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# Synthesis, DFT, and possibility of biological activities' studies for new thiophene hydrazide derivatives

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**Abstract-** Seven new thiophene hydrazide derivatives **3a-e**, **5**, and **7** were prepared through the coupling of active methylene of compound **1** with diazonium salts of aromatic amines **2a-e**, and heterocyclic amines **4** and **6** at 0-5 $^{o}$C in pyridine. The studied compounds **1**, **3a-e**, and **5** could exist in two possible tautomeric forms, which are the enol and keto tautomer. The optimized molecular structures and calculation of the total energies of both tautomers revealed that the enol tautomer is energetically lower than its corresponding keto form. A prediction study for the biological activities of synthesized thiophene hydrazide derivatives **3a-e** and **5** was performed *via* using PASS online software, which displayed promising activities in the treatment of Posttraumatic stress disorder, as Phosphodiesterase X inhibitor (**3a, 3b**), and as Sarcosine oxidase inhibitor (**3d**). In addition, DFT calculations showed that compounds **3a**, **3b**, and **3d** have chemical activity among all the newly synthesized compounds due to their lower band gaps.

**keywords**: Thiophene derivatives, Acetohydrazonic acid, Azo dyes, DFT

## 1. Introduction

Substituted cyanoacetamides play a crucial role as intermediates in the production of various dyes, agrochemicals, and pharmacologically active compounds [1]. Tautomeric dyes, including azo derivatives and azo-hydrazones, showed dual activities with antibacterial and antioxidant properties, respectively [2,3]. Hydrazones have been documented to possess a wide range of biological effects, including anti-HIV, analgesic, anticonvulsant, antitumor, anti-inflammatory, antimicrobial, and anti-tuberculosis properties [4,5]. Also, these compounds have been documented to function through various mechanisms, such as blocking RNA and DNA synthesis, suppressing mitosis [6], triggering caspase-dependent apoptosis, hindering tubulin polymerization, inducing cell cycle arrests in the G2/M phase [7], causing cancer cell cycle arrest in the sub G1/G0 phase [8], and promoting tumor cell apoptosis [9] (**Figure 1**).

Azo dyes derived from thiophene showed colors ranging from red to blue and possess a notably high extinction coefficient when compared to azo dyes derived from anilines [10]. In addition, compounds containing a thiophene nucleus possess attracted significant interest in field of drug synthesis due to their wide range of biological activities, including antimicrobial [11,12], antidepressant [13], anticonvulsant [14], and anti-inflammatory properties [15]. It is worth to highlight that thiophene derivatives serves as a promising structural framework that has made significant contributions to the advancement of anticancer medications. It has demonstrated effectiveness not only in the treatment of various cancer types but also in acting as a chemo preventive agent against cancer [16,17,18,19,20]. Additionally, thiophene derivatives have been reported to function as inhibitors of epidermal growth factor receptor (EGFR), caspase 9 inhibitors, and inducers of apoptosis [21,22,23].

## 2. Materials and methods

Melting points (uncorrected) were measured in degree centigrade on Gallenkamp apparatus. Thermo Scientific Nicolet iS10 FTIR

spectrometer was used to record infrared spectra (KBr). Bruker's spectrometer 400 MHz ($^1$H-NMR), 100 MHz ($^{13}$C-NMR) was used to measure NMR spectra in DMSO-$d_6$ as a solvent and an internal standard. Electron impact mass spectra were determined at 70 eV on Varian MAT 311Kratos instrument.

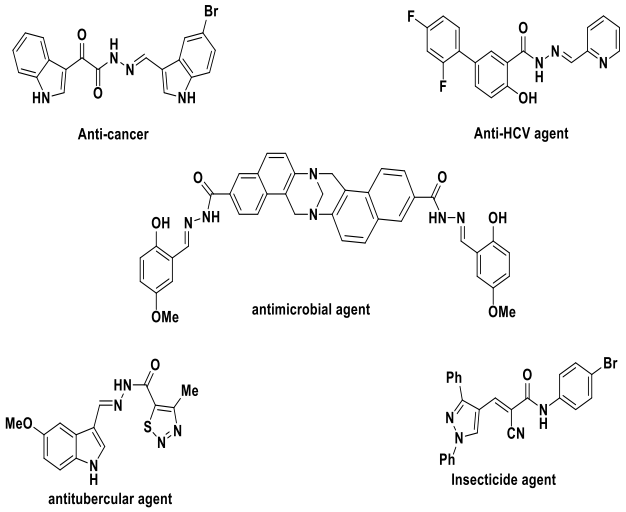



**Figure 1:** Biologically important hydrazonyl compounds

### 2.1. General methodology for preparation of azo compounds (3a-e) and 5.

In an ice-cold bath, the aromatic amines **2a-e** (0.01 mol) underwent diazotization using $NaNO_2$ (1 g, 0.015 mol) in concentrated HCl (10 ml). The diazotized amine was then gradually added into a stirred solution of compound **1** (1.93 g, 0.01 mol) in pyridine (25 ml). The resulting mixture was stirred for 2 hours, followed by standing at the same temperature for an additional 12 hours. The resulting precipitate was then filtered and recrystallized from DMF and EtOH (2:1) to give the anticipated products **3a-e** and **5**.

