

Synthesis of Asymmetric Pyrazoline Derivatives from Phenylthiophenechalcones; DFT Mechanistic Study

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ABSTRACT. New phenylthiophenechalcones, 1-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl)prop-2-en-1-one (**3a**) and 3-(5-phenylthiophen-2-yl)-1-(4-(piperidin-1-yl) phenyl) prop-2-en-1-one (**3b**) were synthesized, next, their treatment with thiosemicarbazide in ethanol afforded their pyrazoline derivatives (**4a**) and (**4b**), respectively. The molecular structures of the synthesized compounds were confirmed via elemental analysis, FT-IR, ¹H, ¹³C NMR and mass spectroscopy. The geometrical elucidation of four suggested conformers has been studied for these compounds. DFT calculations have been performed to study the stability and the structural parameters of the predicted conformers and revealed that orientation of the biphenyl and the phenylthiophene moieties affect the stability of the estimated conformers of the synthesized chalcones and pyrazoline. Moreover, two reaction mechanisms have been proposed to illustrate the reaction products and the DFT calculations have been used to confirm the reaction mechanism of the pyrazoline compounds.

Key words: Phenylthiophenechalcone, Conformers, Carbothioamide, Pyrazole, DFT, Mechanistic study

INTRODUCTION

Over the past decades, research has been focused on α,β -unsaturated ketone which have numerous therapeutic effects, such as, cytotoxicity,¹⁻³ antimitotic,⁴ antimutagenic,⁵ antibacterial, antiviral,⁶ anti-inflammatory,^{4,7,8} and hepatoprotective activities.⁹ Some researchers studied the properties of pyrazolines and pyrazole derivatives forming a cyclic moiety of hydrazine and found high activity.^{10,11} Moreover chalcones, are considered as a key to flavones in flavonoid biosynthesis that is because, in open chain flavonoids two aromatic rings are joined by three carbons with α - β unsaturated system.¹² Also, implementation a pyrazole ring in the chalcones increases the cytotoxic activity towards a series of human cancer cell lines.¹³ In general, acid- or base-catalyzed Claisen-Schmidt condensation of aldehyde and ketone, followed by dehydration is commonly used to synthesize chalcones.¹⁴ In the aromatic chalcones which contain keto-ethenyl group (-CO-CH=CH) may exist either in *cis* or *trans* form.¹⁵ Delocalization of π electrons in the conjugated double bond system reduces its electron density and makes it an intermediate for the synthesis of distinct heterocycles. On the other hand, density functional theory (DFT) was known as an effective tool for providing theoretical guidance into chemical reactivity, and it can help in the expectation of the reaction

mechanism as it generate mechanical quantity descriptors used in quantitative structure-activity relationship.¹⁶⁻²⁸

Such findings have led us to synthesize a novel of phenylthiophene chalcones and its corresponding pyrazoline derivatives and to focus on the reaction mechanism depending on DFT calculations. DFT calculations will be discussed to foresee the molecular confirmations²³⁻²⁵ as well as their thermal parameters. In addition, these calculations will be used to explain mechanistic steps for the formations of pyrazoline derivatives. Density functional theory (DFT) is recognized as an important tool to provide theoretical response to chemical reactivity, which affects the biological properties of many drugs, on the other hand, DFT has been shown to illustrate valuable descriptions of molecular structure, mechanistic study, vibrational frequencies, and the energetics of chemical reactions to investigate the electronic properties of many chalcones. Many DFT studies routinely provide chemical reactivity, but no such studies have been performed on thiophene chalcones.^{27,28}

EXPERIMENTAL

Computational Method

Gaussian 09 software was used for DFT calculations for the studied compounds.²⁹ DFT methods using B3LYP 6-

31G (d, p) basis set was selected for the calculations. The geometries were optimized by minimizing the energies with respect to all geometrical parameters without imposing any molecular symmetry constraints. The structures of the optimized geometries had been drawn with Gauss View.³⁰ Also, calculations of frequencies were carried out by the same level of theory. The frequency calculations showed that all structures were stationary points in the geometry optimization method with none imaginary frequencies.

