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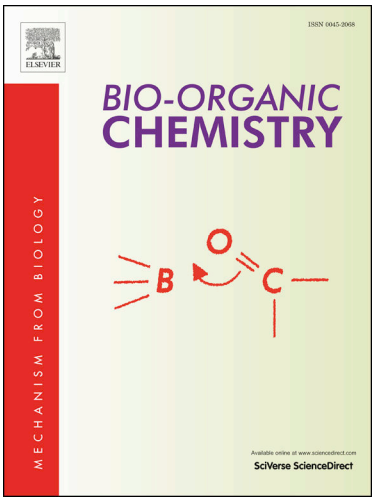

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Derivatives of Pyridine and Thiazole Hybrid: Synthesis, DFT, Biological Evaluation *via* Antimicrobial and DNA Cleavage Activity

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Abstract

A novel series of the 2-pyridine substituted **3a-e** and 4-pyridine substituted **4a-e** thiazole derivatives were synthesized, characterized, and evaluated for the biological activity. Crystallographic parameters and inter- and intramolecular interactions of **3a** and **3c** single crystals were examined through XRD analysis. The chemical reactivity potentials of the compounds were evaluated, by comparing with a theoretical approach based on DFT. The biological activity properties of synthesized compounds were determined by antimicrobial activity with Gram positive, Gram negative, Yeast via minimal inhibitory concentration (MIC) method and DNA cleavage activity studies. The most obvious findings to emerge from this study are that on the basis of both biological activity and chemical reactivity 4-pyridine thiazole hybrid compounds **4a-e** showed more potent activity than **3a-e**. In general, the antimicrobial activity of synthesized compounds follows the *Bacillus cereus*>*Staphylococcus aureus*>*Candida albicans*>*Escherichia coli*>*Pseudomonas aeruginosa*. The most potent compound **4c** (MIC values 0.02 mM) exhibited antimicrobial activity against *Staphylococcus aureus* and *Bacillus cereus*. Furthermore, this compound has a good electrophilicity index value (4.56 eV).

Keywords

Pyridine, Thiazole, DFT, Chemical reactivity, Antimicrobial activity, DNA cleavage activity

1. Introduction

In the late 19th century, a series of successful works by Hofmann [1] and Hantzsch [2] pioneered the development of thiazole synthesis chemistry. Afterwards, synthesis processes having different mechanisms called as Gabriel, Cook-Heilborn and Tcherniac contributed to the obtained of

new thiazole derivative compounds [3]. Thiazole ring having a strong S-C-N fragment which is a member of the family of five-membered heterocyclic compounds; has been the subject of many different types of research to date. Determining that the cyanine dyes contain a thiazole derivative skeleton as a photographic sensitizer [4]; it is considered as one of the first step of its use in different commercial industry branches with its dyestuff feature [5-7]. In 1967, Stoll et al. reported that the strong nut-like odour of cocoa extract originated from thiazole derivative compound [8]. This potential that attracted the attention of the researchers has supported by studies showing that thiazole groups have as a strong flavour component in today's food industry [9-11]. On the other hand, natural compounds such as thiamine (known as vitamin B1), thiamine pyrophosphate (TPP), epothilone, bacitracin, penicillin antibiotics and a wide range of synthetic drug groups contain thiazole moiety. Previous research has shown that it is an undeniable fact that thiazole based-compounds had effective pharmacological importance with antimicrobial [12-15], antitumor [16-18], anti-diabetic [19-21], anticonvulsant [22,23], anti-inflammatory [24-26], antioxidant [27,28], anti-HIV [29,30] and more activity properties.

Another important member of the heterocyclic compounds family is the pyridine skeleton, which is the building block of many natural products such as vitamins, coenzymes, and alkaloids. In the industrial chemistry; it is used as a solvent and reagent, or as a starting or intermediate material in the synthesis processes of high effect insecticide, bactericide and herbicide products [31]. Pyridine moiety plays an active role in the design of many pharmaceutically active compounds with its specific basic structure, water solubility, stability, and the ability to make hydrogen bond [32]. Variety of biological activity studies such as antimicrobial, antiviral, antioxidant, analgesic, anticonvulsant, antidiabetic, anticancer, antimalarial, which are reported at a broad scale prove pyridine derivatives pharmacologic importance [33-39].

Due to the pharmacological properties of the pyridine substituted thiazole compounds were synthesized newly compounds via Hantzsch synthesis [40]. We report herein the synthesis of the thiazole possessing pyridine group and application of the biologically activity. The most important finding of this study is easily generated hybrid molecules thiazole containing pyridine group, which is an important precursor of biologically active synthetic and natural compounds, via single step. As examples, mycothiazole, the natural thiazole compound, shows a selective activity against lung cancer which is isolated from sponge *Spongia mycofijiensis* [41]. Other natural compounds WS75624 A and B, which are similar to the hybrid structure of the synthesized compounds in this work, have hypertensive agents [42]. Also, single crystal forms of compounds **3a** and **3c** were examined X-ray diffraction (XRD) technique. Frontier molecular orbital (HOMO-LUMO) energies, some reactivity

parameters (ionization potential, electron affinity, chemical hardness-softness, etc.) and their potential to be non-linear optical (NLO) material of novel series of pyridine substituted thiazole derivative compounds **3a-e** and **4a-e** were investigated comparatively by theoretical an approach at DFT/B3LYP/6-311G(d, p) level.

2. Material and Methods

2.1. General Methods

All chemicals and reagents were procured from Merck, Alfa-Aesar, Acros and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) SiO_2-precoated (0.2 mm layer) Al sheets (Merck). Products were purified on glass column chromatography (CC) using silica gel (SiO_2) 60 (230-400 mesh) with a solvent gradient of 2:1 (ethyl acetate/ n-hexane). By using Thermo Scientific Barnstead/Electrothermal Apparatus melting points were determined. IR Spectra were conducted Perkin-Elmer FT-IR spectrometer; KBr pellets; in cm^{-1}. NMR spectra were recorded with Bruker AC-400 MHz and Varian Inova (500 MHz) NMR spectrometer. The coupling constants are reported *J* (Hertz) and chemical shift, δ (parts per million). Mass spectra was measured with Agilent 7890-GCMS and the mass spectra showed the expected molecular ion peaks. UV-Vis absorption measurements were performed by Perkin-Elmer LAMBDA 650 UV/Vis spectrometer. Photoluminescence excitation and emission were characterized using a Cary Eclipse G9800A Fluorescence Spectrophotometer (Varian, USA).

General procedure for synthesis of aryl substituted 2-(pyridin-2-yl)thiazole 3a-e and 2-(pyridin-4-yl)thiazole 4a-e compounds:

A solution **1** or **2** (1.2 mmol) of in dry EtOH (25 mL) was stirred under N_2 and refluxed. Then, the appropriate bromo substituted aromatic ketone (1.5 mmol) in (15 mL) dry EtOH was added directly. After cooling to room temperature, the solvent was poured into water, and the insoluble thiazole derivatives were allowed to settle. The residual solid was washed by decantation with water. The solid was solved ethyl acetate, evaporated, and the residue purified by column chromotography

4-([1,1'-biphenyl]-4-yl)-2-(pyridin-2-yl)thiazole, **3a**: Yield: 72%; mp: 185-187 ºC; FTIR (ATR): ν 3110-3002 (Caro-H stretching) 1581 (C-N stretching, pyridine ring), 1556-1453 (thiazole ring skeletal vibration), 852 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.67 (d, *J* = 4.2 Hz, 1H, H10), 8.34 – 8.21 (m, 2H, H7, H5), 8.16 (d, *J* = 8.0 Hz, 2H, H13, H17), 8.01 (m, 1H, H8), 7.79 (d, *J* = 8.1 Hz, 2H, H14, H16), 7.74 (d, *J* = 7.6 Hz, 2H, H19, H23), 7.50 (m, 3H, H20, H21, H22), 7.40 (d, *J* = 7.0 Hz, 1H, H9); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 168.85(C2), 155.70(C6), 150.85(C4), 150.22(C10), 140.27(C12), 140.01(C15), 138.27(C8), 133.52(C18),

129.45(C22-C20), 128.08(C21), 127.52(C14-C16), 127.11(C13-C17), 127.05(C23,C29), 125.74(C9), 119.81(C7), 117.51(C5); GC-MSD: m/z 314.0 ($C_{20}H_{14}N_2S$, M^+); 284 $(C_{20}H_{16}N_2)^+$; 207 $(C_{15}H_{13}N)^+$; 177 $(C_{14}H_{10})^+$; Anal. Calcd for $C_{20}H_{14}N_2S$: C, 76.40; H, 4.49; N, 8.91; S, 10.20; Found: C, 76.28; H, 4.98; N, 8.75%.

4-(benzofuran-2-yl)-2-(pyridin-2-yl)thiazole, **3b**: Yield: 65%; mp: 178-179 ºC; FTIR (ATR): ν 3121-3029 (Caro-H stretching), 1583 (C-N stretching pyridine ring), 1567-1437(thiazole ring skeletal vibration), 787 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.68 (dd, *J* = 2.8, 1.9 Hz, 1H, H10), 8.25 (m, 2H, H5, H7), 8.08 – 7.98 (m, 1H, H8), 7.72 (d, *J* = 7.6 Hz, 1H, H18), 7.66 (d, *J* = 8.0 Hz, 1H, H15), 7.55 (ddd, *J* = 6.6, 3.1, 1.5 Hz, 1H, H16), 7.41 – 7.26 (m, 3H, H9, H17, H20); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 169.99(C2), 154.75(C6), 151.63(C14), 150.43(C12), 150.30(C10), 147.27(C4), 138.38(C8), 128.82(C19), 126.05(C16), 125.48(C17), 123.89(C7), 122.10(C18), 119.86(C9), 119.28(C5), 111.66(C15), 103.97(C20); GC-MSD: m/z 278.1($C_{16}H_{10}N_2OS$, M^+); 249 $(C_{16}H_{12}N_2O)^+$; 145 $(C_{10}H_8O)^+$.

