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Synthesis, spectral characterization, theoretical calculations and antibacterial activity of newly designed 1H-pyrazole-1-carbothioamide

S. Sivapriya[1], H. Manikandan[2]

[1]Department of Chemistry, Faculty of Science, Annamalai University, Annamalainagar, Chidambaram–608 002, Tamilnadu, India.
[2]Department of Chemistry, Faculty of Science, Annamalai University, Annamalainagar, Chidambaram-608002, Tamilnadu, India.

Corresponding author:
Dr. H. Manikandan M.Sc., M.Phil., Ph.D.
Department of Chemistry, Annamalai University, Annamalainagar, Chidambaram-608002, Tamilnadu, India.
Email: [2]profmani.au@gmail.com

Abstract: In this work, a novel heterocyclic compounds such as 1H-pyrazole-1-carbothioamide were synthesized by cyclocondensation reaction of chalcone and thiosemicarbazide as nucleophilic substrate in ethanolic NaOH solution. The structures were characterized by FT-IR, ^{1}H-NMR, ^{13}C -NMR. The molecular geometry of the targeted compounds was optimized using DFT studies. The energy of the HOMO & LUMO and Mulliken atomic charges were also calculated. Besides, electrochemical quantities such as chemical hardness and electronegativity were measured and analyzed by the use of HOMO-LUMO. They also exhibited high antibacterial activities.
Keywords: chalcone, 1H-pyrazole, carbothioamide, DFT, antibacterial.

1. INTRODUCTION

The management of infectious diseases remains a chief and difficult problem because of a variety of factors, together with emerging infectious diseases and the rising number of multi-drug resistant microbial pathogens. Microbial infections, either alone or in combination, have become a global series of antimicrobial drugs with various mechanisms of action used to treat microbial infections, as well as the presence of a lot of compounds used in various phases of clinical trials. There is already evidence that there is a rise in mortality associated with antimicrobial resistance. In addition to rising microbial resistance, the issue with clinically used medications is often followed by the harmful side effects that are sometimes dose-limiting [1-5]. The aggregation of unhealthy bacterial strains on the skin or within the body induces bacterial infections. Bacteria that cause pneumonia, meningitis, respiratory tract infections, sexually transmitted bacterial infections, skin infections, and food poisoning can affect any part of the human body [6].A number of bacteria that cause severe and sometimes fatal infections in humans are Bacillus megaterium, Staphelococcus Aureus, E. coli and Pseudomonas Aerogiosa [7].
Hetero cycles with hetero atoms of nitrogen and sulphur exhibit a numerous biological activities, such as antibacterial [8] and antifungal [9] activities. For their biological activities,

five-membered heterocyclic compounds are essential, both natural and synthetic. Most pharmaceutical products which mimic natural products that are biologically active are heterocyclic in nature [10].
Chalcone cyclization has produced essential applications in the form of veterinary medicines and insecticides as potent agents for farmers [11]. Because of the various pharmacological properties, heterocycles dependent on nitrogen &sulphur are given much more significance by researchers to find out novel medicines for different diseases and have been identified in many drugs that are commercially accessible.
Number of literature has showed that a wide variety of antibacterial and other bioactivities are reported for many indazole and carbothioamide derivatives.[12-16]. On the other hand, a wide variety of biological activities are known to occur in compounds like pyrazole nucleus, such as antimicrobial [17-20], anti-inflammatory [17], anticancer [18], analgesic [18], anti-depressant [18], anti-convulsant [18], anti-hypertensive [19], anti-epieptic [19] and anti-tumor [21-23].Creation of novel and open system for transforming a simple process molecules are a worthwhile addition to heterocycles in organic synthesis. Among the heterocycles, the pyrazole skeleton compounds are the largest lass of active pharmaceutical drugs [24].

There is another method that includes incorporating two or more pharmacophores into a single molecule, in addition to the evolution of completely new molecules with chemical properties that obviously vary from those of current ones. Consequently, a single molecule containing more than one pharmacophore may be of benefit in the treatment of microbial infectious agents, each with a different mode of action. At the active site, these combined pharmacophores will address numerous targets and provide the possibility of overcoming treatment. Moreover, this technique can also minimize adverse side effects [25-30].

This work reveals the synthesis of new **1H-pyrazole-1-carbothioamide** derivatives assimilating various pharmacophores as hybrid molecules having antibacterial activity, keeping this study in mind and following our research on the novel synthesis of bioactive compounds.