Materials and Instrumentations

All melting points were measured using Gallenkamp melting point device. Fourier Infrared (Ft-IR) Spectra were recorded using Perkin Elmer FT-IR Spectrum Nicolet IS10. Nuclear Magnetic Resonance Spectra were recorded on a Bruker NMR spectrometer, ¹H spectrum was run at 300 MHz in deuterated DMSO as a solvent, the chemical shift (δ) was reported in ppm and the coupling constant (J) values in Hertz and the ¹³C NMR spectrum was run at 75 MHz in deuterated DMSO. The reaction courses were monitored by thin layer chromatography (TLC) on silica gel plates and spots were visualized by UV lamp at 250-380 nm. All the chemicals were purchased from Sigma–Aldrich.

Synthesis of 3-(5-phenylthiophen-2-yl)prop-2-en-1-ones 3(a, b)

To a solution of 5-phenylthiophene-2-carbaldehyde (**1**) (0.01 mol, 1.9 mL) and 1-(biphenyl-3-yl) ethanone (**2a**) or 1-(4-(piperidin-1-yl) phenyl) ethanone (**2b**) (0.01 mol, 2 mL) in absolute ethanol (40 mL), potassium hydroxide solution (3 mL, 40%) was added portion-wise. The mixture was stirred for 2 h. The solid product was collected by filtration, washed with water, dried and finally crystallized from ethanol to give compounds **3a** and **3b**, respectively.

1-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl) prop-2-en-1-one (3a). Yellow crystals (yield 82%), m.p. > 300 °C; IR (KBr, ν cm⁻¹): 1638 (C=C) and 1677 (C=O); ¹H NMR (DMSO-*d*₆) δ ppm: 7.17-8.49 (m, 14H, ArH), 7.29-7.51 (d, 1H, J = 7.2 Hz, olefinic hydrogen), 7.85-7.87 (d, 1H, J = 7.2 Hz, olefinic hydrogen), 7.94-7.97 (d, 1H, J = 7.6 Hz, thiophene H), 8.20-8.23 (d, 1H, J = 10.0 Hz, thiophene H); m/z: 365.47 (M-1, 26.13%), Anal. Calcd for C₂₅H₁₈OS (366.1): C, 81.93; H, 4.95. Found: C, 81.91; H, 4.90.

3-(5-phenylthiophen-2-yl)-1-(4-(piperidin-1-yl)phenyl) prop-2-en-1-one (3b). Yellow crystals (yield 78%), m.p. 210-2 °C; IR (KBr, ν cm⁻¹): 1630 (C=C) and 1657 (C=O); ¹H NMR (DMSO-*d*₆) δ ppm: 1.53-1.60 (m, 6H, piperidine H), 3.34-3.41 (m, 4H, piperidine H), 6.97-7.03 (d, 2H, J = 8 Hz, ArH), 7.45-7.67 (m, 5H, ArH), 7.37-7.39 (dd, 1H, J

= 8 Hz, olefinic H), 7.77-7.83 (d, 2H, J = 8 Hz, ArH), 7.95-7.97 (dd, 1H, J = 8 Hz, olefinic H), 7.82-7.84 (d, 1H, J = 7.6 Hz, thiophene H), 7.99-8.01 (d, 1H, J = 10 Hz, thiophene H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm: 185.94 (C=O), 154.34, 146.56, 146.10, 139.95, 139.11, 135.04, 134.04, 133.57, 131.05 (2C), 129.76, 128.98, 126.60, 126.07, 125.57, 121.12, 113.49, 108.87, 48.17 (2C), 25.37(2C), 24.44; m/z: 372.18 (M-1, 7.01%); Anal. Calcd for C₂₄H₂₃NOS (373.5): C, 77.18; H, 6.21; N, 3.75. Found: C, 77.21; H, 6.30; N, 3.77.

Synthesis of 4, 5-dihydro-1H-pyrazole-1-carbothioamide 4(a, b)

To a solution of KOH (0.025 mol) and chalcone **3 (a, b)** (10 mmol, 3.7 g) in ethanol (50 ml), thiosemicarbazone (10 mmol, 0.9 g) was added. The reaction mixture was refluxed for 6 hrs. The resulting solid was filtered, washed with water, dried and recrystallized from EtOH/DMF to give pyrazole derivatives **4 (a, b)**.