4-(4-bromophenyl)-2-(pyridin-2-yl)thiazole, **3c**: Yield: 75%; mp: 162-164 ºC; FTIR (ATR): ν 3063-2957 (Caro-H stretching), 1603(C-N stretching pyridine ring), 1502-1417(thiazole ring skeletal vibration), 787 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.65 (d, *J* = 4.6 Hz, 1H, H10), 8.32 (s, 1H, H5), 8.24 (d, *J* = 7.9 Hz, 1H, H7), 8.07 – 7.92 (m, 3H, H13, H17, H8), 7.67 (d, *J* = 8.5 Hz, 2H, H14, H16), 7.57 – 7.46 (m, 1H, H9); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 168.97(C2), 154.79(C6), 150.70(C4), 150.17(C10), 138.20(C8), 133.60(C12), 132.20(C14-C16), 128.49 (C13-C17), 125.73(C9), 121.87(C15), 119.78(C7), 118.08(C5); GC-MSD: m/z 318.0 $(C_{14}H_9BrN_2S$, $(M+1)^+)$; 242 $(C_{14}H_{10}N_2S\text{-}1)^+$; Anal. Calcd for $C_{14}H_9BrN_2S$: C, 53.01; H, 2.86; Br, 25.19; N, 8.83; S, 10.11 Found: C, 52.91; H, 3.01; N, 8.81 %.

4-(2-(pyridin-2-yl)thiazol-4-yl)benzonitrile, **3d:** Yield: 60%; mp: 175-178 ºC; FTIR (ATR): ν 3094-2991(Caro-H stretching), 2212 (CN, nitrile stretching), 1595(C-N stretching pyridine ring), 1475 (thiazole ring skeletal vibration), 813 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.66 (d, *J* = 4.6 Hz, 1H, H10), 8.52 (s, 1H, H5), 8.30 – 8.21 (m, 3H, H7, H13, H17), 8.01 (td, *J* = 7.8, 1.4 Hz, 1H, H8), 7.95 (d, *J* = 8.3 Hz, 2H,H14,H16), 7.54 (dd, *J* = 7.3, 5.0 Hz, 1H, H9); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 169.37(C2), 154.10(C6), 150.51(C4), 150.25(C10), 138.46(C12), 138.35(C8), 133.37(C14-C16), 127.16(C13-C17), 125.97(C9), 120.69(C7), 119.90(C5), 119.31(C15), 110.90(C18); GC-MSD: m/z 263.1($C_{15}H_9N_3S$, M^+); 234.8 $(C_{15}H_{11}N_3\text{+}1)^+$; 206.9 $(C_{14}H_{12}N_2\text{-}1)^+$; 159.1 $(C_{11}H_{11}N\text{ +}1)^+$.

4-(3-bromophenyl)-2-(pyridin-2-yl)thiazole, **3e**: Yield: 65%; mp: 168-169 ºC; FTIR (ATR): ν 3080-2995 (Caro-H stretching), 1585 (C-N stretching pyridine ring), 1557-1508 (thiazole ring skeletal vibration), 778 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.67 (d, *J* = 4.8 Hz, 1H, H10), 8.30 (d, *J* = 0.8 Hz, 1H, H7), 8.28 (s, 1H, H5), 8.09 (dd, *J* = 7.8, 0.9 Hz, 1H, H8), 8.02 (td, *J* = 7.8, 1.5 Hz, 1H, H17), 7.63 – 7.50 (m, 3H, H13, H15, H16), 7.46 (m, 1H, H9); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 168.93(C2), 154.27(C6), 150.57(C4), 150.16(C10), 138.44(C8), 136.63(C12), 131.52(C13), 131.41(C7), 129.02(C15), 125.90(C9), 125.49(C16), 122.81(C14), 119.99(C17), 118.89(C5); GC-MSD: m/z 318.0 ($C_{14}H_9BrN_2S$, $(M+1)^+$); 242 ($C_{14}H_{10}N_2S$-1)$^+$.

4-([1,1'-biphenyl]-4-yl)-2-(pyridin-4-yl)thiazole, **4a**: Yield: 69%; mp: 189-191 ºC; FTIR (ATR): ν 3098-2987(Caro-H stretching), 1579 (C-N stretching pyridine ring), 1521-1468(thiazole ring skeletal vibration), 792 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.98 (d, *J* = 5.7 Hz, 2H, H8, H10), 8.65 (s, 1H, H5), 8.47 (d, *J* = 5.8 Hz, 2H, H7, H11), 8.21 (d, *J* = 8.2 Hz, 2H, H17, H13), 7.84 (d, *J* = 8.1 Hz, 2H,H16, H14); 7.77 (d, *J* = 8.2 Hz, 2H, H19, H23), 7.51 (t, *J* = 7.6 Hz, 1H), 7.44 – 7.35 (m, 3H, H22, H20, H21); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 162.53 (C2), 156.85(C4), 145.78(C8, C10), 145.34(C6), 140.86(C15), 139.86(C18), 132.73(C12), 129.49(C20-C22), 128.24(C21), 127.67(C17-C13), 127.40(C23-C19), 127.12(C16-C14), 122.70(C7-C11), 120.33(C5); GC-MSD: m/z 314.0 ($C_{20}H_{14}N_2S$, M^+); 284 $(C_{20}H_{16}N_2)^+$; 207 $(C_{15}H_{13}N)^+$;177 $(C_{14}H_{10})^+$; Anal. Calcd for $C_{20}H_{14}N_2S$: C, 76.40; H, 4.49; N, 8.91; S, 10.20 Found: C, 76.30; H, 5.09; N, 8.69 %.

4-(benzofuran-2-yl)-2-(pyridin-4-yl)thiazole, **4b**: Yield: 60%; mp: 183-184 ºC; FTIR (ATR): ν 3109-3045 (Caro-H stretching), 1586 (C-N stretching pyridine ring), 1568-1436 (thiazole ring skeletal vibration), 789(C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 9.02 (d, *J* = 6.4 Hz, 2H, H8, H10), 8.56 (s, 1H, H5), 8.48 (d, *J* = 6.4 Hz, 2H, H7, H11), 7.75 (d, *J* = 7.6 Hz, 1H, H18), 7.69 (d, *J* = 8.2 Hz, 1H, H15), 7.50 (s, 1H, H20), 7.44 – 7.36 (m, 1H, H16), 7.32 (t, *J* = 7.5 Hz, 1H, H17); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 163.64(C2), 154.85(C4), 150.85(C14), 148.20(C12), 145.66(C8-C10), 145.11(C6), 128.64(C19), 125.88(C16), 124.06(C17), 122.94(C7-C11), 122.31(C18), 121.92(C5), 111.78(C15), 104.94(C20); GC-MSD: m/z 278.1($C_{16}H_{10}N_2OS$, M^+); 249 $(C_{16}H_{12}N_2O)^+$; 145 $(C_{10}H_8O)^+$.

4-(4-bromophenyl)-2-(pyridin-4-yl)thiazole, **4c**: Yield: 72%; mp: 164-168 ºC; FTIR (ATR): ν 3050-3028 (Caro-H stretching), 1602 (C-N stretching pyridine ring), 1520-1495 (thiazole ring skeletal vibration), 784 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.97 (d, *J* = 5.0 Hz, 2H, H8, H10), 8.72 (s, 1H, H5), 8.47 (d, *J* = 2.6 Hz, 2H, H7, H11), 8.32 (s, 1H, H13), 8.12 (d, *J* = 7.7 Hz, 1H, H17), 7.63 (d, *J* = 7.8 Hz, 1H, H15), 7.49 (t, *J* = 7.9 Hz, 1H, H16); ^{13}C NMR (101 MHz,

DMSO-d6, ppm) δ 162.32(C2) , 155.47(C4), 145.97(C6), 144.89(C8, C10), 135.78(C12), 132.02(C16), 131.64(C13), 129.30(C15), 125.78(C17), 123.12(C7,C11), 122.91(C14), 121.96(C5); GC-MSD: m/z 318.0 ($C_{14}H_9BrN_2S$, $(M+1)^+$); 242 ($C_{14}H_{10}N_2S$-1)$^+$.

4-(2-(pyridin-4-yl)thiazol-4-yl)benzonitrile, **4d:** Yield: 55%; mp: 182-184 ºC; FTIR (ATR): ν 3102-3058 (Caro-H stretching), 2221 (CN, nitrile stretching), 1583 (C-N stretching pyridine ring), 1540-1486 (thiazole ring skeletal vibration), 802 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.96 (d, *J* = 4.8 Hz, 2H, H8,H10), 8.83 (s, 1H, H5), 8.59-8.54 (m, 3H, H7, H10, H11), 8.19 (d, *J* = 7.6 Hz, 1H, H17), 7.82 (d, *J* = 7.7 Hz, 1H, H15), 7.65-7.59 (m, 1H, H16); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 163.41(C2), 156.16(C4), 150.09(C8-C10), 147.27(C6), 138.92(C12), 136.15(C16-C14), 132.48 (C13-C17), 126.24 (C7-C11), 124.32(C18), 120.49(C15), 117.61(C5); GC-MSD: m/z 263.1($C_{15}H_9N_3S$, M^+); 234.8 ($C_{15}H_{11}N_3$+1)$^+$; 206.9 ($C_{14}H_{12}N_2$-1)$^+$; 159.1 ($C_{11}H_{11}N$ +1)$^+$.