**2.1.1. 2-Cyano-*N*-(-thiophen-2-ylmethylene)-2-(2-(p-tolyl)hydrazono)aceto-hydrazonic acid (3a)**. Hydrazone derivative 3a was obtained in 75% yield as a yellow sheet, m.p.= 198 $^o$C. $R_f$= 0.67, EtOAc/Petroleum ether (60-80) (1.5:4). IR (KBr) ν'/cm$^{-1}$: 3499 (OH stretch), 3232 (N-H, stretch), 3073 (sp$^2$ C-H, stretch), 2206 (CN stretch), 1651, 1599, 1545 (C=N, C=C, stretch). $^1$H-NMR (DMSO-d$_6$): δ 2.30 (s, 3H, $CH_3$), 7.16-7.69 (m, 7H, Ar-H), 8.77 (s, 1H, CH=N), 11.43 (s, 1H, NH), 11.90 (s, 1H, OH); $^{13}$C-NMR (DMSO-d$_6$): δ 20.95, 106.70, 111.80, 116.73 (2C), 128.38, 129.48, 130.23, 131.44 (2C), 134.11, 139.45, 140.21, 144.10, 158.10 (C-OH); MS (EI) m/e (rel.int.) for $C_{15}H_{13}N_5OS$; 311.20 (M$^+$, 11.16), 149.50 (100).

**2.1.2 2-Cyano-2-(2-(4-methoxyphenyl)-hydrazono)-*N*-(-thiophen-2-ylmethylene)-acetohydrazonic acid (3b).** Hydrazone derivative **3b** was obtained in 73 % yield as a yellow crystal, m.p.= 172 $^o$C. $R_f$= 0.48, EtOAc/Petroleum ether (60-80) (2:4). IR (KBr) ν'/cm-1: IR (KBr) ν'/cm$^{-1}$: 3225 (NH stretch), 3071 (sp$^2$ C-H, stretch), 2208 (CN, stretch), 1656 (C=O, stretch), 1599, 1545, 1484 (C=N, C=C, stretch). $^1$H-NMR (DMSO-d$_6$); δ 3.77 (s, 3H, $OCH_3$), 6.98-7.67 (m, 7H, Ar-H), 8.76 (s, 1H, CH=N), 11.41 (s, 1H, NH), 11.93 (s, 1H, OH). $^{13}$C-NMR (DMSO-d$_6$); δ 55.83, 105.90, 111.99, 115.15 (2C), 118.20 (2C), 128.37, 129.43, 131.37, 136.05, 139.49, 143.91, 157.00, 158.26 ppm (2C). MS (EI) m/e (rel.int.) for $C_{15}H_{13}N_5O_2S$; 327.58 (M$^+$, 81.58), 135.02 (100).

**2.1.3. 2-Cyano-2-(2-(4-nitrophenyl)-hydrazono)-*N*-(thiophen-2-ylmethylene)-acetohydrazonic acid (3c)**. Hydrazone derivative **3c** was obtained in 76% yield as an orange powder, m.p.= 222 ℃. $R_f$= 0.64, EtOAc/petroleum ether (60-80) (2:4). IR (KBr) ν'/cm$^{-1}$: 3228 (N-H stretch), 3083 (sp$^2$ C-H, stretch), 2214 (CN, stretch), 1667 (C=O, stretch), 1600, 1512 (C=N, C=C, stretch). $^1$H-NMR (DMSO-$d_6$); δ δ 7.16-8.28 (m, 7H, Ar-H), 8.80 (s, 1H, CH=N), 11.67 (s, 1H, NH), 12.34 (br, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$): δ 111.04, 111.65, 116.69 (2C), 125.74 (2C), 128.44, 129.81, 131.85, 139.23, 144.92 (2C), 147.98, 157.26. MS (EI) m/e (rel.int.) for $C_{14}H_{10}N_6O_3S$; 342.13 (M$^+$, 15.30), 40.16 (100).