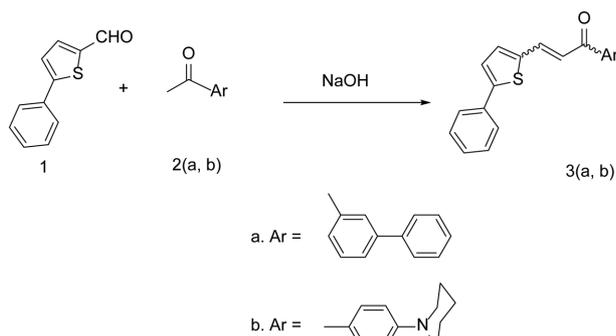
5-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (4a). Yellow crystals (yield 70%), m.p. 210-212 °C; IR (KBr, ν cm⁻¹): 3241 & 3134 (NH₂), 1584 (C=N) and 1259 (C=S); ¹H NMR (DMSO-*d*₆) δ ppm: 3.8-4.0 (m, 1H, H_a of pyrazole), 4.8-5.0 (m, 1H, H_b of pyrazole), 6.2-6.4 (m, 1H, H_c of pyrazole), 7.02-7.90 (m, 14H, ArH), 7.94-7.96 (d, 1H, J = 7.6 Hz, thiophene H), 8.01-8.03 (d, 1H, J = 10 Hz, thiophene H), 8.5 (s, 2H, NH₂); m/z: 438.52 (M-1, 4.62%); ¹³C NMR (75 MHz, DMSO-*d*₆) δ ppm: 198.51 (C=S), 161.13, 146.06 (2C), 137.01 (2C), 135.06 (2C), 129.90 (2C), 129.63 (2C), 127.82 (6C), 126.31 (4C), 121.19 (2C), 120.13, 40.62; m/z: 372.18 (M-1, 7.01%); Anal. Calcd for C₂₆H₂₁N₃S (439.6): C, 71.04; H, 4.82; N, 9.56. Found: C, 71.14; H, 4.83; N, 9.50.

3-(5-phenylthiophen-2-yl)-5-(4-(piperidin-1-yl)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (4b). Brown crystals, (yield 87%), m.p. 160-162 °C; IR (KBr, ν cm⁻¹): 3376 & 3266 (NH₂) and 1532 (C=N) and 1242 (C=S); ¹H NMR (DMSO-*d*₆) δ ppm: 1.56-1.60 (m, 6H, piperidine H), 3.28-3.34 (m, 4H, piperidine H), 4.1-4.49 (m, 2H, H_a & H_b of pyrazole), 5.10-5.3 (m, 1H, H_c of pyrazole), 6.94-6.97 (d, 2H, J = 8.0 Hz, ArH), 7.36-7.56 (m, 5H, ArH), 7.70-7.73 (d, 2H, J = 8.0 Hz, ArH), 7.93-8.09 (d, 1H, J = 7.6 Hz, thiophene H), 8.28-8.29 (d, 1H, J = 10.0 Hz, thiophene H), 8.63 (s, 2H, NH₂); m/z: 446.2 (M⁺, 1.02%), Anal. Calcd for C₂₅H₂₆N₄S₂ (446.6): C, 67.23; H, 5.87; N, 12.54. Found: 67.20; H, 5.85; N, 12.51.

RESULTS AND DISCUSSION

Two new chalcones were synthesized by condensing 5-

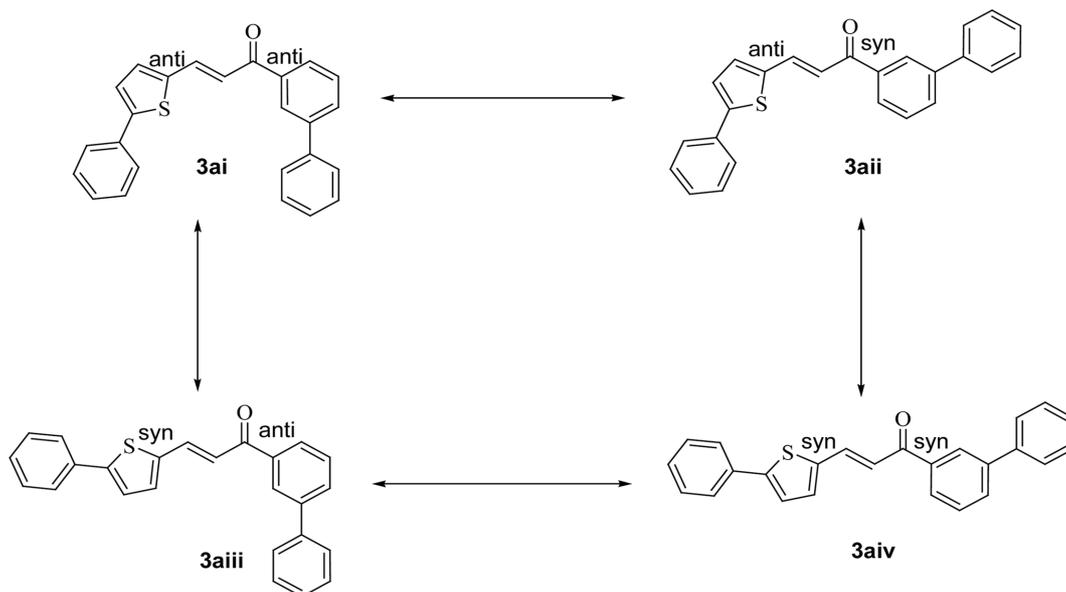
phenylthiophene-2-carbaldehyde (**1**) with 1-(biphenyl-3-yl)ethanone (**2a**) or 1-(4-(piperidin-1-yl) phenyl)ethanone (**2b**) in ice bath in absolute ethanol (40 mL), potassium hydroxide solution (3 ml, 40%) was added portion-wise. The mixture was stirred for 2 h. The solid product was collected by filtration, washed with water, dried and finally crystallized from ethanol to give prop-2-en-1-ones **3a** and **3b** in pure state and high yield. The structure of the new synthesized chalcones was confirmed by spectroscopic data