4-(3-bromophenyl)-2-(pyridin-4-yl)thiazole, **4e**: Yield: 61%; mp: 172-174 ºC; FTIR (ATR): ν 3078-3019 (Caro-H stretching), 1574 (C-N stretching pyridine ring), 1524-1498 (thiazole ring skeletal vibration), 795 (C-S stretching) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d6, ppm) δ 8.99 (d, *J* = 6.3 Hz, 2H, H8, H10), 8.67 (s, 1H, H5), 8.47 (d, *J* = 6.1 Hz, 2H, H7, H11), 8.07 (d, *J* = 8.5 Hz, 2H, H13, H17), 7.73 (d, *J* = 8.5 Hz, 2H, H14, H16); ^{13}C NMR (101 MHz, DMSO-d6, ppm) δ 162.45(C2), 156.01(C4), 145.72(C6), 145.24(C8-C10), 132.82(C12), 132.42(C14-C16), 128.83(C13-C17), 122.92(C7-C11), 122.61(C15), 121.22(C5); GC-MSD: m/z 318.0 ($C_{14}H_9BrN_2S$, $(M+1)^+$); 242 ($C_{14}H_{10}N_2S$-1)$^+$.

2.3. Single crystal XRD analysis

The single-crystal X-ray data were collected on a Bruker D8 QUEST (Bruker, USA) diffractometer. X-ray diffraction study and all diffraction measurements were performed at room temperature 296 K. Data collection with XAREA [43], cell refinement with X-AREA, data reduction with XRED32 [43]. The hybrid structures were solved by direct methods using SHELXS-2013 [44] and refined with full-matrix least-squares calculations on F^2 using SHELXL-2014 [44] implemented in Win-GX [45] program suite. All carbon bound H atoms were placed geometrically and treated using a riding model, fixing the bond length at 0.93 Å.

2.4. Theoretical details

Theoretical approaches for pyridine substituted thiazole compounds **3a-e** and **4a-e** were performed with the Gaussian 09W package [46] and GaussView 5.0 [47] molecular visualization programmes. The geometric optimization process of the compounds was fulfilled with Density

Functional Theory (DFT) [48], Becke's Three-Parameter Hybrid Functional using the Lee, Yang and Parr correlation (B3LYP) [49] method with 6-311G(d,p) basis set in the ground state and gas phase. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energy values of the groups of compounds were calculated by at a level of time dependent (TD)-DFT in order to specify the intramolecular charge transfer interactions. Some chemical activity parameters such as *I;* ionization potential (I=-E_{HOMO}), *A;*electron affinity (A=-E_{LUMO}), χ*;*electronegativity ($\chi=(I+A)/2$), η*;*chemical hardness ($\eta=(I-A)/2$), *S;*chemical softness ($S=1/2\eta$), μ*;*chemical potential ($\mu=-(I+A)/2$) and ω;electrophilicity index ($\omega=\mu^2/2\eta$) of the molecular groups were calculated by using HOMO-LUMO energy values [50-52]. To determine the potentials of compounds to be non-linear optical material (NLO); parameters of total electric dipole moment (μ_{tot}) mean polarizability ($<\alpha>$) and total first-order hyperpolarizability (β_{tot}) with x, y, z components were calculated as theoretical by using the following equations given [53-55].

$$\mu_{tot}=(\mu_x^2+\mu_y^2+\mu_z^2)^{1/2} \quad (1)$$

$$<\alpha>=(\alpha_{xx}+\alpha_{yy}+\alpha_{zz})/3 \quad (2)$$

$$\beta_{tot}=[(\beta_{xxx}+\beta_{xyy}+\beta_{xzz})^2+(\beta_{yyy}+\beta_{yzz}+\beta_{yxx})^2+(\beta_{zzz}+\beta_{zxx}+\beta_{zyy})^2]^{1/2} \quad (3)$$

2.5. Minimal Inhibitory Concentration (MIC) Method

In this study according to MIC method, Gram positive *Staphylococcus aureus* ATCC 6538P, *Bacillus cereus* ATCC 7064, Gram negative *Escherichia coli* W3110, *Pseudomonas aeruginosa* ATCC 27853 and yeast *Candida albicans* ATCC 10231 were used as microorganisms. Stock solutions of all synthesized complexes were prepared in DMSO-d6 and used in experiments. All cultures were incubated in nutrient broth in 37°C for 24 hours. Bacterial and yeast cells were suspended and used in 50 ml of nutrient medium. The turbidity of bacterial and yeasts suspensions was adjusted at a concentration of approximately 10^6 cells/ml by matching with 0.5 McFarland turbidity standards. The microorganisms grown were transferred to test tubes with 1 ml and then complexes were added. After serial dilutions, hybrid compounds were incubated at 37°C degrees for 1 night in the incubator. The minimum inhibitor concentration, at which no growth was observed, was taken as the MIC value (mM). For control purposes, vancomycin and cefepime were used as antibacterial and fluconazole was used as antifungal. For control purposes, amikacin and cefepime were used as antibacterial and fluconazole was used as an antifungal.

2.6. DNA cleavage activity

DNA cleavage activity of pyridine substituted thiazole compounds was carried out on double-stranded pBR322 circular plasmid DNA by using gel electrophoresis. 10 mM concentration of complexes were prepared in DMSO-d6 (Dimethyl sulfoxide) and treated with 0.25 ppm pBR322 plasmid DNA at 37 °C for 2 hours in pH 8 Tris Buffer. The reactions were carried out in the presence and absence of 30 mM H_2O_2 as an activator. Control experiments were done in the presence of DMSO-d6. After incubation, 1 µl 6X gel loading buffer was added then this mixture was loaded on 1% agarose gel for 90 min at 80V in TBE buffer (pH 8). Gels were stained with ethidium bromide for 15 min and washed deionized water for 15 min. Then gels were photographed under UV transilluminator.

3. Results and Discussion

3.1. Chemistry

The derivatives of the pyridine substituted thiazole were depicted as a synthesis from acetophenone, thioamide and synthesis process was presented in Scheme 1. The pyridine-2-carbothioamide **1** was condensed with acetophenone derivatives followed by cyclization to give aryl substituted 2-(pyridin-2-yl)thiazole 3a-e and pyridine-4-carbothioamide **2** afforded aryl substituted 2-(pyridin-4-yl)thiazole 4a-e compounds. In this reaction; 1-([1,1'-biphenyl]-4-yl)-2-bromoethan-1-one (**a**), 1-(benzofuran-2-yl)-2-bromoethan-1-one (**b**), 2-bromo-1-(4-bromophenyl)ethan-1-one (**c**), 4-(2-bromoacetyl)benzonitrile (**d**), 2-bromo-1-(3-bromophenyl)ethan-1-one (**e**) were subjected to Hantzsch reaction with thioamides to give thiazole ring.

For comparison, we synthesized the aryl substituted 2-(pyridin-2-yl)thiazole and 2-(pyridin-4-yl)thiazole derivatives. Not surprisingly, increase of the reaction yield was more the replacement pyridine-2-carbothioamide than pyridine-4-carbothioamide.

The reactions employing α-bromoketone provided high yields of 2-pyridyl substituted thiazoles compounds **3a-e**. However the reaction with 4-(2-bromoacetyl)benzonitrile gave a low yield of the appropriate products 4a-e under different reaction conditions.

The variation of 1-([1,1'-biphenyl]-4-yl)-2-bromoethan-1-one, and 2-bromo-1-(4-bromophenyl)ethan-1-one gave high yields of 2,4-disubstituted thiazoles. Other α-bromoketones were allowed moderated yield of 1,3-thiazole ring. On the other hand, the performance control in the reactions was found to be related to the ratio of ketone compound as using 1.5 equivalents of α-bromoketones. After the purification with column chromatography, all products were obtained good

yield range from 55% to 75%. The chemical structure and yield values of the synthesized groups of compounds are shown in Scheme 1.

Scheme 1 is here

The NMR spectral data show the evidence of the products. The thiazole ring proton was determined at δ= 8.25 – 8.72 ppm singlet around. The **3a-e** compounds of the thiazole ring proton shifted upfield than **4a-e.** The NMR spectrum of structure **3b** revealed at 8.25 ppm while benzonitrile derivatives, **3d**, of thiazole ring proton was 8.52 ppm shifted due to the electron donating and electron withdrawing substituents. ^{13}C NMR spectrum of compounds **3** and **4** derivatives showed signals the range of 162-169 ppm at the pyridine substituted carbon in thiazole ring. Although analogously **4** were chemical shift closed 162 ppm, 3a-e compounds closed 169 ppm downfield shifts. The synthesized hybrid thiazole-pyridines display characteristics stretching frequency of thiazole ring C=N around 1540-1450 cm^{-1} and C-S-C vibration 840-740 cm^{-1}, which these values results correlated similar compounds in literature [56]. Moreover, ^{1}H NMR and ^{13}C NMR values are in accordance with the chemical structure of title compounds as similar literature [57]. ^{1}H and ^{13}C NMR spectrums of the **3a-e** and **4a-e** compounds are given in the section of Supplementary Materials with Figure S1-S10.

The TG/DTA curves were obtained using Hitachi / SII 7300. 3.5 mg samples were run in ceramic sample pans under nitrogen atmosphere. The TG curves of the **3b** and **4b** are given in Figure 1 and thiazole compounds showed similar thermal behaviour with only the first stage.

Figure 1 is here

Comparing the emission spectrum of all compounds with the excitation and absorption, there is a significant Stokes shift in the range of 1093-2393 cm^{-1}. To determine the emission of the **3c**, the excitation spectra of the samples at 332 nm monitored at 352 nm in Figure 2. The excitation, emission, and absorption values and Stokes shift are summarized in Table 1.