2. EXPERIMENTAL

Materials and methods: In the present analysis of the desired compounds, all analytical grade reagents and chemicals were used and purchased from sigma Aldrich. The melting points of the prepared compounds were taken deep vision (230V) apparatus by open capillary tubes were resolved and uncorrected. Their structures were diagnosed FT-IR, NMR, Elemental analysis (CHN). FT-IR recorded (ATR) Agilent Resolution Pro Cary -630 spectrometer.^{1}H NMR (400 MHz) &^{13}C NMR (100MHz) spectra were acquired on Brucker Avance III AMX-400 spectrometer in $CDCl_3$ and chemical shifts were recorded in δ ppm relatives to TMS as the internal standard. To verify the pureness of the targeted products was find out by TLC using Alumina sheets precoated with silica gel 60 F2 54 200µm in thickness with multiple solvents system of various polarities. The spots were visualizes at254 nm by illumination under UV light. Purification was achieved by Column chromatography using silica gel.
*A. General method for the synthesis of novel 5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (5a-5c):*A mixture of (E)-3-(benzo[c][1,2,5]oxadiazol-4-yl)-1-arylprop-2-en-1-ones (0.01 mol) and thiosemicarbazide (0.01 mol) was dissolved in ethanol (30 mL). To that mixture aq.NaOH (10%, 1 mL) was slowly added and refluxed for around 6-8 h. After the completion of reaction that is identified using TLC, the reaction blend was permitted to cool and then poured over ice and the crude

was filtered, washed with water and dried. Purification by recrystallization (in EtOH) gave 1H-pyrazole-1- carbothioamide.

B. Theoretical analysis: DFT studies were performed using the Gaussian09/DFT software package [31]. The best results are given using the B3LYP,6-31G (d,p) basis set and determined improved calculation.

C. Antibacterial activity:

Collection of bacterial pathogens: The Clinical isolates of bacterial strains viz., Escherichia coli, Klebsiella pneumonia, Basillus subtilis, Enterobacter aerogens were obtained from the **Scientific Research Lab,** helikem biotek industrial research pvt ltd, Trichy. The collected strains were incubated on a sterile medium and sub- cultured on Mueller Hinton Agar plates, these strains are keeping on agar slant at 4^0C.

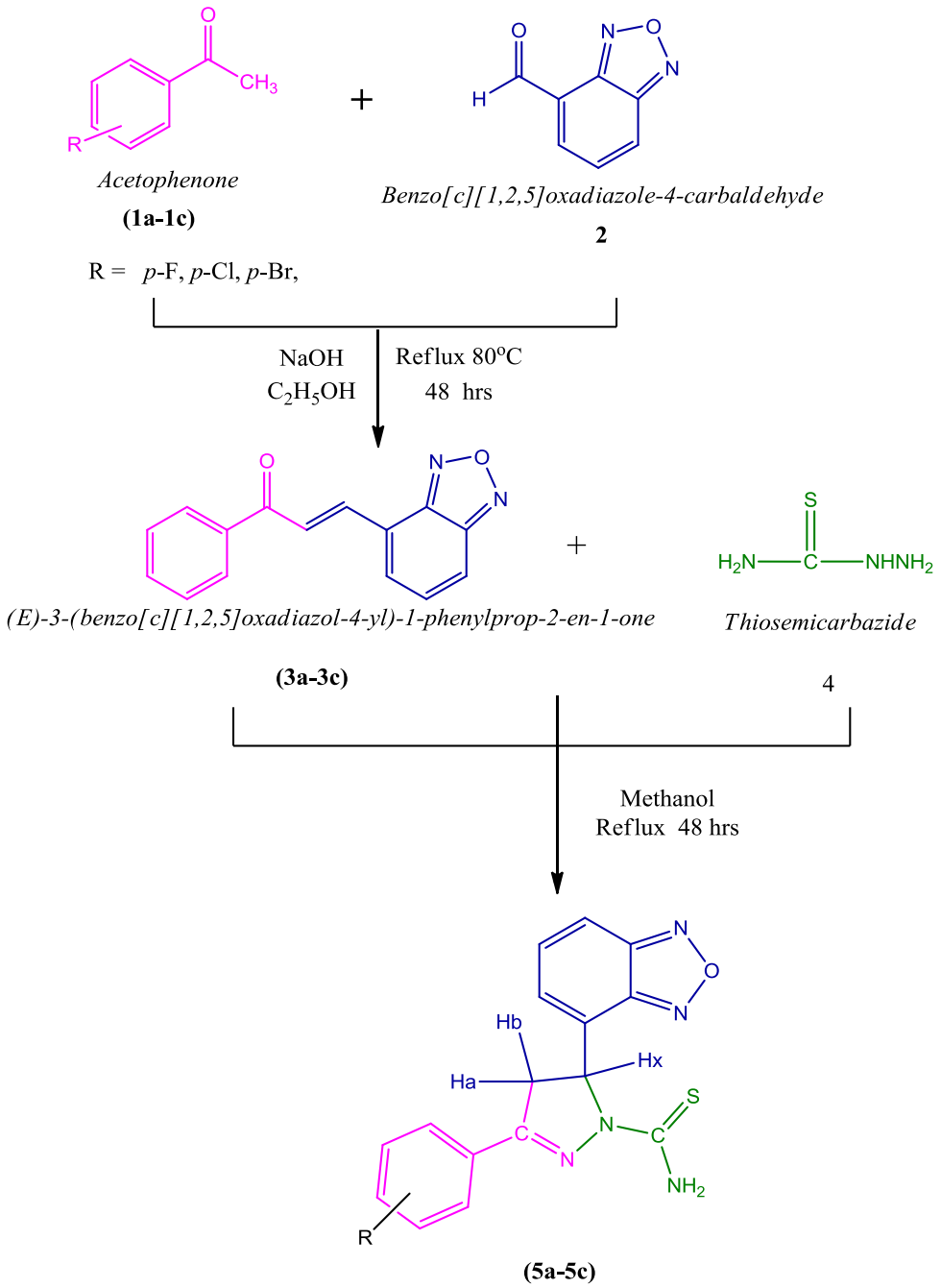
Disc diffusion method: By the method of disc diffusion, the antibacterial result of the test compounds was determined. By dissolving the test compounds (5a-5c) into 50 percent DMSO, around 1 mg/mL of stock solution was prepared with a concentration of 200 mg/mL, the sterile paper disc with a diameter of 6 mm was soaked and the discs were positioned on the Mueller Hinton agar plates. The plates were incubated at 37^0C. The zone of inhibition was visually examined at 37^0C for 24h. In this method, Ciprofloxacin (positive control)was used as a standard. The Inhibition zones of the tested compounds were measured and compared with the standard positive control. Each treatment consists of three replicates and repeated at least thrice.