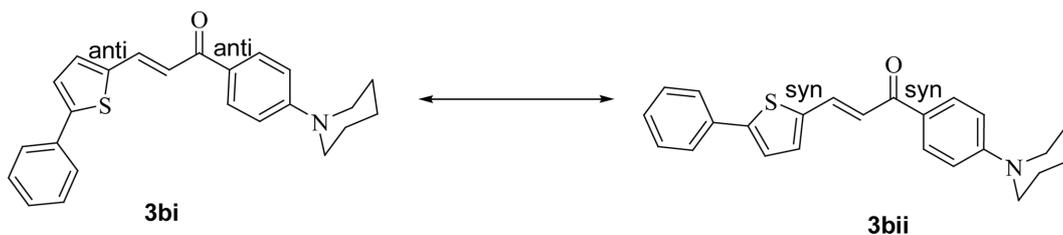
Scheme 1. Synthesis of chalcones **3 (a, b)**.

as well as elemental analysis. FT-IR data revealed that the absorption bands in the region 1630-1677 cm^{-1} corresponding to the conjugated carbonyl system of chalcones. The ^1H NMR spectra of **3a**, **3b** exhibit the presence of doublet signals at $\delta = 7.29$ - 7.97 ppm due to the olefinic hydrogen.

Four conformers have been suggested as products of Aldol condensation reactions, four isomers for **3a**, *Scheme 2*, and two for **3b**, *Scheme 3*. DFT calculations have been performed to study the stability of the estimated conformers [**3a (i-iv)**, **3b (i, ii)**]. The DFT calculations were carried out in gas phase with B3LYP 6-311G basis set. The absence of the imaginary frequency for all optimized structures is an evidence of their stability. The thermal parameters have been summarized in *Table 1*. The results of the theoretical calculations for the four conformers **3ai-iv** revealed that the conformer **3aii** is the most stable isomer and **3bii** for the other derivative. However, the energy difference between the most stable isomer and the least stable one is 2.03 Kcalmol^{-1} for **3a** and 157.71 Kcalmol^{-1} for **3b**. The lower enthalpy value (ΔH) between isomers of **3a** is an evidence of their presence in equilibrium. Both compounds



Scheme 2. Structures of conformers **3a**.



Scheme 3. Structures of conformers **3b**.

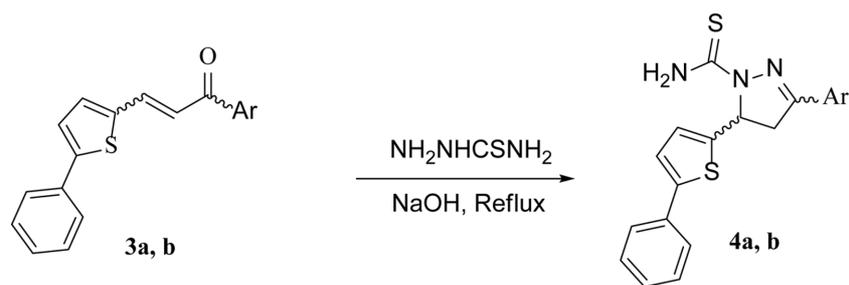
showed the same geometrical structure of the stable isomer, *syn* geometrical configuration of the C=O with aryl group and anti-configuration of the thiophene ring with the β -unsaturated bond. These results could be explained in terms of the formation of the proper geometrical structure for the maximum conjugation. Fig. 1 (in Supplementary Material) shows the geometrical structures of the most stable conformers of **3a** and **3b**. The figure emphasizes the twisting of the phenyl ring of the biphenyl part as well as the phenyl ring attached to the thiophene, this could illustrate the non co planarity of the investigated chalcones.