Figure 2 is here

Table 1 is here

*3.2. Crystal structure of compound **3a** and **3c***

Since the single crystal form of pyridine substituted thiazole compounds **3a** and **3c** can be obtained, the findings from the single crystal XRD analysis of these compounds are given in this section.

The crystal structure of **3a** consists of biphenyl, pyridine and thiazole groups. The molecule crystallized the orthorhombic structure and $Pca2_1$ space group. There are four molecules in the unit cell. In the thiazole ring, C1-S1 and C2-S1 bond lengths are 1.706 (7) Å and 1.726 (8) Å, respectively. Similarly, the C2-N1 and C3-N1 bond length values are 1.296 (8) Å and 1.373 (8) Å, respectively. These values are consistent with the C-S and C-N values in the thiazole ring in the literature [58]. The C-N values in the pyridine ring, C5-N1 and C1-N1 bond lengths are 1.45 (2) Å and 1.359 (2) Å.

Details of the data collection conditions and the parameters of the refinement process of **3a** crystal are given in Table 2 and molecular structure with the atomic numbering scheme ORTEP view for the compound is shown in Figure 3.

Table 2 is here

Figure 3 is here

The crystal structure of **3a** has an intramolecular C—H···N type hydrogen bond and details are given in Table 4. Also, C8—H8···Cg3 type intermolecular interaction holds the crystal structure together and packing diagram of the **3a** is given with Figure S.11 in the Supplementary Material.

The **3c** formed by the combination of three important groups such as 4-bromophenyl, pyridine and thiazole crystallized in monoclinic structure and $P2_1$ space group. There are two molecules in the unit cell. As can be seen from Table 3, the unit cell parameters a, b, c; 4.0396 (10) (Å), 10.504 (3) (Å), 14.839 (4) (Å) and α, β, γ; 90 (°), 91.642 (8) (°), 90 (°). Molecular structure with the atomic numbering scheme ORTEP view for the **3c** is shown in Figure 3.

Thiazole ring C7-S1 and C6-S1 bond lengths for **3c** are 1.698 (18) Å and 1.74 (2) Å, respectively. Similarly, the C6-N2 and C8-N2 bond length values are 1.292 (18) Å and 1.377 (18) Å, respectively. These values are consistent with the C-S and C-N values in the thiazole ring in the literature [58]. The C-N values in the pyridine ring, we see that C5-N1 and C1-N1 bond lengths are 1.29 (2) Å and 1.34 (2) Å. The Br1-C12 bond length value in the bromophenyl ring is 1.905(13) Å, and this value is 1.909 (3) Å in the literature, and the Br-C value in the molecule is not very different from the literature [59].

The dihedral angle between the thiazole ring and the bromophenyl group is 14.93°. Similarly, the dihedral angle value between the thiazole ring and the pyridine ring is 4.83º. The **3c** crystal has only one intramolecular C—H ⋯ N type hydrogen bond and details are given in Table 3.

Table 3 is here

3.3. Theoretical

Optimized molecular structures with total energy values of pyridine substituted thiazole derivative **3a-e** and **4a-e** compounds with DFT/B3LYP/6-311G(d,p) are given in Figure 4. According to the calculated total energy values of molecular structures; in view of that compounds of the group **3a-e** having 2-pyridine position have lower energy values than those of group **4a-e**, they can be said to exhibit a more stable structure.

Figure 4 is here

Frontier molecular orbital energies namely HOMO-LUMO energy values play an important role in determining some reactivity properties of structures, especially in modelling studies involving molecular groups derived from different substituents. Considering that the high HOMO energy value is related to the ability of the molecular structure to donate electrons and the low LUMO energy value is associated with the ability to accept electrons [60-62]; it will be possible to identify those which tend to exhibit nucleophilic or electrophilic character within the molecular groups. Besides, the HOMO-LUMO (ΔE) energy gap value contains clues about the stability or reactivity of molecular systems; it can be said that structures with a narrow energy gap can be less stable and more reactive. The calculated HOMO and LUMO, (ΔE) energy gap values of the **3a-e** and **4a-e** compounds are given in Table 4.

It can be seen from Table 4 that the **3a-e** group was higher HOMO and LUMO energy values than the **4a-e** group. In other words, compounds having 2-pyridine position (with high HOMO

values) exhibit electron donor character, while those at 4-pyridine position (with low LUMO values) exhibit electron acceptor character. Compound **4b** with a value of 3.70 eV has the smallest energy gap (ΔE), while compound **4d** with a value of 4.19 eV has the largest energy gap (ΔE), so **4b** is considered to be more reactive and less stable than others. HOMO-LUMO orbital diagrams of **4b** and **4d** compounds represent in Figure 5 and others in Figure S.12 (see Supplementary Material).

Table 4 is here

By calculated the values of some parameters, also known as global reactivity descriptors, tabulated in Table 4; the hybrid compounds whose properties are prominent within the groups have been identified. According to the ionization potential (*I*) and electron affinity (*A*) values associated with HOMO and LUMO energy, **3b** with low *I* value and **4d** with high *A* value come into prominence for given compounds. Hence **3b** compound has displayed a nucleophilic character while **4d** has better electrophilic character compared to others. The 4-pyridine substituted compound group has high χ with decreasing order of **4d**>**4e**>**4c**>**4a**>**4b** and high ω values with decreasing order of **4d**>**4c**>**4e**>**4b**>**4a** as regards **3a-e** group, and the compound **4d** with 4.56 and 4.97 eV values has a higher electronegativity and good electrophilic character than the others. According to the chemical hardness-softness (η, *S*) values which are effective in determining the intramolecular charge transfer of the molecular structures that the compound having the high *S* and low η value is **4b** has been observed.

Figure 5 is here

The delocalized π-electron charge density or donor-acceptor groups which connected through the π-conjugation bridge (D-π-A) are the factors that affect the potential of being nonlinear optical materials of the molecular structures [63-65]. It is known that the thiazole derivative compounds have a strong π-conjugation effect and the conjugate systems formed by with different electron-donating groups with their character of electron-attracting exhibit high NLO properties, and this potential keeps the interest in these compounds for the researchers [66-69].

In order to determine the potential in NLO applications of synthesized **3a-e** and **4a-e** compounds; total dipole moment, mean polarizability, first-order hyperpolarizability parameters were calculated at DFT/B3LYP/6-311G(d,p) level using Equations (1-3) and results are presented in Table

5. (The detailed version of all the components of the parameters is given with Table S.13-15 in the Supplementary Material).

Table 5 is here

As can be seen from the table, the total electric dipole moment (μ_{tot}) values and mean polarizability (<α>) values were obtained as **3d**>**4d**>**4e**>**4b**>**4a**>**3c**>**4c**>**3e**>**3a** and **4a**>**3a**>**3b**>**4b**>**3d**>**3c**>**4d**>**4c**>**3e**>**4e** in decreasing order. The comparison of compound groups according to β_{tot} values, which is another determinant parameter for molecular structures exhibiting NLO properties, is **4b**>**4c**> **3b**>**3c**>**3d**>**4a**>**4d**>**3a**>**4e**>**3e**. Further, these parameters were calculated at the same theoretical level for the urea molecule which is considered a threshold value in such analyses and obtained values are 3.8872 Debye for μ_{tot}, 5.0098x10^{-24} esu for <α>, 621.3132x10^{-33} esu for $\beta_{tot.}$ Comparing the results, compound **4b** functionalized with benzofuran and position 4 of the pyridine moiety, characterized by a high β_{tot} value (10584.11x10^{-33} esu), are seen to be 17 times higher than the urea molecule, so it is a good candidate for NLO material. The compound **4b** also had higher potential for intramolecular charge transfer as expected due to its narrow energy gap (3.70 eV) and high chemical softness value (0.27 eV^{-1}) and the higher β_{tot} value supported this result.

3.4. Antimicrobial activity

In the study, it was determined that MIC values of positive control DMSO-d6 for the thiazole derivates were prepared more than 5 mM. New synthesized thiazole hybrid compounds have different effects on microorganisms. As shown in the Table 6, it can be stated that thiazole derivatives have moderate effect on gram negatives.

Table 6 is here

In addition, only **3c** and **4c** derivatives have more effect on *E. coli* than other gram negative ones. When the effects of thiazole derivatives on Gram positives are examined, it is seen that this effect is more than gram negatives. When the gram positive bacteria *S. aureus* were examined, the MIC values for **3c** and **4a** were found to be 1.2 mM. Furthermore, the MIC values for **4e** and **4b** are 0.15 mM, it can be stated that this value has a value of 0.02 mM for **4c**. MIC values for *B. cereus*, the

other gram positive bacteria, were 1.2 and 1.4 mM for **3c** and **4d** respectively, 0.6 mM for **4a**, 0.3 mM for **3b**, 0.15 mM for **4b**, 0.04 mM for **4e** and 0.02 mM for **4c**. The effect of thiazole compounds is quite high on gram positives. According to the findings, it would be correct to make a **3c**<**4b**<**4e**<**4c** order on the gram positives. As shown the results, **4c** was found to be the most effective compound on gram positives with a value of 0.02 mM. It has been reported that new thiazole derivatives have antimicrobial effects [70].

In this study with *C. albicans*, an important pathogen for humans and also yeast, derivatives were generally found to be effective. As a matter of fact, when the MIC values were examined, we found that these values were 1.2 mM for **3a** and **4b**, 0.6 mM for **3e**, **3b**, **4a** and **4e**, and 0.15 mM for **3c** and **4c**. The result of the study with *C. albicans*, **3c** and **4c** were found to be more effective than the others.

For the standard antibiotics MIC values ranging from 0.01- 8.65 mM. Compound 4c has a lower mic value than the reference antibiotic cefepime against *Bacillus cereus* ATCC 7064 strain. This value reinforces the possibility that compound **4c** may be a new and more effective antimicrobial agent for gram positive microorganisms.