3. RESULTS AND DISCUSSION

In **Scheme 1**, the synthetic pathway to the target compounds is illustrated. Intermediate chalcones (**3a-3c)** preparation is the first step. Add equimolar mixture of *benzo[c] [1,2,5]oxadiazole-4-carbaldehyde* and substituted acetophenones in the presence of a NaOH via traditional Claisen-Schmidt condensation. *5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (5a-5c)* were synthesized by refluxing compounds **3a-3c** and thiosemicarbazide in presence of base medium. The prepared compounds were isolated in good yields (70-80%) and purified via recrystallization method using ethanol. Thin layer chromatography (TLC) and CHN analysis have confirmed the purity of the compounds.

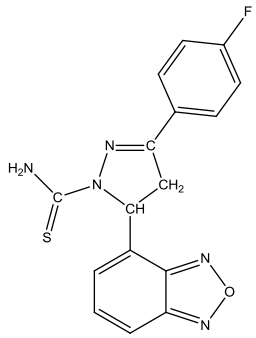
The FT- IR spectra of the compounds (5a-5c) provided pyrazoline C=N stretching (1617-1580 cm^{-1}), thiocarbamoyl group N-H stretching (3445-3315 cm^{-1}) and C=S stretching (1397-1356 cm^{-1}) bands. In the ^{1}H NMR spectra, peaks for H_a and H_b protons appears as two double doublets at δ3.34-3.36 & δ 3.96-4.20 ppm corresponding to magnetically non-equivalent protons Ha and H_b of methylene formed due to ring closure. δ 3.36ppm(H_a); δ3.96ppm (H_b) (***3a***; R= *p*-F), δ3.34ppm(H_a); δ 3.98ppm (H_b) (***3b***; R=*p*-Cl), δ 3.34 ppm (H_a); δ 3.97 ppm (H_b) (***3c***; R= *p*-Br). There exists another double doublet in downfield at 5.97-6.48 ppm corresponding to H-5 (H_x) proton. 6.48ppm (H_x) (***3a***; R= *p*-F), 5.97 ppm (H_x) (***3b***; R= *p*-Cl),6.47ppm (H_x) (***3c***; R= *p*-Br).A broad singlet at7.92-7.94 ppm was due to the NH_2 protons of the semicarbazide moiety. 7.93ppm (NH_2), (***3a***; R= *p*-F),7.92ppm(NH_2),(***3b***; R= *p*-Cl),7.94 ppm(NH_2), (***3c***; R= *p*-Br), The signals around 6.53-7.90 ppm were due to the aromatic protons appeared in the compound. In the ^{13}C NMR spectrum of compounds 5a-5c**,** the downfield signal at 177.4 ppm(***3a***; R= *p*-F), 175.8 ppm(***3b***; R= *p*-Cl), 169.4 ppm(***3c***; R= *p*-Br) was assigned to the C=S of semicarbazone group. The methylene carbon C-4 was observed in the upfield at 41.0 (C_4) (***3a***; R= *p*-F), 41.1 (C_4) (***3b***; R= *p*-Cl), 41.0 (C_4) (***3c***; R= *p*-Br) ppm and the methine carbon C-5 bearing H_x proton appeared at 50.7 (C_5) (***3a***; R= *p*-F), 60.7 (C_5) (***3b***; R= *p*-Cl), 50.7 (C_5) (***3c***; R= *p*-Br)ppm. A signal at 155.8 (C_3) (***3a***; R= *p*-F), 155.4(C_3) (***3b***; R= *p*-Cl), 155.4 (C_3) (***3c***; R= *p*-Br) ppm was corresponding to the C=N (C-3)