**2.1.4. 4-(2-(1-Cyano-2-hydroxy-2-(thiophen-2-ylmethylene)hydrazono)ethylidene)-hydrazinyl)benzoic acid (3d)**. Hydrazone derivative **3d** was obtained in 77% yield as a Yellow powder, m.p.= 268 $^o$C. $R_f$= 0.30, EtOAc/petroleum ether (60-80) (3.5:4). IR (KBr) ν'/cm$^{-1}$: 3448 (OH, stretch), 2212 (CN, stretch), 1666 (C=O, stretch), 1604, 1534 (C=N, C=C, stretch). $^1$H-NMR (DMSO-$d_6$): δ 7.15-7.97 (m, 7H, Ar-H), 8.79 (s, 1H, CH=N), 11.55 (s, 1H, NH), 12.13 (s, 1H, OH), 12.75 (br, 1H, COOH). $^{13}$C-NMR (DMSO-$d_6$): δ 109.59, 111.30, 116.29 (2C), 126.51, 128.42, 129.65, 131.13, 131.35, 139.30 (2C), 144.65,

146.07, 157.63, 167.37. MS (EI) m/e (rel.int.) for $C_{14}H_{10}BrN_5OS$; 341.70 ($M^+$, 16.42), 301.63 (100).

**2.1.5. 2-(2-(4-Bromophenyl)hydrazono)-2-cyano-*N*-(thiophen-2-ylmethylene)aceto-hydrazonic acid (3e)**. Hydrazone derivative **3e** was obtained in 75% yield as a yellow powder, m.p.= 202 $^oC$. $R_f$= 0.64, EtOAc/petroleum ether (60-80) (1.5:4). IR (KBr) ν'/$cm^{-1}$ 3430 (OH, stretch), 3235 (N-H, stretch), 3078 ($sp^2$ C-H, stretch), 2213 (CN stretch), 1666 (C=O, stretch), 1598, 1530, 1482 (C=N, C=C, stretch). $^1$H-NMR (DMSO-$d_6$): δ 7.15-7.68 (m, 7H, Ar-H), 8.78 (s, 1H, CH=N), 11.53 (s, 1H, NH), 12.01 (s, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$): δ 108.32, 111.54, 116.72, 118.71 (2C), 128.41, 129.41, 131.64, 132.40 (2C), 139.35, 141.86, 144.38, 157.77. MS (EI) m/e (rel.int.) for $C_{14}H_{10}BrN_5OS$; 374.32 ($M^+$, 9.26), 55.09 (100).

**2.1.6. 2-Cyano-2-(2-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)-hydrazono)-*N*-(thiophen-2-ylmethylene)-acetohydrazonic acid (5)**. Hydrazone derivative **5** was obtained in 72% yield as a yellow powder, m.p.= 172 $^oC$. $R_f$= 0.45, EtOAc. IR (KBr) ν'/$cm^{-1}$: 3443 (OH, stretch), 3174 (N-H, stretch), 2208 (CN, stretch), 1658 (C=O, stretch), 1600, 1519 (C=N, C=C, stretch). $^1$H-NMR (DMSO-$d_6$): δ 2.31 (s, 3H, $CH_3$), 3.17 (s, 3H, N-$CH_3$), 7.13-7.67 (m, 8H, Ar-H), 8.64 (s, 1H, CH=N), 11.01 (br, 1H, NH), 11.38 (br, 1H, OH). $^{13}$C-NMR (DMSO-$d_6$): δ 11.33, 35.88, 111.58, 124.71, 127.41, 128.32 (3C), 129.35 (2C), 129.71 (3C), 131.23, 135.02, 139.52, 143.48, 160.86 (2C). MS (EI) m/e (rel.int.) for $C_{19}H_{17}N_7O_2S$; 407.15 ($M^+$, 9.48), 44.05 (100).

**2.2. 4-Amino-8,10-dimethyl-*N*'-(thiophen-2-ylmethylene)pyrido[2',3':3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carbohydrazide (7).** The suspension solution of heterocyclic amine **6** (1.62 g, 0.01 mol) in a mixture of AcOH and concentrated HCl (15 ml: 5 ml) was subjected to diazotization using $NaNO_2$ (1 g, 0.015 mol) *via* stirring in an ice bath. This diazotized solution was then slowly added into a stirred solution of compound **1** (1.93 g, 0.01 mol) in pyridine (25 ml). The resulting mixture was stirred overnight, and the resultant precipitate was filtered and subjected to recrystallization from a mixture of DMF and EtOH (2:1) to obtain the anticipated product **7**. Compound 7 was obtained in 67% yield as a dark brown solid, m.p.> 300 $^oC$. $R_f$= 0.52, EtOAc: EtOH (4:0.5). IR (KBr) ν'/$cm^{-1}$: 3316- 3262 (NH2, stretch), 1670 (C=O, stretch), 1632, 1580 (C=N, C=C stretch). MS (EI) m/e (rel.int.) for $C_{16}H_{14}N_8OS$; 366.06 ($M^+$, 96.09), 248.80 (100).

