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Synthesis, reactions and DFT calculations of novel bis(chalcones) linked to a thienothiophene core through an oxyphenyl bridge

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A synthesis of novel isomeric bis(chalcones) based-thienothiophene and study of their synthetic utilities as building blocks for novel bis(dihydroisoxazoles), bis(dihydropyrazoles) and bis(dihydropyrimidines) each linked to a thienothiophene core through an oxyphenyl bridge is reported. Density functional theory (DFT) calculations at the B3LYP/6-31G level of theory have been carried out to investigate the equilibrium geometry of the novel isomeric chalcones **7** and **10**. Moreover, total energy, energy of the HOMO and LUMO and Mullikan atomic charges were calculated. In addition, the dipole moment and orientation of the two π-isoelectronic chalcones **7** and **10** have been measured and their interactions with hydrazine hydrate to form dihydropyrazoles have been studied.

1. Introduction

Chalcones are very interesting molecules due to their diverse applications in different fields. They display a wide range of pharmacological properties, including antimutagenic and antitumor-promoting activities, antibacterial, anti-inflammatory, antiulcerative, and hepatoprotective activities.[1] They are also useful in materials science fields such as nonlinear optics,[2] optical limiting,[3] Langmuir films, and photoinitiated polymerization.[4] Chalcones are also useful intermediates for the synthesis of five-, six- and seven-membered heterocyclic compounds.[5]

Heterocyclic compounds containing the pyrazole unit have a broad spectrum of biological activities, such as monoamine oxidase inhibitor,[6] anticonvulsant,[7] antibacterial,[8] hypotensive,[9] antipyretic[10] and anti-inflammatory[11] activity. Moreover, the pyrazole nucleus represent the core unit in a variety of drugs (Fig. 1) such as celecobix (Celebrex) **I**, sildenafil (Viagra) **II**, and rimonabant (Acomplia) **III**.[12]

In addition, isoxazoles are reported to show potent anti-tuberculosis,[13] antimicrobial[14] and anti-inflammatory activities.[15]

The literature survey indicated also that compounds encompassing pyrimidines nucleus exhibited a wide range of pharmacological activities including antifungal,[16] anti-inflammatory,[17] antihypertensive,[18] antiviral,[19] antidiabetic,[20] antioxidant,[21] anticancer activities.[22] During the last two decades several pyrimidine derivatives **IV–VII** (Fig. 2) have been reported as antibacterial drugs.[23,24]

In addition, considerable attention has been focused on thienothiophenes due to their interesting biological activities. They have been tested as potential antitumor, antiviral, antibiotic and antiglaucoma drugs or as inhibitors of platelet aggregation.[25] Thienothiophenes are also of potential interest as π-electron donors and have potential applications in a wide variety of optical and electronic systems.[26]

Furthermore, attention has been increasingly paid in recent years to the synthesis of bis-heterocyclic for their numerous applications as electrical materials,[27] chelating agents, and metal ligands.[28] They also exhibit various biological activities including antibacterial, fungicidal, tuberculostatic, and plant growth regulative properties.[29] Moreover, compounds including bis-heterocyclic moieties were encountered in many bioactive natural product and recent reports showed that among libraries of derivatized heterocycles, the most active library compounds had a bis-heterocyclic structure.[30] Some bis-heterocycles **VIII** and **IX** (Fig. 3) exemplified by LU 79553 and WMC-26, both showing high effectiveness against tumor xenografts *in vivo*.[31]

The estimation of relative energies of molecules is very important both in theoretical studies and in the investigation of their chemical reactivity as well as to understand the possible interactions of reactants. Theoretical calculation can give an insight into some of these issues since it can determine the structure of the molecules, the active sites, and atomic level description of interaction mechanisms on the intermediate formation involved in a given reaction.[32–35] Recently, because of their high accuracy theoretical calculations have also significantly contributed to drug discovery and design.[36–38]

In connection with these findings, we report herein on the synthesis of some novel bis(chalcones) and studied their synthetic utility as versatile synthons for the synthesis of novel

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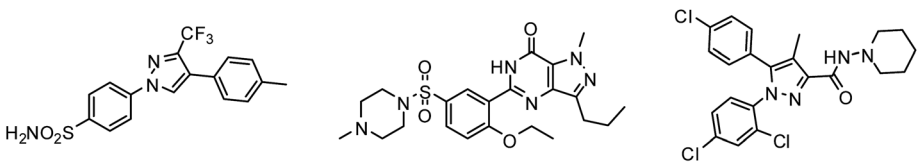


Fig. 1 Some drugs incorporating pyrazole ring.