of pyrazole ring. Obviously, the signals observed in the range of 114.5-169.5 (Ar-C) (***3a***; R= *p*-F), 114.8-149.7 (Ar-C) (***3b***; R= *p*-Cl), 115.8-149.6 (Ar-C) (***3c***; R= *p*-Br) were due to aromatic carbons.



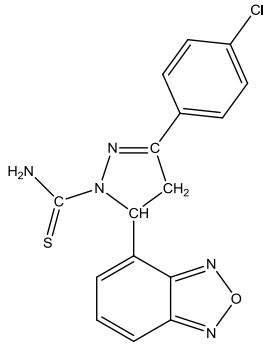
Scheme-1 Synthesis of novel 1H-pyrazole-1- carbothioamides

A. 5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide



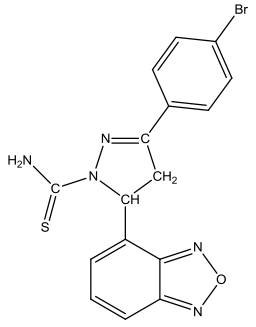
Brown Solid; Yield 80%; mp.146-148^{0}C; IR (ATR, cm^{-1}): γ_{max}1377(C=S), 1617(C=N), 3340(N-H), 1008 (C-N), 3091(ArC-H), 2919(Ali C-H) cm^{-1}. ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.93 s, (NH_2), 6.48 dd, H-5 (H_x), 3.36 dd, (H_a) and 3.96 dd, (H_b), 6.62-7.86 (m, Ar-H, 7H) . ^{13}C NMR (100MHz, CDCl3) δ (ppm): 177.4 (C=S), 41.0 (C_4), 50.7 (C_5), 155.8 (C_3), 114.5-169.5 (Ar-C).Anal. Calcd ($C_{16}H_{12}FN_5OS$): C, 56.30; H, 3.51; N, 20.52%; Found: C, 56.30; H, 3.54; N, 20.52%.

B. 5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide



Brown Solid; Yield 80%; mp.160-162^{0}C; IR (ATR, cm^{-1}): γ_{max}1397(C=S), 1593(C=N), 3315(N-H), 1007 (C-N),3093(Ar C-H), 2921(Ali C-H) cm^{-1} . ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.92 s, (NH_2), 5.97 dd, H-5 (H_x), 3.34 dd, (H_a) and 3.98 dd, (H_b), 6.53.-7.90 (m, Ar-H, 7H) .^{13}C NMR (100MHz, CDCl3) δ (ppm): 175.8 (C=S), 41.1 (C_4), 60.7 (C_5), 155.4(C_3), 114.8-149.7 (Ar-C). Anal. Calcd ($C_{16}H_{12}ClN_5OS$): C, 53.78; H, 3.36; N, 19.60%; Found: C, 53.71; H, 3.38; N, 19.57%.

C. 5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-bromophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide



Brown Solid; Yield 75%; mp.152-154^{0}C; IR (ATR, cm^{-1}): γ_{max}1356(C=S), 1580(C=N), 3445(N-H), 1004 (C-N),3082(ArC-H), 2921(Ali C-H) cm^{-1} .^{1}H NMR (400MHz, $CDCl_3$) δ (ppm): 7.94 s, (NH_2), 6.47 dd, H-5 (H_x) 3.34 dd, (H_a) and 3.97dd, (H_b), 7.26-7.83 (m, Ar-H, 7H) .^{13}C NMR (100MHz, CDCl3) δ (ppm): 169.4 (C=S), 41.0 (C_4), 50.7 (C_5), 155.4 (C_3), 115.8-149.6 (Ar-C). Anal. Calcd ($C_{16}H_{12}BrN_5OS$): C, 47.72; H, 2.98; N, 17.40%; Found: C, 47.77; H, 3.01; N, 17.41%.