## 3. Results and Discussion

### 3.1. Chemistry

Azo compounds exhibit impressive coloring properties owing to the inclusion of the chromophore group (-N=N-), which is linked to aromatic or heterocyclic systems [24]. Typically, these compounds are produced through the diazo coupling of a diazonium salts **2a-e** with the preferred active methylene of compound **1**. Chemical structures of the new hydrazono thiophene derivatives **3a-e**, (Scheme 1) were confirmed according to their spectral analyses. As IR spectra for compounds **3a-e** revealed the appearance of hydroxyl and nitrile groups with vibrations in the range of 3430 to 3499 (OH group) and 2206 to 2214 $cm^{-1}$ (CN group), respectively. The $^1$H-NMR spectra of **3a** & **3b** showed new singlet signals three protons each corresponding for *p*-methyl, *p*-methoxy at δ 2.30 and 3.77, respectively; in addition, two singlet signals (one proton each) at δ 8.77, 8.76 for CH=N (methine protons), 11.43, 11.41 for NH and 11.90, 11.93 for OH, respectively. Also, $^{13}$C-NMR spectra of compounds **3a** & **3b** displayed 15 carbon-signals each for their carbon networks with characteristic carbons at δ 20.95 (*p*-methyl, **3a)** and 55.83 (*p*-methoxy, **3b**). Furthermore, Mass spectra of **3a** & **3b** displayed a molecular ion peaks with m/z = 311.20 ($M^+$, 11.16) and 327.58 ($M^+$, 81.58), respectively. Once more, $^1$H-NMR of **3c** gave three singlet signals (one proton each) at δ 8.80, 11.67 and 12.34 for CH=N, NH and OH, correspondingly, and its $^{13}$C-NMR showed characteristic signals at δ 111.04, 139.23 and 157.26 for C=N, CH=N, and C-OH, respectively. Moreover, mass spectrum of compound **3c** furnished m/z at 342.13 ($M^+$, 15.30). Furthermore, $^1$H-NMR of compound of hydrazono derivative 3d showed singlet signals attributed to CH=N, NH, OH and COOH groups at δ 8.79, 11.55, 12.13, and 12.75, respectively. Also, $^{13}$C-NMR of compound 3d displayed 14 carbon-signals of its

carbon network with characteristic signal at δ 157.63 and 167.37 for carbon of C-OH and COOH groups, respectively. Mass spectrum of compound 3d gave m/z at 341.70 ($M^+$, 16.42). In addition, the $^1$H-NMR of compound **3e** displayed three singlet signals (one proton each) at δ 8.78, 11.53, and 12.01 ppm for CH=N, NH, and OH, respectively, and its $^{13}$C-NMR spectrum revealed the attendance of carbon signals at appropriate chemical shift values. Hydrazone derivative **3e** mass spectrum revealed a molecular ion peak at m/z = 374.32 ($M^+$, 9.26).

Numerous derivatives of pyrazole have been employed clinically as nonsteroidal anti-inflammatory drugs, including analgesic and antipyretic medications like anti-pyrine. Additionally, these derivatives exhibit diverse biological activities, encompassing antimicrobial, antifungal, antitubercular, anti-inflammatory, anticonvulsant, anticancer, and antiviral properties [25-28]. So, acetohydrazide **1** coupled with diazonium salt of heterocyclic amine **4** to afford the anticipated phenylpyrazoloacetohydrazonoic acid derivative **5** (Scheme 2). Spectral analyses were used to characterize the structure of compound **5**. The IR analysis of compound 5 showed an absorption peak at ν'= 3443, 3174, 2208, and 1658 cm–1, confirmed the existence of OH, NH, CN and C=O groups, respectively. Also, the $^1$H-NMR spectrum of pyrazolo **5** showed four singlet signals at δ 2.31, 3.17, 11.01, and 11.38 ppm, corresponding to $CH_3$, N-$CH_3$, NH, and OH groups, respectively. Furthermore, $^{13}$C-NMR spectrum for pyazolo derivative **5** showed carbon signals at δ 11.33 and 35.88 ppm attributed to carbon of $CH_3$, N-$CH_3$, respectively, which verified its structure. Additionally, the mass spectrum of compound 5 showed an ion peak at m/z= 407.15 ($M^+$, 9.48) equaling to the molecular formula $C_{19}H_{17}N_7O_2S$, which coincides with its proposed structure.

The amino pyrazolopyridine served as a crucial core structure in various drug compounds and played a significant role in bioactivities, such as antitumor effects [25,29], antimicrobial activities [30], as well as antifungal, antiplatelet, and antioxidant properties [31]. In light of these data, we aimed to utilize the 3-amino-pyrazolopyridine **6** as a building block for the synthesis of the pyrazolopyridine derivative **8**, but the reaction furnished the tricyclic derivative **7**. The skeleton of the new tricyclic **7** was confirmed based upon its IR and mass spectral data. The IR spectra for compound **7** revealed the appearance of stretching peaks at ν'= 3316, 3262 ($NH_2$), 1670 (C=O), and 1632 (C=N). In addition, mass spectrum of compound **7** gave a m/z = 366.06 ($M^+$, 96.09).