Compound **3a** and **3b** were treated with thiosemicarbazide in presence of NaOH in refluxing ethanol to afford thioamide derivatives **4a** and **4b**, Scheme 4. The IR spectra of the latter compounds showed absorption bands at 1584-1532 cm^{-1} corresponding to C=N group and at 1242-1259 cm^{-1} stretching band of C=S group, and the absorption band of NH_2 group at 3376-3134 cm^{-1} . Its $^1\text{H-NMR}$ spectrum showed the signals of H_a , H_b , and H_c of pyrazole ring as multiplet in

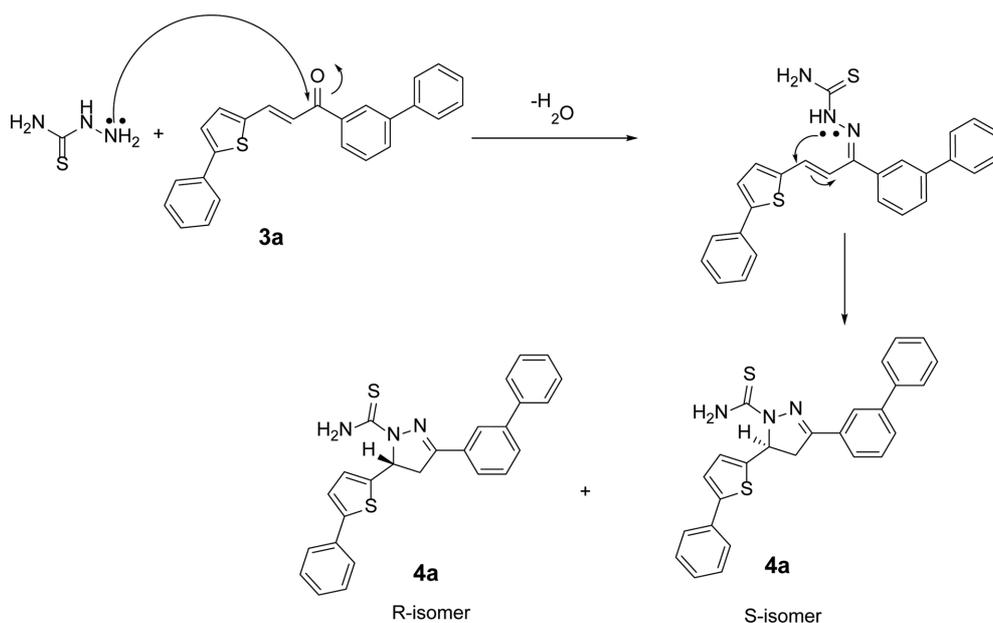
the region of 3.26-3.40, 3.95-4.8 and 5.88-6.4 ppm, respectively, and the weak signals at 8.5-8.6 due to NH_2 protons.

The reaction mechanism of the addition of thiosemicarbazide to chalcones is studied for **3a** as representative example. The mechanism could involve the intermediate formation of thiosemicarbazone and subsequent nucleophilic addition of N-H to the β -unsaturated carbon to give the pyrazole ring; condensation followed by Michael type reaction mechanism, Scheme 5.³¹ Moreover, there is another reaction mechanism that could compete, Michael type reaction on the β -unsaturated carbon atom followed by nucleophilic attack on the carbonyl group, Scheme 6.