4. COMPUTATIONAL STUDIES

The optimized structure of compounds 5a-5cisgiven in **Fig. 1.**In order to examine molecular structural activity within the gas phase, compounds 5a-5c was subject to geometry optimization. Thus, using theB3LYP/6-31G(d,p) as basis set and determine the improved calculation[31].

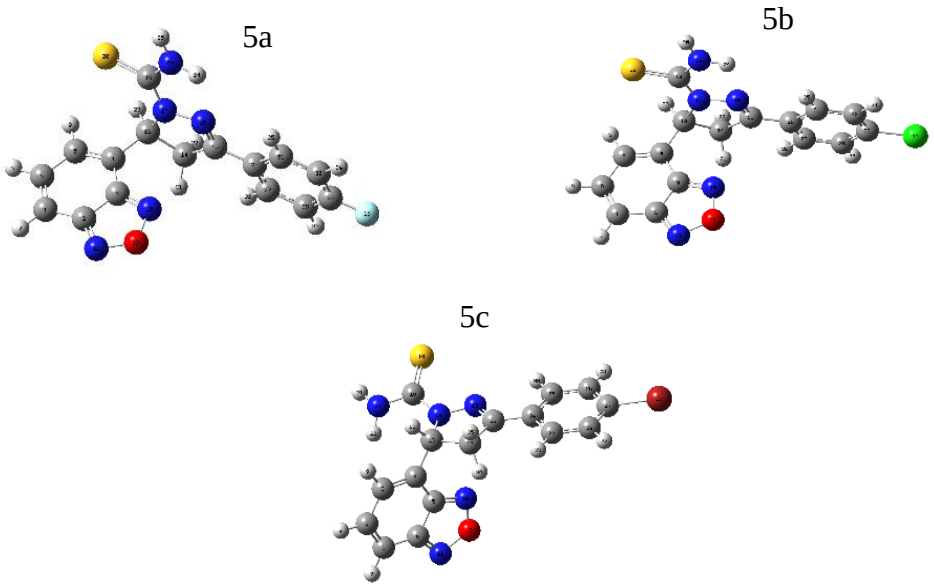


Fig. 1 Optimized geometry of novel carbothioamide

A.HOMO LUMO: Molecular orbital energies are effective tool that play a key role in both electrical and optical properties and quantum chemistry. The two significant orbitals called HOMO and LUMO define the conjugated molecules. These are referred to as FMOs found at the outermost boundaries of electron molecules [32]. The HOMO-LUMO energy was used to find out the energetic activity of the molecule using the B3LYP/6-31G (d,p) package.