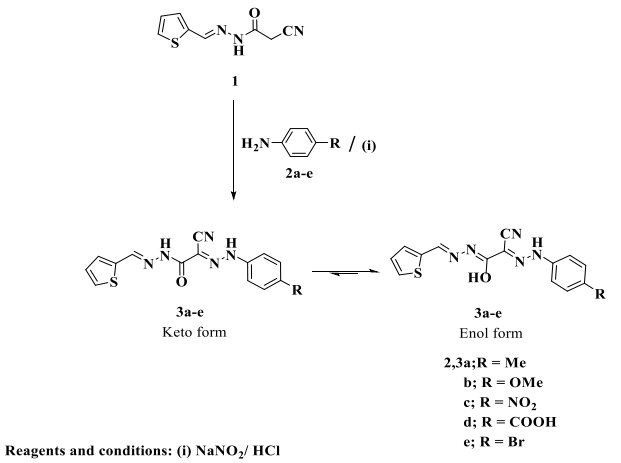
### 3.2. Computational approaches

#### 3.2.1. Molecular modeling

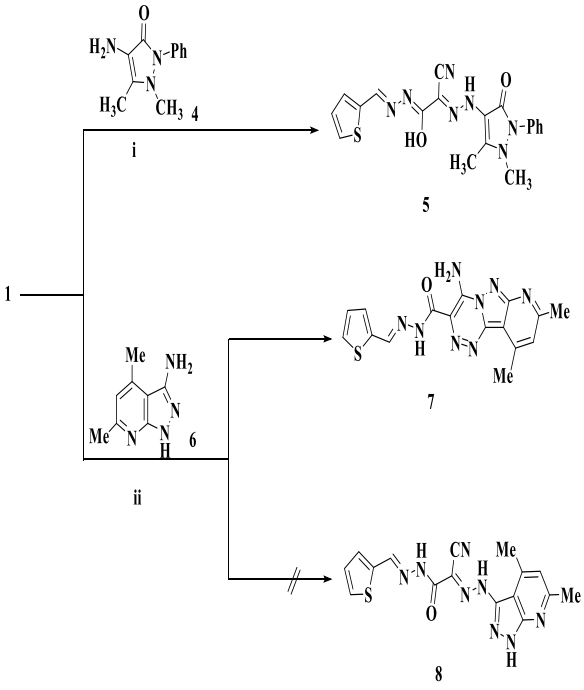
Computational calculations were conducted to assess the chemical reactivity and obtain initial insights into the anticipated biological evaluation, employing the Gaussian 09 program package. The DFT approach, specifically B3LYP as a functional and the 6-311G (d,p) basis set, was employed in the gaseous state to investigate the optimized structures of the synthesized compounds [32-35]. The studied compounds could exist in two possible tautomeric forms. The optimized molecular structures of the enol and ketone tautomer of compounds **1, 3a-e** and **5** calculation of total energies of both tautomers are listed in of are shown in Figure 2 & 3. It is clear that the enol tautomer is energetically lower than the ketone.

The HOMO/LUMO symbolize the highest occupied and lowest unoccupied molecular orbital energies, which indicate the chemical reactivity and stability of the prepared molecules. As the energy gap is the difference between the orbitals, energies (EHOMO-ELUMO) indicates the reactivity of the synthesized compounds. The molecules that have high (ΔEHOMO-LUMO) are called hard molecules, meaning less reactivity in the treatment biological strains. Conversably, molecules that have lower gap energies are called soft molecules, besides have high ability as biological molecules. Calculations of the hydrazono thiophen derivatives **1**, **3a-e** and **5** (Figure 4-7) showed that compound **3a** is the most effective and reactive molecule, as it has a lower band gap (-3.641ev) comparing to other hydrazono thiophen whose energies gap ranged between (-3.600, -2.474 ev), and it is predicted to be the most active molecule compared to other hydrazono thiophen **1**, **3b-e** and **5**.

**3.2.2. Computational prediction of biological activities:** The anticipated biological activity was obtained through the utilization of PASS online software for the synthesized compounds, as outlined in **Tables 1** and **2**. This tool affords predictions correlating *Pi* (probability to be inactive) and *Pa* (probability to be active) [36]. From the results of various biological activity predictions, starting compound **1** displayed possibility of activity against to Posttraumatic stress disorder treatment, Phosphodiesterase 10A inhibitor, Phosphodiesterase X inhibitor, Complement factor D inhibitor, Sarcosine oxidase inhibitor, and Malate oxidase inhibitor ranging from *Pa*= 0.909 to *Pa*= 0.787. Comparing biological activity predictions for synthesized compounds **3a-e** and **5** Against to start compound **1**, we notice that compounds **3a, b** displayed more possibility of activity *Pa*= 0.946, 0.933 towards Posttraumatic stress disorder treatment, and 0.912, 0.928 towards Phosphodiesterase X inhibitor, respectively, in the order of **3a**> **3b**, which be related to the presence of methyl group in **3a** (**Table 1**). Also, compound **3d** displayed more biological activities towards Sarcosine oxidase inhibitor (**Table 2**) comparable to start compound **1**. On the contrary, the hydrazone thiophene derivatives **3c, 3e** and **5** showed less predict biological activities against Posttraumatic stress disorder treatment, Phosphodiesterase X inhibitor and Sarcosine oxidase inhibitor. Moreover, the obtained predicated biological activities are fully compatible with the theoretical studies which accomplished *via* Gaussian studies. As compound **3a** showed the best predicted biological activities confirmed it as the softest molecule.