CN and Br groups can capture radical groups and accellerate the antimicrobial activity of compounds. When compared antimicrobial activity of CN and Br groups, thiazole derivates containing Br have more potent atimicrobial activity against test microorganisms.

Increased antibiotic resistance made it necessary to obtain new chemicals as shown antimicrobials behaviours. In recent years, it has been shown that rapid bactericidal activity is important in the treatment of diseases caused by staphylococci such as endocarditis, meningitis and osteomyelitis, and diseases caused by *E. coli* such as digestion and urogenital [71,72].

It has been earlier shown that one of the most important heterocyclic units is a thiazole moiety in several known antimicrobial agents which penicillin, abafungin, amoxicillin etc. [73]. Oniga et al. reported 12 different pyridine-thiazole derivatives that were active against *S. aureus*, *B. cereus*, *C.albicans* [74]. In our study to the present, we have found the activity of **4c** including against *S. aureus*, *B. cereus*.

Also, the thiazole group compounds may have an advantage in that they are used in the treatment of more severe clinical diseases than bacteriostatic agents. Therefore, antimicrobial use of thiazole derivatives with high antimicrobial activity may be possible.

3.5. DNA cleavage activity

DNA cleavage study revealed Tris-HCl buffer (50 mM, pH:8) and H_2O_2 (30mM) conditions. H_2O_2 induces the formation of hydroxyl radicals which attack the DNA bounds and cause DNA cleavage. These cause different mobility properties of pBR 322 plasmid DNA on agarose gel electrophoresis. The DNA cleavage was controlled by the relaxation of the supercoiled circular form of pBR322 DNA into the nicked and linear form. The supercoiled form is the fastest migration form on the agarose gel. If one strand is cleaved, the supercoils will relax to produce a slower moving open circular form (Form II). If both strands are cleaved, a linear form (Form III) will be generated that migrates in between Form I and Form II.

In this study**, 4d** (Figure 6 A11 and B11) and **4e** (Figure 6 A10 and B10) compounds have been caused cleavage activity both buffer and H_2O_2 conditions. Other compounds haven't been caused effective cleavage of pBR 322 DNA but in the presence of H_2O_2 increased cleavage activity were observed. **3d** (Figure 6 B5), **4a** (Figure 6 B8), **4c** (Figure 6 B9), **4e** (Figure 6 B10) and **4d** (Figure 6 B11) caused cleavage of DNA in the presence of H_2O_2. DMSO-d6 scavenging activity was observed compared with H_2O_2 control (Figure 6 B1 and B2). **3a** (Figure 6 B3), **3e** (Figure 6 B4), **3c** (Figure 6 B6), **3b** (Figure 6 B7) and **4b** (Figure 6 B12) showed DMSO-d6 like activity.

Figure 6 is here

DNA cleavage activity was observed in CN group when Br and CN groups were compared. This may be due to the radical capture and hydrolysis of the CN group. No effect of Br and CN groups in buffer conditions at the 2 pyridine positions (Figure 6 A5 and A6), while the CN group showed DNA cleavage activity under hydrogen peroxide conditions (Figure 6 B5). Furthermore, 4-pyridines are more effective than 2-pyridines relative to the position of the pyridine ring (Figure 6 A and B). The groups **3a**, **4a** and **3b**, **4b**, unlike other substances, do not contain electron attractive groups. Although π-conjugation increased, no effect was seen in both.

Conclusion:

Based on the extensive analyses, this paper consists to (*i*) obtain an effective synthesis of all the ten types of pyridine skeleton thiazole, (*ii*) conduct structural features based-DFT as theoretical approach, (*iii*) characterize the antimicrobial and DNA cleavage activity. The most stable in terms of

total energy values **3a-e** derivative compounds showed the highest yield. Furthermore, we confirmed that **3a-e** compounds were exhibited highest HOMO value based on the comparison result of with the **4a-e** compounds via DFT. Compound **4b** was identified not only by having the potential to be the highest NLO material, but also by the lowest energy gap. We found that the pyridine substituted thiazole compounds effective antimicrobial activity on the Gram (+) bacteria. Also, it can be emphasized **4c**, **4e**, **4b** have an effect on *Bacillus cereus*. However, **3a-e** groups haven't effect on Gram (+), Gram (-) and Yeast as compared with **4a-e**. In addition, compounds **4d** and **4e** exhibited strong cleavage activity both buffer and H_2O_2 conditions. The findings of this study will be undoubtedly important for the systematic analysis and thus facilitate biological activity evaluations of thiazole derivatives in the literature, and we believe that may serve to design antimicrobial drugs.

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Supplementary Material

Supplementary material includes spectral characterization of pyridine substituted thiazole compounds, frontier molecular orbital diagrams, the components of the dipole moment, polarizability, first-order hyperpolarizability, packing diagram of the **3a**. CCDC 1935341 for **3a** and CCDC 1825209 for **3c** contain supplementary crystallographic data (excluding structure factors) for the structures reported in this article. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax:+44 1223336033.

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Figure Captions

Scheme 1. Synthesis of thiazole compouds **3a-e** and **4a-e**. Reaction condition: (i) ethanol, reflux, under N_2 atm, 18h.

Figure 1. The TG/DTA curves of the compounds **3b** and **4b.**

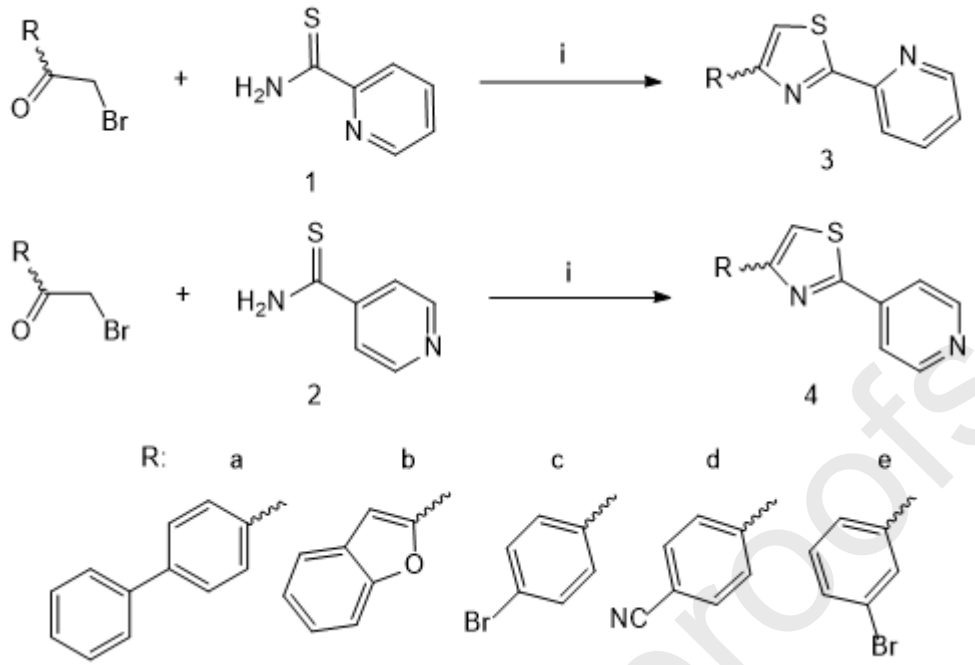
Figure 2. The excitation emission, absorption spectra of the **3c**

Figure 3. ORTEP views of the a) **3a** and b) **3c** compounds with showing the atom-numbering scheme.

Figure 4. Optimized molecular structures and total energy values of the compounds **3a-e** and **4a-e** by DFT/B3LYP/6-311G(d,p).

Figure 5. HOMO-LUMO molecular orbital diagrams of the compounds **4b** and **4d** (TD-DFT/B3LYP/6-311G(d,p).

Figure 6. A. DNA Cleavage activity of the compounds **3a-e** and **4a-e** in buffer conditions. 1. pBR322 control. 2. DMSO control. 3. **3a** + pBR322 DNA 4. **3e** + pBR322 DNA 5. **3d**+ pBR322 DNA 6. **3c** + pBR322 DNA 7. **3b** + pBR322 DNA 8. **4a** + pBR322 DNA 9. **4c** + pBR322 DNA 10. **4e** + pBR322 DNA 11. **4d** + pBR322 DNA 12. **4b** + pBR322 DNA **B.** DNA Cleavage activity of compounds in H_2O_2 conditions. 1. pBR322 + H_2O_2. 2. DMSO + H_2O_2. 3. **3a** +H_2O_2 + pBR322 DNA 4. **3e** + H_2O_2 + pBR322 DNA 5. **3d** + H_2O_2 + pBR322 DNA 6. **3c** + H_2O_2 + pBR322 DNA 7. **3b** + H_2O_2 + pBR322 DNA 8. **4a** + H_2O_2 + pBR322 DNA 9. **4c** + H_2O_2 + pBR322 DNA 10. **4e** + H_2O_2 + pBR322 DNA 11. **4d** + H_2O_2 + pBR322 DNA 12. **4b** + H_2O_2 + pBR322 DNA.



Scheme 1. Synthesis of thiazole compouds **3a-e** and **4a-e**. Reaction condition: (i) ethanol, reflux, under N_2 atm, 18h.