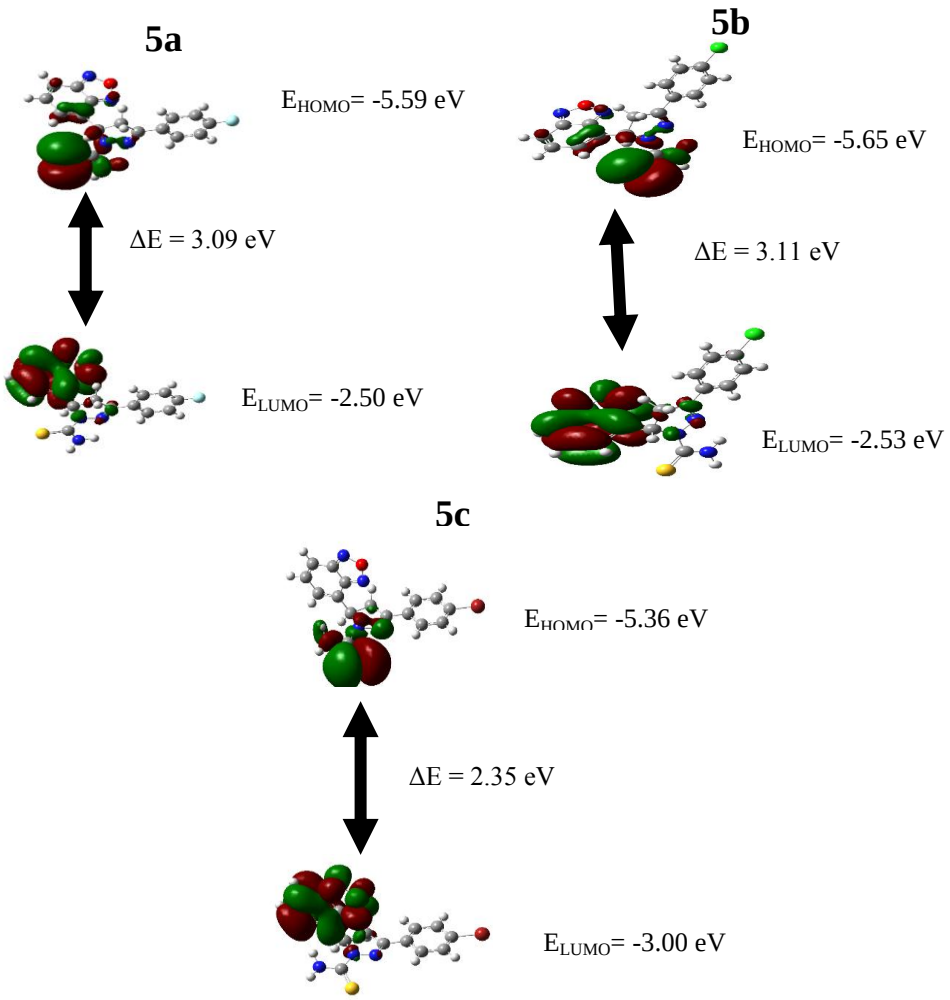


Fig.2 Energy level diagram of compound 5a-5c

The energy differentiation of HOMO –LUMO is displayed in **Fig.2.**The HOMO is located over the C=S group, LUMO located over the oxadiazole moiety. The energy variation between the HOMO and LUMO is 2.35 – 3.11eV, indicating the possible conclusive transfer of charge within the molecule, and therefore chemical and biological reactivity with consider to electronic jump.

B. Electrostatic potential map: MEP diagram is most applicable in the prediction of structure of the designed molecules and its physiochemical property relationships [33]. The red region represent the negative potential and the blue region represent the positive potential correspond to the electron rich and electron deficient regions.

From the **Fig.3,** the negative region located the sulphur atom which is prefers for electrophilic attack and the positive region located all over the molecule which prefers the nucleophilic attack.

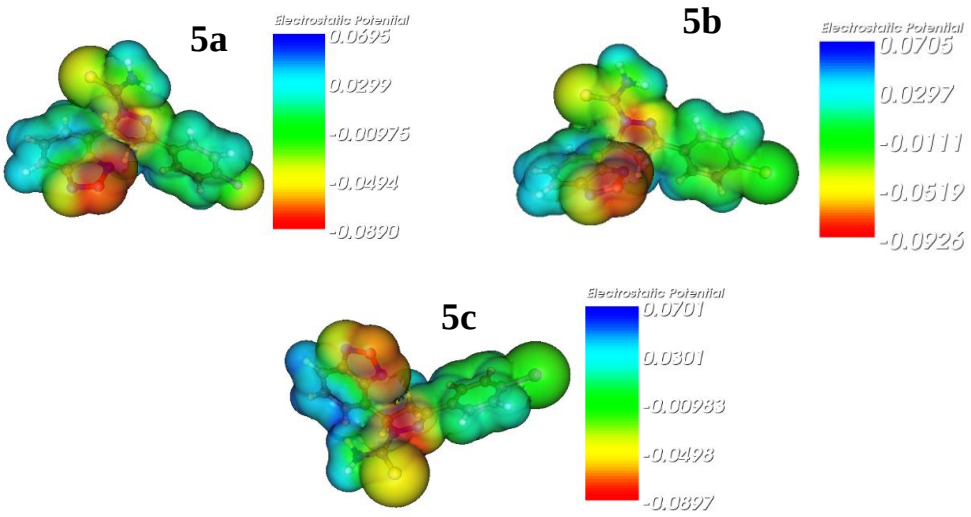


Fig.3 Molecular electrostatic potential of compound 5a -5c

C. Mulliken population analysis: Mulliken population analysis is a chief method for applying quantum chemical calculation to molecular systems [34]. The atomic charge distribution of every atom of the synthesized compounds was determined and the corresponding mulliken plot is displayed in the **Fig.4.**

The charges of the atoms are shown in **Fig.4.**From Fig.4, (5a-5c) a strong negative charge value is found for nitrogen atom N19 and the carbon atoms attached to these nitrogen atoms have a high positive charge due to the nitrogen atoms having electronegative character than other atoms. All hydrogen atoms are carrying a positive charge. These large positive and negative charge locations are the more active sites of the synthesized compounds.