**Scheme 1**: Scheme for preparation of the new hydrazono thiophenes **3a-e.**




**Scheme 2**: Scheme for preparation of the new hydrazono thiophenes **5** and **7.**

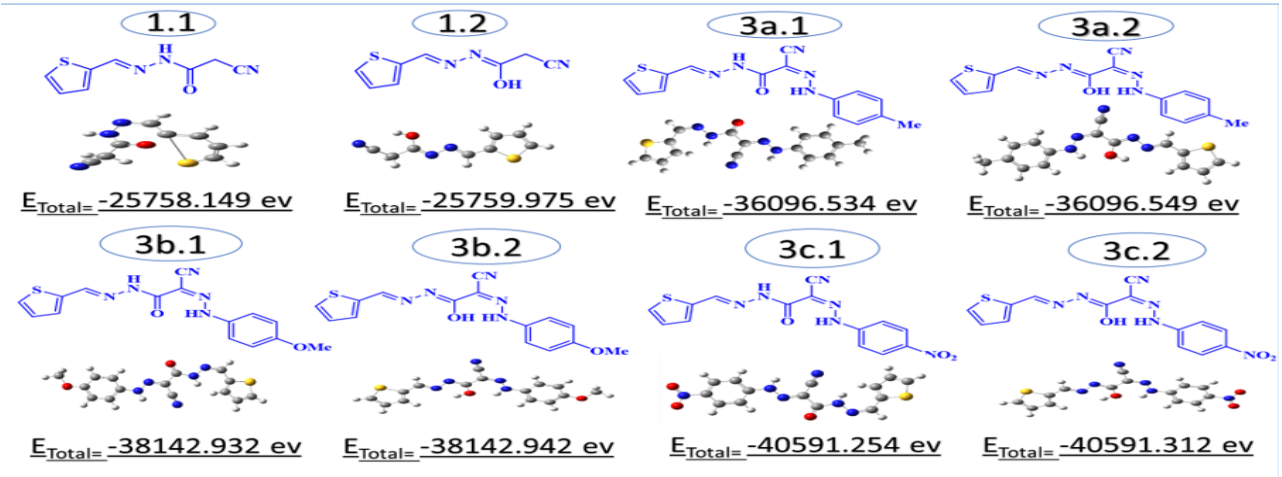



**Figure 2:** Geometrical optimization of hydrazono thiophenes **1** and **3a-c**.

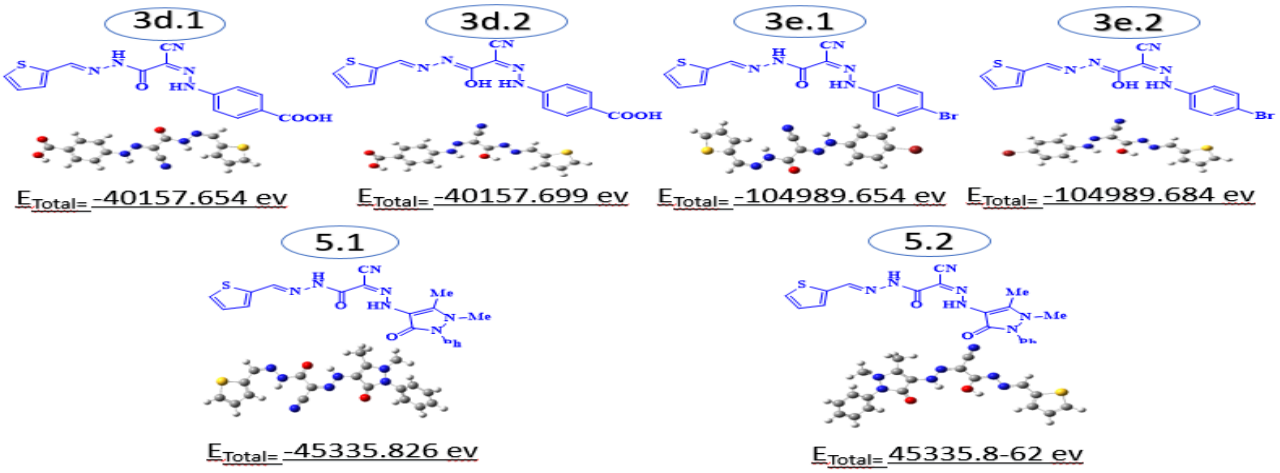



**Figure 3:** Geometrical optimization of hydrazono thiophenes **3d-e, 5.**

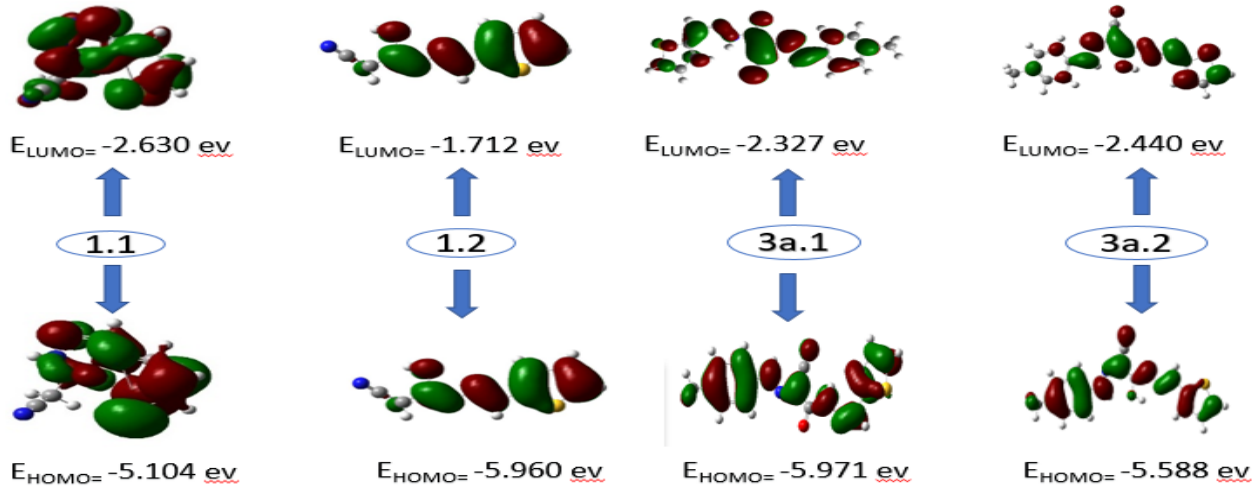



**Figure 4:** Spatial distributions orbitals of hydrazono thiophenes **1** and **3a**.

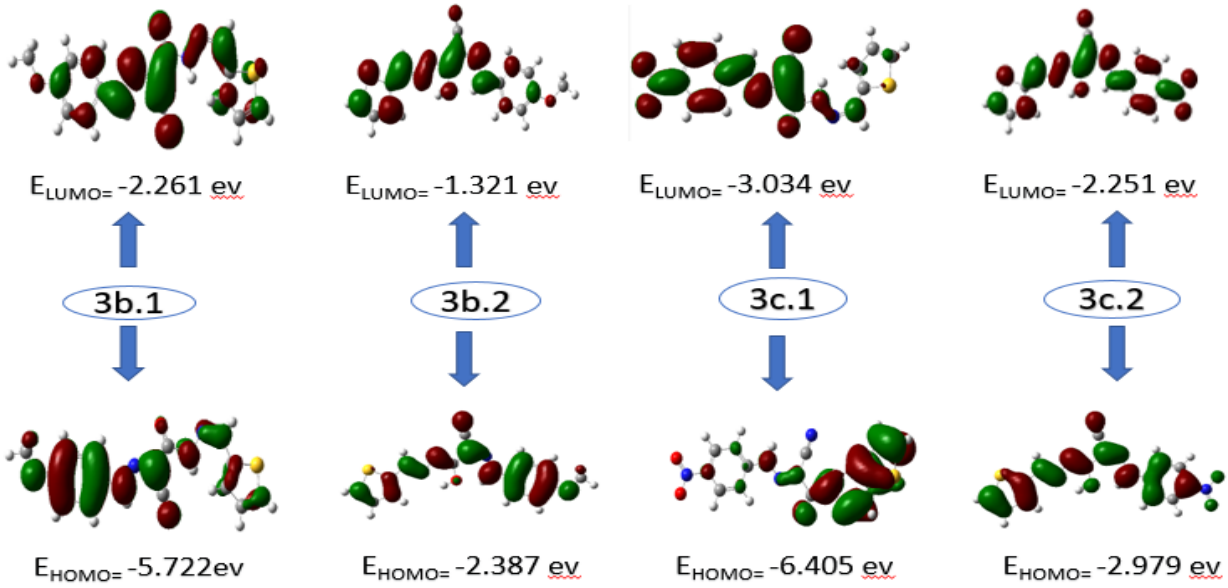



**Figure 5:** Spatial distributions orbitals of hydrazono thiophenes **3b** and **3c**.

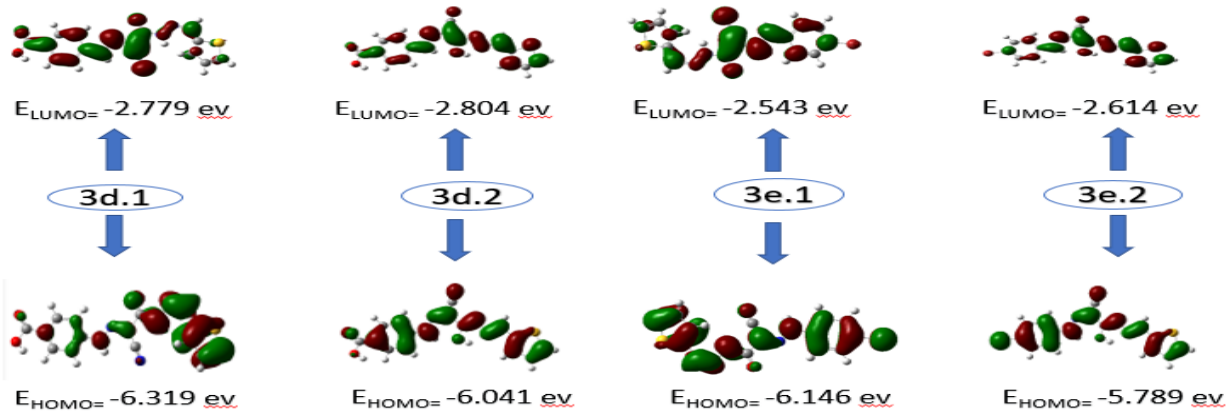



**Figure 6:** Spatial distributions orbitals of hydrazono thiophenes **3d** and **3e**.


**Figure 7:** Spatial distributions orbitals of hydrazono thiophenes **5.**

**Table 1**: PASS online biological activities' assessments for compounds **1** and **3a-c.**

| Biological Activity | Compd# 3d | | Compd# 3e | | Compd# 5 | |
|---|---|---|---|---|---|---|