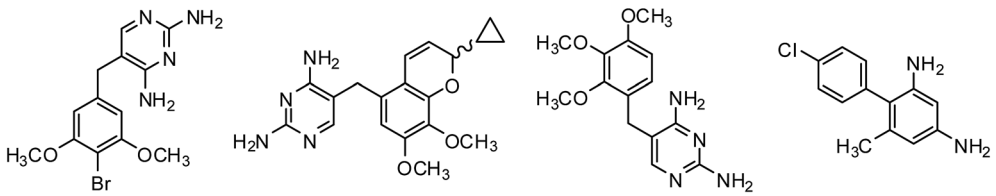


Fig. 2 Some pyrimidine derivatives as antibacterial drugs.

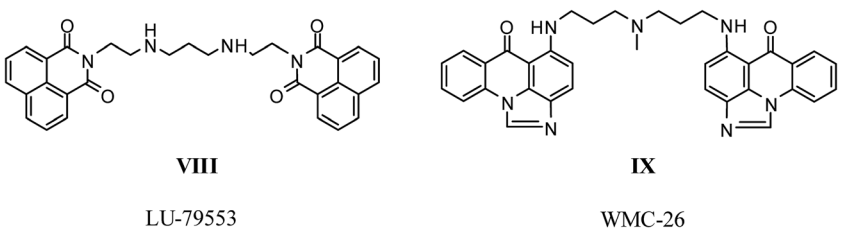


Fig. 3 Some bis-heterocycles with anti-tumor activity.

bis(dihydroisoxazoles), bis(dihydropyrazoles) and bis(dihydropyrimidines) each linked to a thienothiophene core through an oxyphenyl bridge. DFT calculations have also been carried out to investigate the equilibrium geometry of the synthesized chalcones as well as their interaction with binucleophilic reagents.

2. Results and discussion

2.1. Synthesis

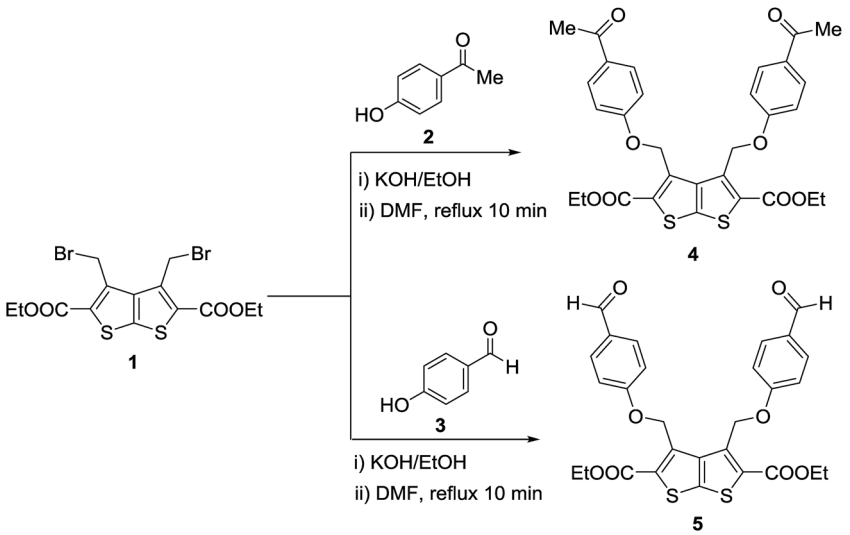
Very recently, we reported the synthesis of diethyl 3,4-bis-(bromomethyl)-5-(ethyloxycarbonyl)thieno[2,3-*b*]thiophene-2-carboxylate **1** [39] and studied its use as a key intermediate for the synthesis of the novel bis(acetophenone) **4** as well as the novel bis(aldehyde) **5**. The latter compounds can be prepared by the reaction of **1** with *p*-hydroxyacetophenone **2** or *p*-hydroxybenzaldehyde **3**, respectively, in basic media[40] (Scheme 1).

The synthetic utility of **4** and **5** as precursors for novel bis-(chalcones) were thus investigated. A classical method for synthesis of chalcones is Claisen–Schmidt condensation in which the appropriate aldehyde reacted with the corresponding acetophenone in the presence of aqueous alkaline bases[41,42] under conventional heating, microwave irradiation or ultrasound irradiation.[43]

Accordingly, we studied the synthesis of the bis(chalcone) **7** by Claisen–Schmidt condensation reaction of the bis(acetyl) compound **4** with benzaldehyde **6** in basic solution. Unfortunately, we were not be able to isolate a pure sample of the corresponding bis(chalcone) **7** neither by stirring at room temperature nor by heating at reflux and the reaction gave instead a mixture of products that cannot be handled.