3b **4b**

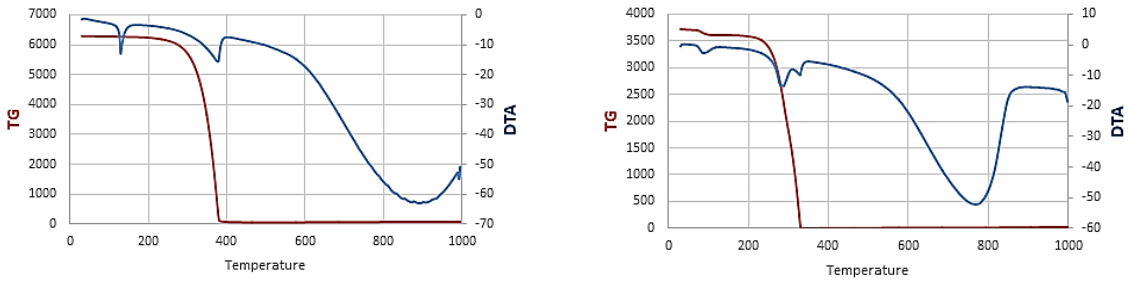


Figure 1. The TG/DTA curves of compounds **3b** and **4b**

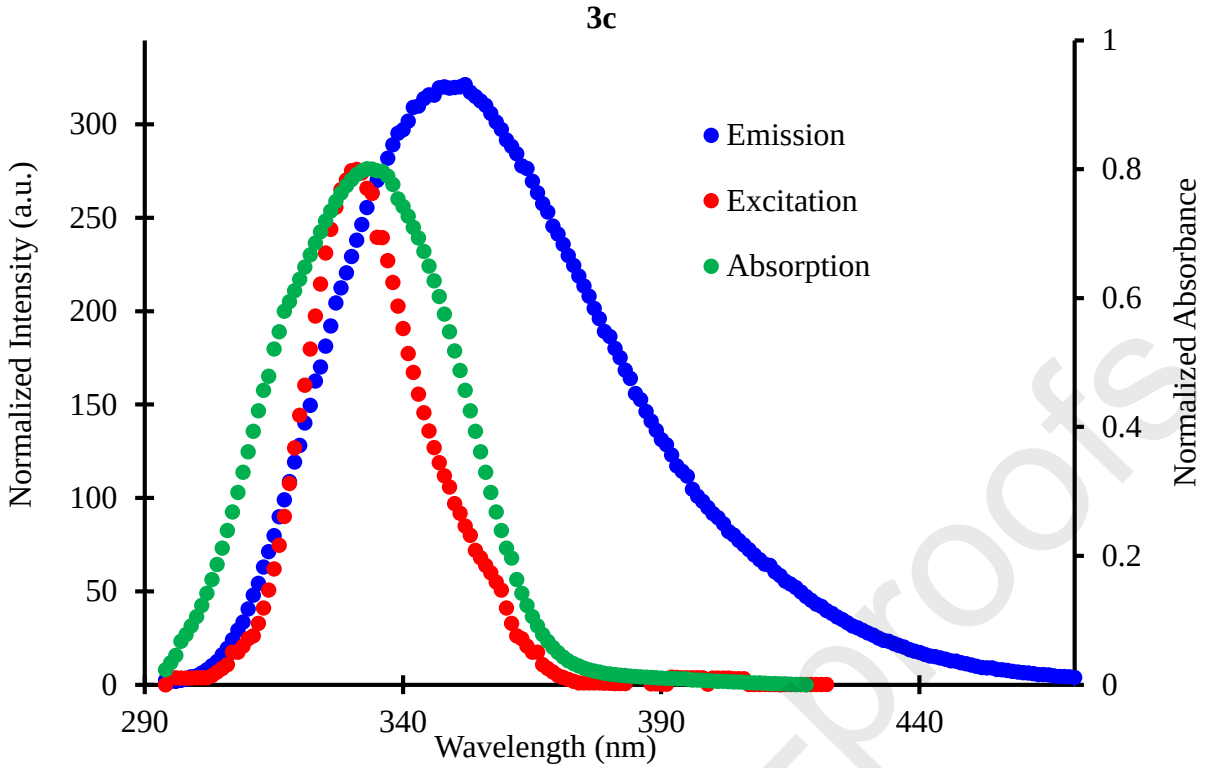


Figure 2. The excitation emission, absorption spectra of the compound **3c**

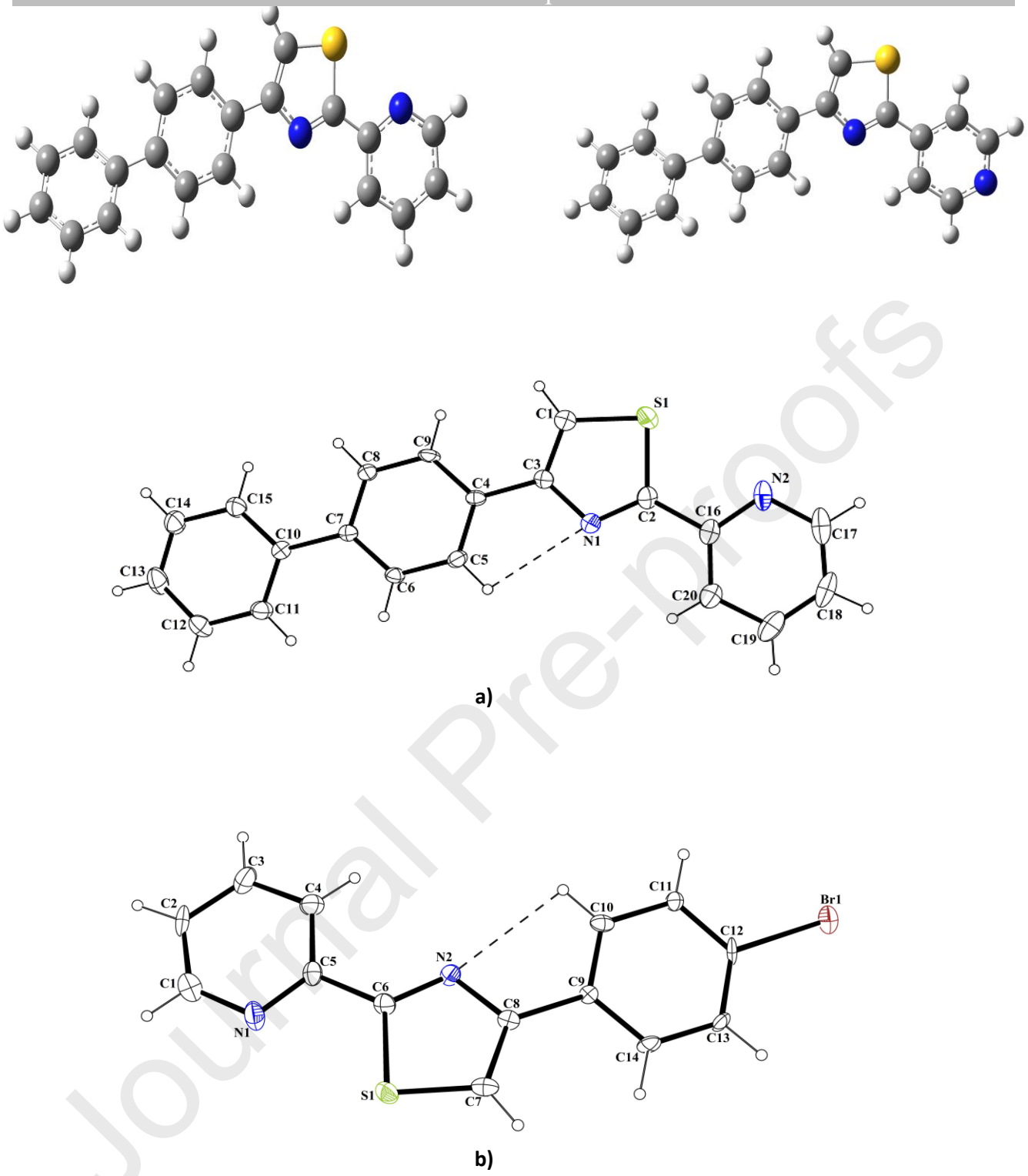
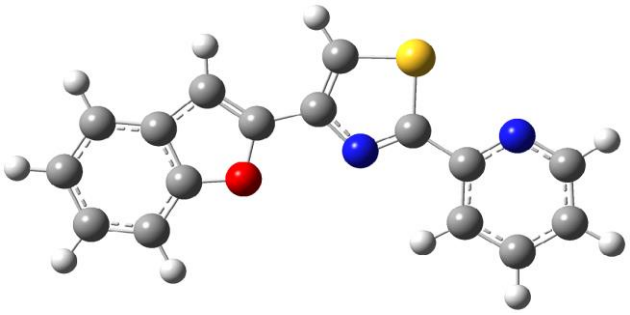


Figure 3. ORTEP views of the a) **3a** and b) **3c** compounds with showing the atom-numbering scheme.

3a

Total Energy:-1278.37098096 a.u.