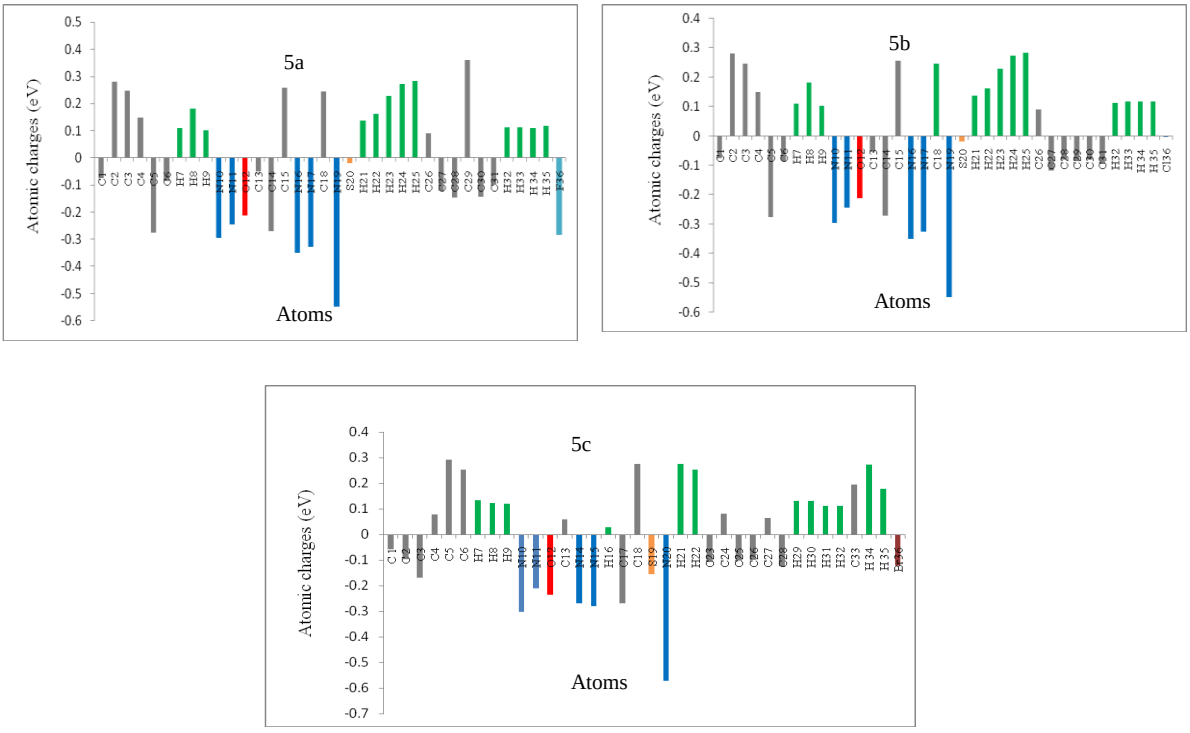


Fig.4 pictorial representation of mulliken atomic charges of compounds 5a-5c

d. NLO analysis: The B3LYP/6-31G(d,p) technique was used to examine molecular structure and NLO properties, polarisabilites and first-order hyperpolarisabilites of the synthesized compounds [35].They play key role in providing main functions such as optical logic, optical memory, switching, and frequency shifting [36-39].The value of first order hyperpolarizability is a measure of NLO behavior. Hence, density functional theory has been used extensively to investigate organic Non Linear Optical materials [40-44].

Table .1 NLO behaviour of compounds 5a-5c

Dipole moment (Debye)			
Parameter	5a	5b	5c
μ_x	-2.6323	-1.8739	-5.3928
μ_y	3.0070	3.2491	-3.5826
μ_z	-1.1135	-1.0354	2.6944
μ_{total}	4.1486	3.8911	7.0126
Parameter	Polarisability (a.u)		
α_{xx}	-142.1485	-154.5121	-131.3949
α_{yy}	-151.5874	-159.6324	-175.6328
α_{zz}	-144.7326	-152.7970	-158.7239
α_{xy}	8.6275	8.4363	13.3726
α_{xz}	-0.8326	-1.8717	-10.7805
α_{yz}	-3.9102	-3.8315	4.2706
Parameter	Hyperpolarisability (a.u)		
β_{xxx}	27.1681	86.2323	-32.6570
β_{yyy}	35.8249	51.8114	-69.1921
β_{zzz}	-1.7918	0.9650	5.0815
β_{xyy}	-98.0671	-95.7683	87.5255
β_{xxy}	77.3217	75.4694	-53.1722
β_{xxz}	-5.0377	-7.1423	54.0875
β_{xzz}	-10.4822	-0.1253	50.9968
β_{yzz}	-8.3152	-5.9763	-3.0808
β_{yyz}	-30.9028	-29.9317	31.6265
β_{xyz}	-0.0259	-3.5125	-12.7800
β_0 (esu) $x10^{-30}$	**1.19**	**1.09**	**1.62**
α_o (esu)$x10^{-23}$	**2.16**	**2.30**	**2.30**
$\Delta\alpha$ (esu) $x10^{-24}$	**2.57**	**2.54**	**6.33**

The dipole moment of compounds **5a-5c (Table 1)** were calculated and increasing goes up like 5b<5a<5c .The calculated polarizability (α), is range from 2.16-2.30x10^{-23}.The premeditated first order hyperpolarizability (β_0) of **5a-5c** is in the range of 1.09-1.62x10^{-30}esu. The values of hyperpolarizability are also higher than the values of urea. It is observed from the above results that the molecular polarisabity and hyperpolarizability of the synthesized compounds are more active in all coordinates and can thus be used to prepare NLO crystals that can give rise to harmonic waves of the second order.