The bis(chalcone) **7** can be prepared by another strategy, in which the chalcone **8** [44] was prepared separately by the reaction of *p*-hydroxyacetophenone **2** with benzaldehyde **6** in the presence of 20% alcoholic KOH solution. Reaction of the potassium salt of 4-benzoylvinylphenol **8** (obtained upon treatment of **8** with ethanolic KOH) with dibromo compound **1** in boiling DMF afforded **7** in 82% yield (Scheme 2).

Similarly, the bis(chalcone) **10** was prepared firstly by preparation of chalcone **11** [45] from the reaction of *p*-hydroxybenzaldehyde **3** and acetophenone **9** in presence of 20%



Scheme 1 Synthesis of bis(acetophenone) **4** and bis(aldehyde) **5**.

alcoholic KOH solution. This was then treated with dibromo compound **1** in the presence of anhydrous KOH in refluxing DMF to give **10** in 75% yield (Scheme 3).

It is noteworthy to mention that the direct synthesis of the bis(chalcone) **10** by treatment of the bis(formyl) compound **5** with acetophenone **9** under basic conditions was also unsuccessful.

Presence of α,β-unsaturated keto function makes chalcone very prone to undergo reactions with bidentate nucleophiles to give five-, six- and seven-membered heterocyclic compounds. This property of chalcone was exploited in the present work to generate pyrazole, isoxazole, and pyrimidine rings linked on 3,4-positions of a thienothiophene core through an oxyphenyl spacer. Thus, condensation of **7** with each of hydrazine hydrate **12** and semicarbazide **13** in refluxing acetic acid afforded the corresponding bis(4,5-dihydropyrazoles) **15** and **16** in 88 and 85% yields, respectively. Furthermore, reaction of bis(chalcone) **7** with thiosemicarbazide **14** in refluxing acetic acid afforded directly bis(3-aryl-4,5-dihydro-1*H*-pyrazole-1-thiocarboxamide) **17** in 80% yield (Scheme 4).

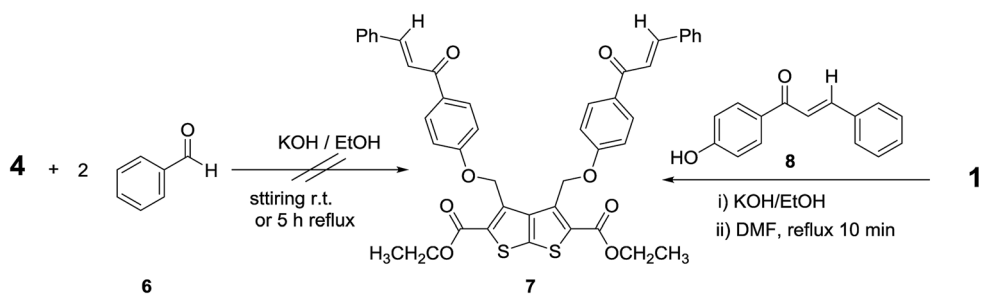
Bis(chalcone) **7** was further reacted with hydroxylamine hydrochloride **22** in alkaline medium to yield the corresponding isoxazoline derivative **23** in 68% yield (Scheme 4).

Moreover, cyclocondensation of **7** with urea **18** and thiourea **19** in refluxing ethanolic KOH solution gave bis(dihydroarylpyrimidin-2(1*H*)-one) **20** in 70% yield and pyrimidin-2(1*H*)-thione **21** in a 72% yield, respectively (Scheme 4).

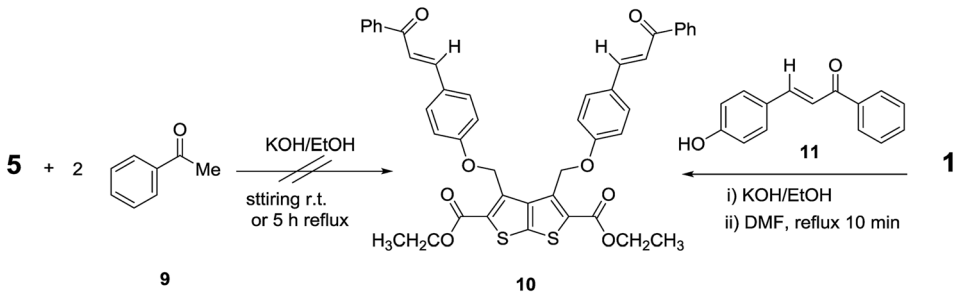
On the other hand, the cyclizations of bis(chalcone) **10** with hydrazine hydrate **12** or semicarbazide **13**, respectively, in refluxing acetic acid did not lead to the formation of pure samples of the corresponding bis(pyrazolines) **24** and **25**. The NMR spectra of the reaction products indicated the presence of characteristic signals for both of the target bis(dihydropyrazoles) as well as those of the precursors bis(chalcones). Repeated attempts to isolate pure samples of **24** and **25** by carrying out the reaction under a variety of conditions (varied temperatures, reaction time, *etc.*) were also unsuccessful.