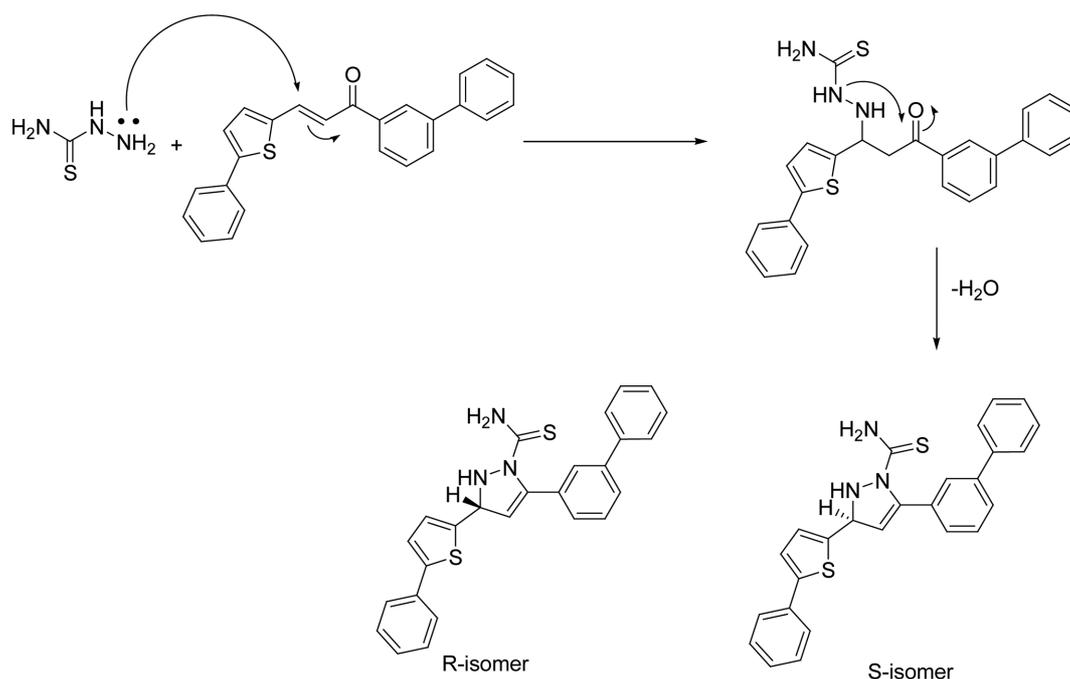
It has been reported by Hawaiz *et al.*³² that the preparation of thiocarbamoyl pyrazoline derivatives from substituted chalcones and thiosemicarbazide were achieved in high yields on the basis of the condensation then Michael type addition reaction mechanism. The DFT calculations have been used to confirm the reaction mechanism. The atom polar tensor (APT) charges are calculated at the same



Scheme 4. Synthesis of pyrazole derivative **4a, b**.



Scheme 5. Condensation followed by Michael type reaction mechanism.

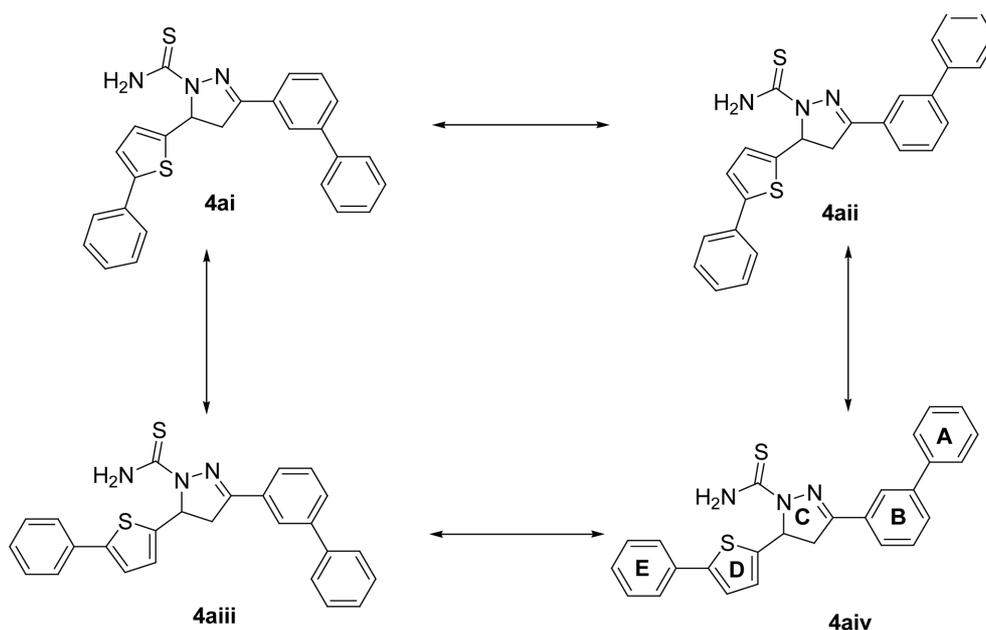


Scheme 6. Michael type followed by condensation reaction mechanism.

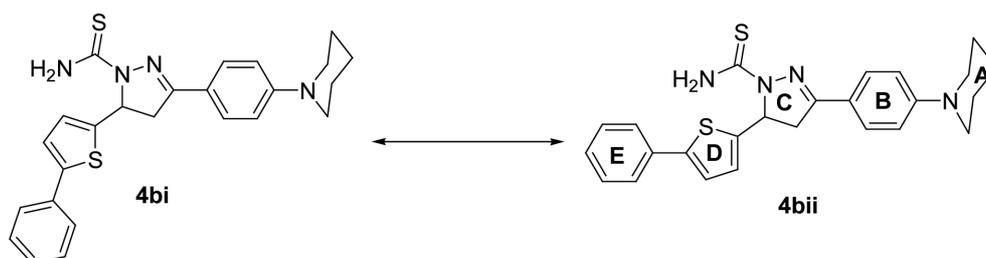
method with the same base set, *Table 2, Fig. 2* (in Supplementary Material). According to the calculated APT charges, the most significant variations of the APT charges at the different atomic sites of the studied chalcones are due to change in the position and the type of the attached ring of the ketone. The highest positively charged centers is the C1, carbonyl carbon, of compounds **3aii** (1.542513) and **3bii** (1.694828). Consequently, the nucleophilic attack of the NH_2 of the thiosemicarbazide might be started on the carbon of the carbonyl group of the highest positive charge rather than the β -unsaturated carbon atom (C4), then by the elimination of one water molecules affords the thiosemicarbazone. Successfully, a second nucleophilic addition of the NH group to the β -unsaturated carbon atom (C4) gives the corresponding pyrazole derivatives **4aii** and **4bii**. This mechanism is a good evidence of the condensation then Michael type mechanism, *Scheme 5*, rather than Michael type then the condensation mechanism, *Scheme 6*.

The reaction of chalcones with thiol compounds is reported to give two diastereomeric adducts.³³ Stereochemical investigation of thiol addition reaction of hydroxychalcone and its bis-Mannich derivative was studied. In these reactions, the nucleophilic addition to the beta-carbon atom of the enone moiety generates a new chiral centre. Due to the chiral centres, formation of the enantiomeric forms of the new chiral centre results in formation of two diastereomeric adducts. Accordingly, the observed diastereoselectivity

is reflecting enantioselectivity of the addition reactions. A series of bi- and tricyclic 4,5-dihydropyrazoles were reported to afford two diastereoisomers. The reaction of chalcones with semicarbazide gave only one diastereoisomer.^{10,32} In our present investigation, many isomers (conformational as well as stereo-isomers) could be expected as products of this reaction. Compound **4a** is expected to be in four major conformers **4a (i-iv)** *Scheme 7*, however, **4b** is expected to be in only two, **4b (i, ii)** *Scheme 8*. Since the reaction created a chiral centre, each conformer could exist in two stereoisomers *R* and *S*. The thermal parameters tabulated in *Table 3* were calculated by DFT method at B3LYP 6-31G (d, p) basis set. The *S* and *R* configurations of **4a** have been calculated, and only the *S* isomer of **4b** was calculated. The results of the DFT calculations of the thermal parameters revealed that the pyrazoles **4aiv** and **4bii** are the least in energy. Regardless of the position of the ring A or its saturation issue, the same geometrical isomer was obtained for both compounds **4aiv** and **4bii**. This result might be explained in terms of the steric and strain effects, *Fig. 3* (in Supplementary Material). Moreover, the absolute configuration of these diastereoisomers has insignificant effect on the stability. However, the *S* isomer is more stable than the *R* one by 7.7 Kcalmol^{-1} . This DFT result is confirmed by the reported X-ray structure of its analogues pyrazoles [10], as single crystal X-ray analysis showed the absolute (*S*)-configuration of the products of these reactions.



Scheme 7. Conformers' structures of pyrazole derivative, **4a**.



Scheme 8. Conformers' structures of pyrazole derivative, **4b**.