4a

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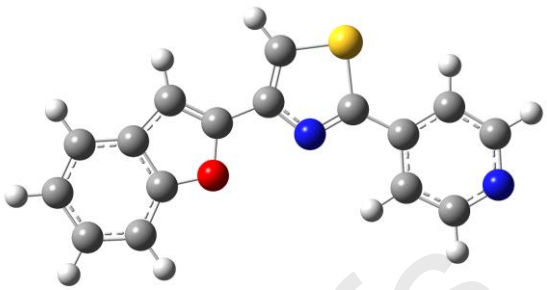

3b

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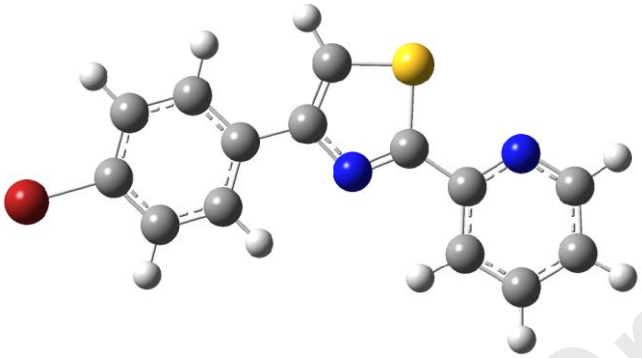

4b

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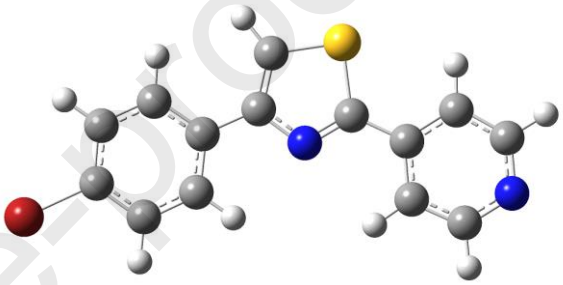

3c

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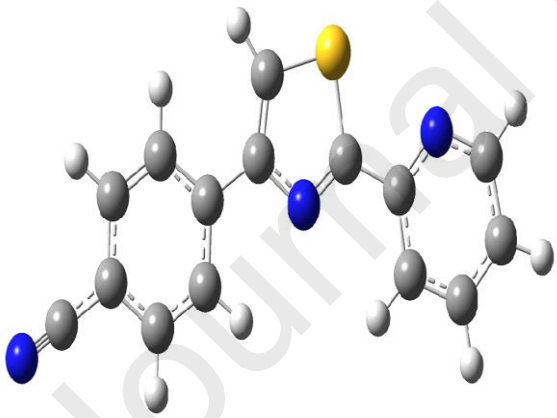

4c

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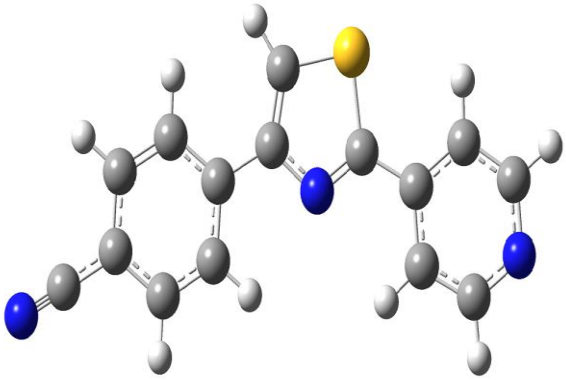
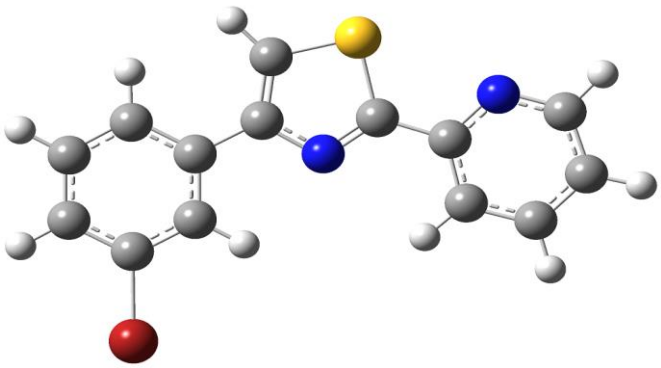


3d

Total Energy:-1139.51551501 a.u.

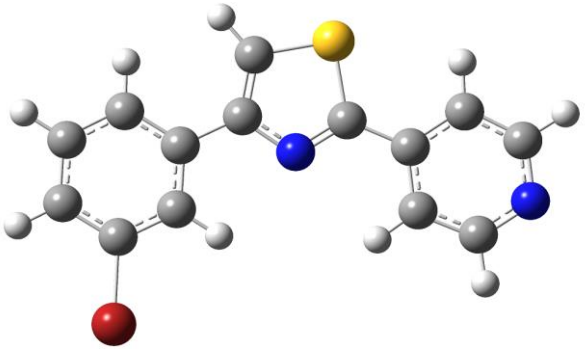
4d

Total Energy:-1139.50674367 a.u.



3e

Total Energy:-3620.79429139 a.u.



4e

Total Energy:-3620.78629790 a.u.

Figure 4. Optimized molecular structures and total energy values of the compounds **3a-e** and **4a-e** by DFT/B3LYP/6-311G(d,p).

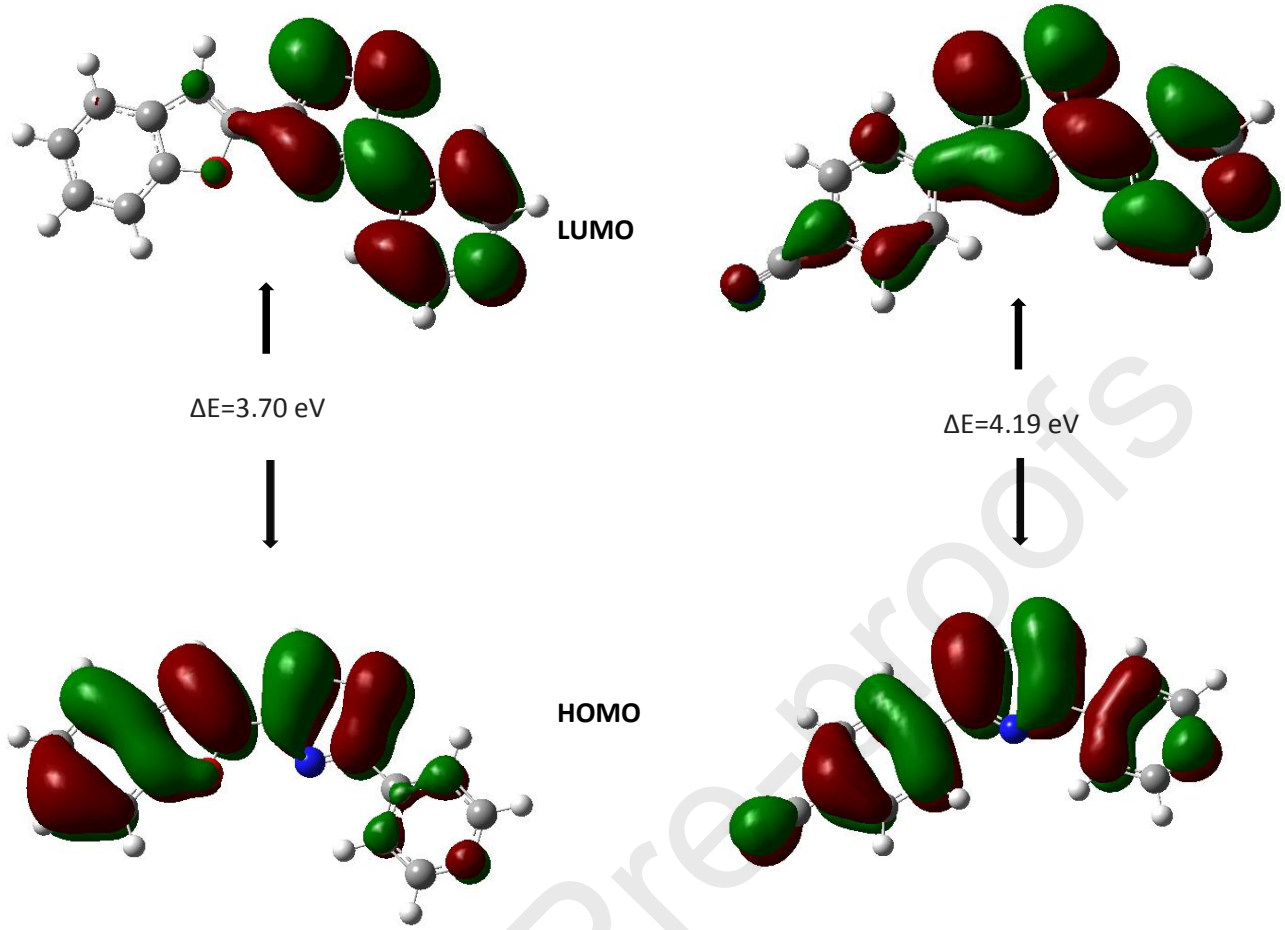


Figure 5. HOMO-LUMO molecular orbital diagrams of the compounds **4b** and **4d** (TD-DFT/B3LYP/6-311G(d,p).