| | $P_a$ | $P_i$ | $P_a$ | $P_i$ | $P_a$ | $P_i$ |
| Posttraumatic stress disorder treatment | 0.799 | 0.001 | 0.811 | 0.000 | 0.809 | 0.000 |
| Phosphodiesterase 10A inhibitor | 0.541 | 0.002 | 0.566 | 0.002 | 0.524 | 0.002 |
| Phosphodiesterase X inhibitor | 0.541 | 0.002 | 0.566 | 0.002 | 0.524 | 0.002 |
| Complement factor D inhibitor | 0.410 | 0.119 | 0.337 | 0.178 | NA | NA |
| Sarcosine oxidase inhibitor | 0.801 | 0.004 | 0.179 | 0.034 | NA | NA |
| Malate oxidase inhibitor | 0.452 | 0.026 | 0.285 | 0.126 | NA | NA |

**Table 2**: PASS online biological activities' assessments for compounds **3d-e** and **5.**

| Biological Activity | Compd# 1 | | Compd# 3a | | Compd# 3b | | Compd# 3c | |
|---|---|---|---|---|---|---|---|---|
| | $P_a$ | $P_i$ | Pa | Pi | Pa | Pi | Pa | Pi |
| Posttraumatic stress disorder treatment | 0.909 | 0.010 | 0.946 | 0.004 | 0.933 | 0.006 | 0.808 | 0.034 |
| Phosphodiesterase 10A inhibitor | 0.900 | 0.002 | 0.740 | 0.005 | 0.740 | 0.005 | 0.618 | 0.014 |
| Phosphodiesterase X inhibitor | 0.848 | 0.020 | 0.928 | 0.004 | 0.912 | 0.006 | 0.837 | 0.023 |
| Complement factor D inhibitor | 0.817 | 0.003 | NA | NA | NA | NA | NA | NA |
| Sarcosine oxidase inhibitor | 0.799 | 0.004 | 0.752 | 0.006 | 0.752 | 0.006 | 0.535 | 0,049 |
| Malate oxidase inhibitor | 0,787 | 0,019 | 0,773 | 0,024 | 0,711 | 0,038 | 0,658 | 0,053 |

## 4. Conclusion:

In conclusion, we successfully conducted an azo coupling reaction involving 2-cyano-*N*′-(thiophen-2-ylmethylene)acetohydrazide **1** with diazonium salts derived from aromatic amines and heterocyclic amines **2a-e**, **4**, and **6**, leading to the synthesis of novel hydrazono thiophene derivatives **3a-e**, **5**, and **7**, These compounds were stutdied *via* DFT simulations to assess their stability and reactivity. Furthermore, the predicted biological activities of compounds **1**, **3a-e** and **5** were screened using pass online software. It's important to note that this study represents a preliminary investigation, as further research on the biological activities of

these compounds is currently ongoing and will be published in due course**..**

## 5. References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