5. ANTIBACTERIAL ACTIVITY

The synthesized1H-pyrazole-1-carbothioamide **5a-5c** was evaluated for their invitro antibacterial activity against two gram positive bacteria, B. subtilis and E. aerogens, and two gram negative bacteria, E.coli and K.pheumoniae. All synthesized compounds were screened using the disc diffusion method.

Table 2.Antibacterial activity of novel1H-pyrazole-1- carbothioamides 5a-5c

Compounds/bacteria	*B. subtilis*	*E. aerogens*	*E. coli*	*K. pneumoniae*
5a	17mm	16mm	15mm	12mm
5b	14mm	10mm	≤5mm	12mm
5c	14mm	11mm	10mm	14mm

In general, all compounds showed good activity in the antibacterial assay. The results were depicted in **Table 2** and **Fig.5**.The mean inhibition zones ranged from the lowest (≤5mm at 30 µL) to the highest (17mm at 30 µL). All the synthesized compounds (5a-5c) shows best activity against B.substilis and E.aerogens.

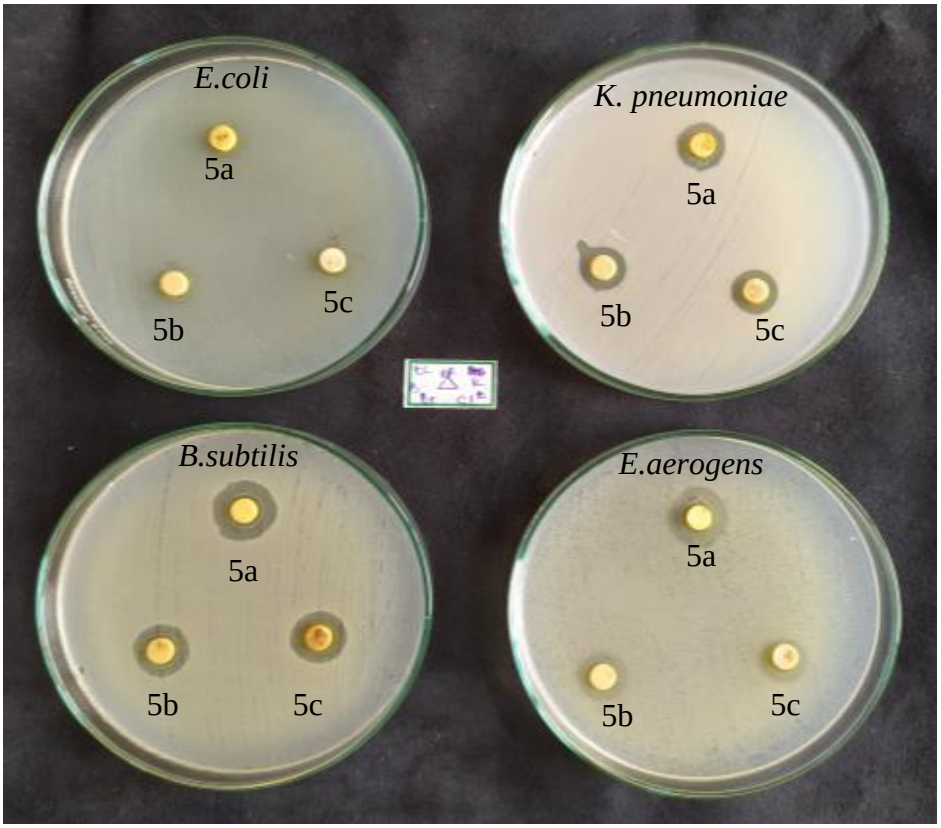


Fig.5 Antimicrobial activity of compounds 5a-5c with high efficacy by disc diffusion method

6. CONCLUSION

The purpose of this paper was to synthesize heterocyclic compounds of some successfully synthesized substituted novel sequence of ***5-(benzo[c][1,2,5]oxadiazol-4-yl)-3-(4-aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamide*.** The Mulliken population and electrostatic potential map (MEP) demonstrated the more reactive sites of the designed compounds. The smallest energy gap (HOMO-LUMO) shows the synthesized compounds have bioactive sites. The newly synthesized compound shows excellent antibacterial activity against both (B. subtilis and E. aerogens) gram positive and (E.coli and K.pheumoniae) gram negative bacteria.

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