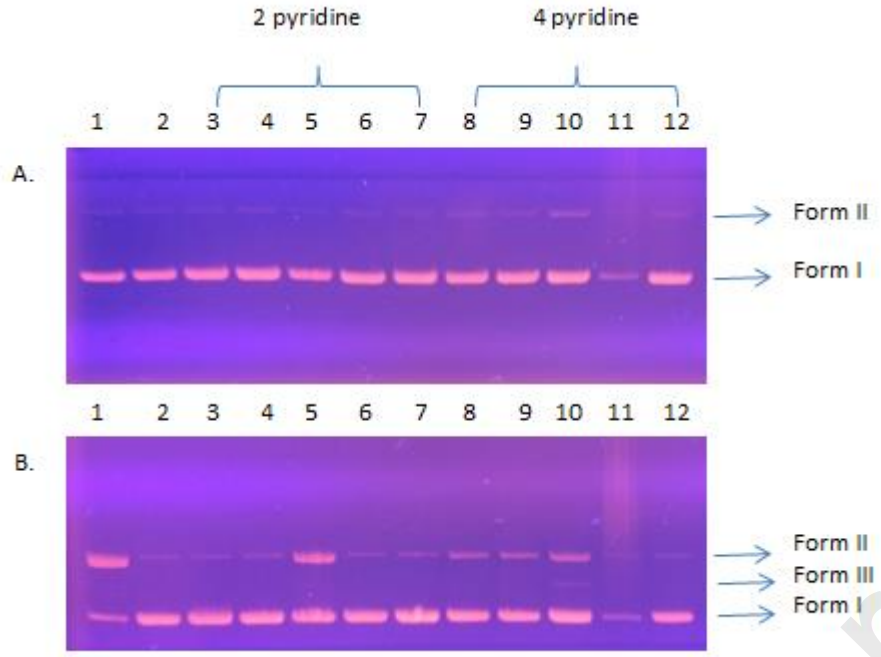


Figure 6. A. DNA Cleavage activity of the compounds **3a-e** and **4a-e** in buffer conditions. 1. pBR322 control. 2. DMSO control. 3. **3a** + pBR322 DNA 4. **3e** + pBR322 DNA 5. **3d**+ pBR322 DNA 6. **3c** + pBR322 DNA 7. **3b** + pBR322 DNA 8. **4a** + pBR322 DNA 9. **4c** + pBR322 DNA 10. **4e** + pBR322 DNA 11. **4d** + pBR322 DNA 12. **4b** + pBR322 DNA **B.** DNA Cleavage activity of compounds in H_2O_2 conditions. 1. pBR322 + H_2O_2. 2. DMSO + H_2O_2. 3. **3a** +H_2O_2 + pBR322 DNA 4. **3e** + H_2O_2 + pBR322 DNA 5. **3d** + H_2O_2 + pBR322 DNA 6. **3c** + H_2O_2 + pBR322 DNA 7. **3b** + H_2O_2 + pBR322 DNA 8. **4a** + H_2O_2 + pBR322 DNA 9. **4c** + H_2O_2 + pBR322 DNA 10. **4e** + H_2O_2 + pBR322 DNA 11. **4d** + H_2O_2 + pBR322 DNA 12. **4b** + H_2O_2 + pBR322 DNA.

Table Captions

Table 1. Absorption, excitation, emission wavelengths and Stokes shifts of the compounds **3a-e** and **4a-e** (concentration: 1.0×10^{-5} mol dm^{-3}).

Table 2. The crystal data and structure refinement parameters for the compounds **3a** and **3c**.

Table 3. Hydrogen bonding geometry for the compounds **3a** and **3c**.

Table 4. Some reactivity parameters of the compounds **3a-e** and **4a-e**.

Table 5. The values of total electric dipole moment, mean polarizability and first-order hyperpolarizability of the compounds **3a-e** and **4a-e**.

Table 6. Antimicrobial activity results of the compounds **3a-e** and **4a-e**.

Table 1. Absorption, excitation, emission wavelengths and Stokes shifts of the compounds **3a-e** and **4a-e** (concentration:1.0×10^{-5} mol dm^{-3}).

Compounds	Absorption (EtOH/DMSO)-nm	Excitation (EtOH)-nm	Emission (EtOH)-nm	Stokes Shift (cm^{-1})
3a	347/342	344	361	1368.9
4a	374/365	370	396	1774.5
3b	361/356	363	378	1093.1
4b	366/353	360	376	1182.1
3c	332/329	330	352	1893.9
4c	340/331	337	358	1740.6
3d	341/335	338	365	2188.5
4d	357/349	350	382	2393.4
3e	335/328	329	357	2383.9
4e	339/327	332	355	1951.5

Table 2. The crystal data and structure refinement parameters for the compounds **3a** and **3c**.

	3a	**3c**
CCDC deposition no.	1935341	1825209
Colour	Colourless	Colourless
Chemical formula	$C_{20}H_{14}N_2S$	$C_{14}H_9BrN_2S$
Formula weight	314.39	317.20
Temperature (K)	296	296
Wavelength (Å)	0.71073 Mo-*Kα*	0.71073 Mo-*Kα*
Crystal system	Orthorhombic	Monoclinic
Space group	$Pca2_1$	$P2_1$
Unit cell parameters		
a, *b*, *c* (Å)	33.960 (3), 5.7442 (5), 7.9280 (7)	4.0396 (10), 10.504 (3), 14.839 (4)
α, β, γ (°)	90	90, 91.642 (8), 90
Volume (Å^3)	1546.5 (2)	629.4 (3)
Z	4	2
D_{calc} (g/cm^3)	1.350	1.674
μ (mm^{-1})	0.21	3.41
F(000)	656	316
Crystal size (mm^3)	0.06 × 0.03 × 0.02	0.15 × 0.08 × 0.05
Diffractometer/measurement method	Bruker *APEX*-II CCD/ω scan	Bruker APEX-II CCD/ω scan
Index ranges	$-41 \le h \le 41$, $-6 \le k \le 6$, $-9 \le l \le 9$	$-4 \le h \le 4$, $-12 \le k \le 12$, $-17 \le l \le 17$
ϑ range for data collection (°)	$2.8 \le \vartheta \le 25.5$	$3.4 \le \vartheta \le 28.3$
Reflections collected	14994	9626
Independent/observed reflections	2854/2018	2178
R_{int}	0.122	0.066, 0.1652
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.05	1.26
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e/Å^3)	0.23, −0.25	0.83, -0.87

Table 3. Hydrogen bonding geometry for the compounds **3a** and **3c**.

	D—*H*···*A*	D—H (Å)	H···A (Å)	D···A (Å)	D—H···A
3a	C5—H5···N1	0.93	2.58	2.896 (8)	100
	C8—H8···Cg3^{i}	0.93	2.96	3.654	132
3c	C10—H10···N2	0.93	2.55	2.87 (2)	100

Symmetry code (i) 1-x,1-y,1/2+z

Table 4. Some reactivity parameters of the compounds **3a-e** and **4a-e**.

	E_{HOMO} (eV)	E_{LUMO} (eV)	ΔE (eV)	*I* (eV)	A (eV)	*χ* (eV)	*η* (eV)	*S* (eV^{-1})	*μ* (eV)	*ω* (eV)
3a	-5.8156	-1.9178	3.8978	5.8156	1.9178	3.8667	1.9488	0.2565	-3.8667	3.8359
4a	-6.0219	-2.1502	3.8717	6.0219	2.1502	4.0860	1.9358	0.2582	-4.0860	4.3123
3b	-5.7147	-1.9763	3.7384	5.7147	1.9763	3.8455	1.8691	0.2674	-3.8455	3.9558
4b	-5.9185	-2.2155	3.7030	5.9185	2.2155	4.0670	1.8514	0.2700	-4.0670	4.4669
3c	-6.0796	-2.0332	4.0464	6.0796	2.0332	4.0564	2.0231	0.2471	-4.0564	4.0665
4c	-6.3169	-2.2740	4.0429	6.3169	2.2740	4.2954	2.0214	0.2473	-4.2954	4.5639
3d	-6.4042	-2.2256	4.1786	6.4042	2.2256	4.3149	2.0893	0.2393	-4.3149	4.4557
4d	-6.6660	-2.4708	4.1952	6.6660	2.4708	4.5684	2.0976	0.2383	-4.5684	4.9748
3e	-6.1824	-2.0272	4.1552	6.1824	2.0272	4.1048	2.0776	0.2406	-4.1048	4.0551
4e	-6.4358	-2.2691	4.1667	6.4358	2.2691	4.3524	2.0833	0.2400	-4.3524	4.5466

Table 5. The values of total electric dipole moment, mean polarizability and first-order hyperpolarizability of the compounds **3a-e** and **4a-e**.

Compounds	μ_{tot} (Debye)	$\langle\alpha\rangle$ ($\times10^{-24}$ esu)	β_{tot} ($\times10^{-33}$ esu)
3a	1.3601	41.45074	6167.37
4a	2.9041	41.49583	7370.54
3b	1.1016	34.24318	9619.93
4b	3.3005	33.73563	10584.11
3c	2.8936	32.31239	9491.81
4c	2.6660	31.82302	10323.95
3d	6.1653	32.45179	9163.21
4d	4.9099	31.87637	6296.53
3e	1.7716	31.5371	2880.35
4e	4.0364	31.04205	3010.93

Table 6. Antimicrobial activity results of the compounds **3a-e** and **4a-e**.

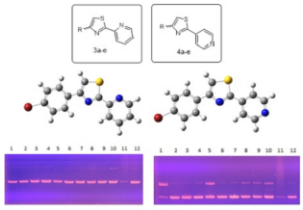
	Gram (-) Bacteria		**Gram (+) Bacteria**		**Yeast**
	***Escherichia coli* W3110**	***Pseudomonas aeruginosa* ATCC 27853**	***Staphylococcus aureus* ATCC 6538P**	***Bacillus cereus* ATCC 7064**	***Candida albicans* ATCC 10231**
3a (mM)	4.8	2.4	2.4	2.4	1.2
4a (mM)	2.4	2.4	1.2	0.6	0.6
3b (mM)	2.4	2.4	2.4	0.3	0.6
4b (mM)	2.4	2.4	0.15	0.15	1.2
3c (mM)	1.2	2.4	1.2	1.2	0.15
4c (mM)	1.2	2.4	0.01	0.01	0.15
3d (mM)	5.7	5.7	5.7	5.7	2.8
4d (mM)	2.8	2.8	2.8	1.4	0.7
3e (mM)	4.7	2.4	2.4	2.4	0.6
4e (mM)	2.4	4.7	0.15	0.04	0.6
DMSO (mM)	>5	>5	>5	>5	>5
Cefepim (mM)	0.06	0. 02	0.001	0.02	-
Amikacin (mM)	ND	0.02	0.01	ND	-
Fluconazole (mM)	-	-	-	-	8.65

ND: Non Detected

Highlights

- Synthesis and characterization of a series 10 functionalized thiazoles.
- A comparative study of some reactivity parameters and NLO behaviours with a theoretical approach based-DFT.
- Biological evaluation *via* antimicrobial and DNA cleavage activity.

Graphical abstract



Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: