density functional theory".J. Chem. Sci., 2005, 117(5): 369–377.
27. Bahrami MJ, Hosseini SM, Pilvar P. Experimental and theoretical investigation of organic compounds as inhibitors for mild steel corrosion in sulfuric acid medium. Corrosion Science. 2010;52(9):2793-2803.
28. M. A. Migahed A. M. Al-Sabagh E.A. Khamis M.Abd-EL-Raouf E. G. Zaki , Antimicrobial Activity and Quantum Chemical Calculations of Pyrazol-2,3-Dihydrothiazole Sugar Derivatives , Chem. Mater. Res., 2014 ; 6 (12): 46-54.