Table S4 (in Supplementary Material) showed selected structure parameters of optimized geometry of stable *S* isomers of **4aiv** and **4bii** calculated by B3LYP/6-311G method. The bond length of C1-C2 is also affected by the conjugation of the phenyl ring B to have double bond character that decreases the bond length to be in the range of 1.46 Å. Neither the attachment of the saturated piperidine ring nor its position has a significant effect on the bond length. Moreover, there is insignificant effect of the absolute configuration of the chiral center. Additionally, C2-N6 has a single bond character, its bond length is in between 1.30 Å instead of 1.25 Å for an un-conjugated C=N bond. The long bond lengths of C10-C12 and C22-C26 (1.46 Å) is an evidence of the twisting of the phenyl rings A and E of compounds **4aiv R** and **4aiv S**. The co-planarity of the aromatic π -bonds decreases the C-C bond length to be lower than 1.4 Å. Another confirmation of these results is achieved by calculations of bond angles for the studied compounds. They showed deviation from the normal trigonal planer for

all the unsaturated groups which confirm some single bond character for those groups. Moreover, the dihedral angles showed the degree of twisting of the rings A and E with respect to the conjugated rings B and D; respectively.

On the other hand, a detailed study of the spectrophotometric absorption of the most stable compounds has been achieved either experimentally or theoretically. The experimental UV-Vis spectrum of the most stable conformers of the prepared compounds **3a**, **b** and **4a**, **b** in alcoholic solutions was recorded in the region of 200-550 nm, Fig. S4 (in Supplementary Material). Moreover, energy levels of the frontier molecular orbitals (FMOs), the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) were calculated by the same method at the same set. The calculated energy gap between HOMO and LUMO orbitals was tabulated in Table S5 (in Supplementary Material). The maximum absorbance wavelengths (λ_{max}) were also calculated and compared with the experimentally measured one. The experimental and the

theoretical results of the spectrophotometric data were in comparable values. It is obvious that the attachment of pyrazine ring of compound **3a** and **4a** afforded bathochromic shift in case of the chalcone derivatives **3** and hypsochromic shift for pyrazoline derivatives **4**, this result could be illustrated in terms of the degree of conjugation.

CONCLUSIONS

Aldol condensation of 5-phenylthiophene-2-carbaldehyde (**1**) with 1-(biphenyl-3-yl)ethanone (**2a**) or 1-(4-(piperidin-1-yl)phenyl)ethanone (**2b**) in ice bath using basic condition produced in pure state and high yield of prop-2-en-1-ones **3a** and **3b**, which then reacted with thiosemicarbazide to form its pyrazoline derivatives (**4a**) and (**4b**). The structures of the newly synthesized compounds were confirmed by spectroscopic data as well as elemental analysis. The DFT calculations revealed that the most stable conformers are (**3aii**) and (**3bii**), also confirmed the reaction mechanism. The stability and the structural parameters of the predicted conformers revealed that orientation of the biphenyl and the phenylthiophene moieties affect the stability of the estimated conformers of the synthesised chalcones and pyrazoline.

Supplementary Materials. The following are available online, Fig. 1: The geometrical structure of **3aii** and **3bii**, Fig. 2: APT charges of **3aii** and **3bii**, Fig. 3: The geometrical structures of the most stable conformers of pyrazole derivative **4a, b**, Fig. 4: Experimental Ultraviolet visible spectrum of the compounds **3a, b** and **4a, b**, Fig. 5: ¹H NMR of 1-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl)prop-2-en-1-one (**3a**), Fig. 6: ¹H NMR of 3-(5-phenylthiophen-2-yl)-1-(4-(piperidin-1-yl)phenyl)prop-2-en-1-one (**3b**), Fig. 7: ¹H NMR of 5-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**4a**), Fig. 8: ¹H NMR of 3-(5-phenylthiophen-2-yl)-5-(4-(piperidin-1-yl)phenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**4b**), Fig. 9: ¹³C NMR of 3-(5-phenylthiophen-2-yl)-1-(4-(piperidin-1-yl)phenyl)prop-2-en-1-one (**3b**), Fig. 10: ¹³C NMR of 5-(biphenyl-4-yl)-3-(5-phenylthiophen-2-yl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**4a**); Table 1: Thermal parameters (Hartree/Particle) of **3a (i-iv)** and **3b (i, ii)**, Table 2: APT charges of **3aii** and **3bii**, Thermal parameters (Hartree/Particle) of **R** and **S** of **4a(i-iv)** and **S** of **4b (i, ii)**, Table 4: Selected structure parameters of optimized geometry of stable *S* isomers of **4aiv** and **4bii** calculated by DFT B3LYP/6-311G method.

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Conflicts of interest. Authors declare “no conflicts of interest”.

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