The bis(dihydropyrazole) **24** was successfully prepared by another strategy, in which the dihydropyrazole **26** [46] was prepared separately by the condensation of chalcone **8** with hydrazine hydrate **12** in refluxing acetic acid. Subsequent reaction of **26** with 3,4-dibromo compound **1** in basic medium afforded **24** in 65% yield (Scheme 5).

Similarly, the bis(dihydropyrazole) **25** can also prepared in 72% yield firstly by reaction of chalcone **8** with semicarbazide **13** in refluxing acetic acid to give dihydropyrazole **27** in 60% yield followed by reaction with dibromo compound **1**.



Scheme 2 Synthesis of bis(chalcone) **7**.



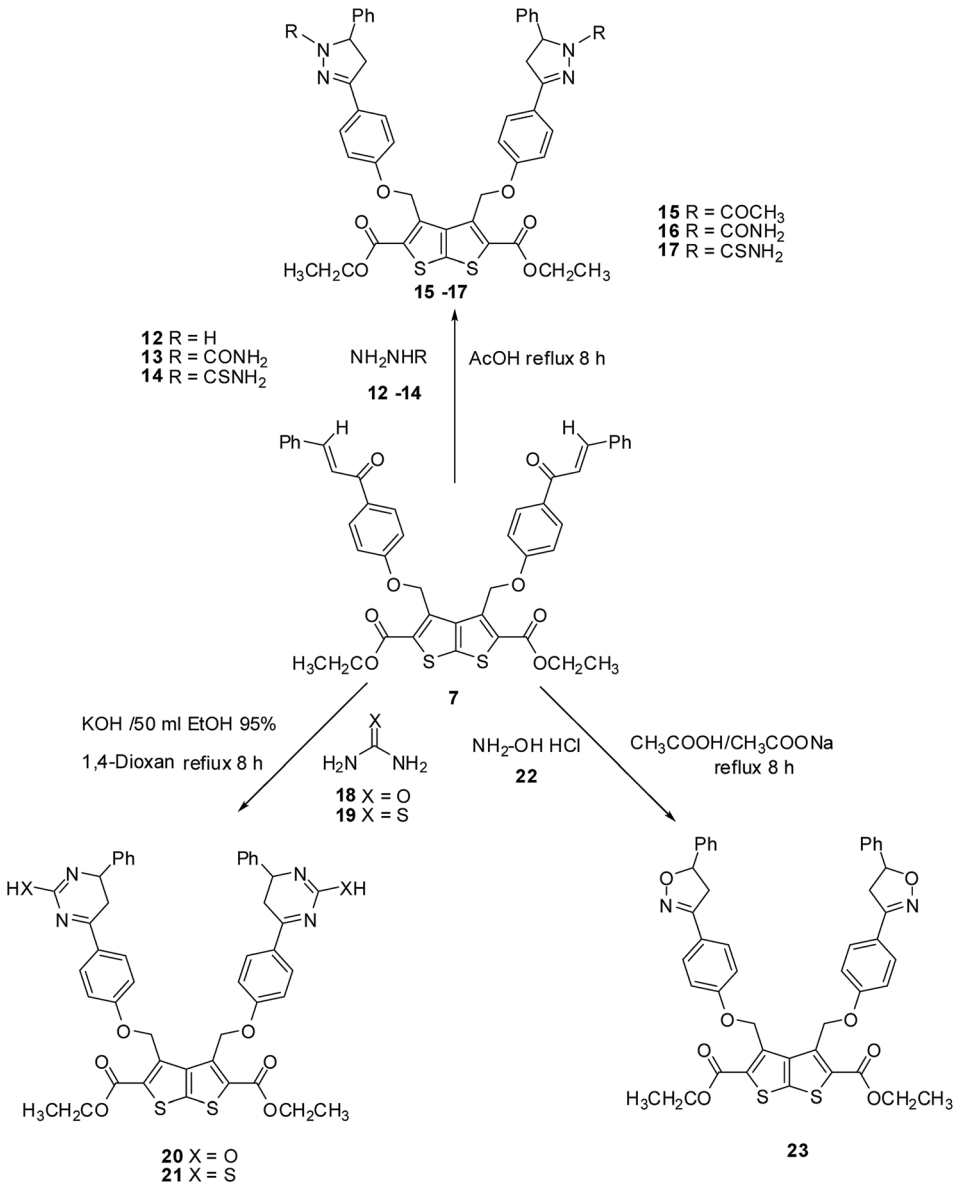
Scheme 3 Synthesis of bis(chalcone) **10**.

2.2. Spectroscopy

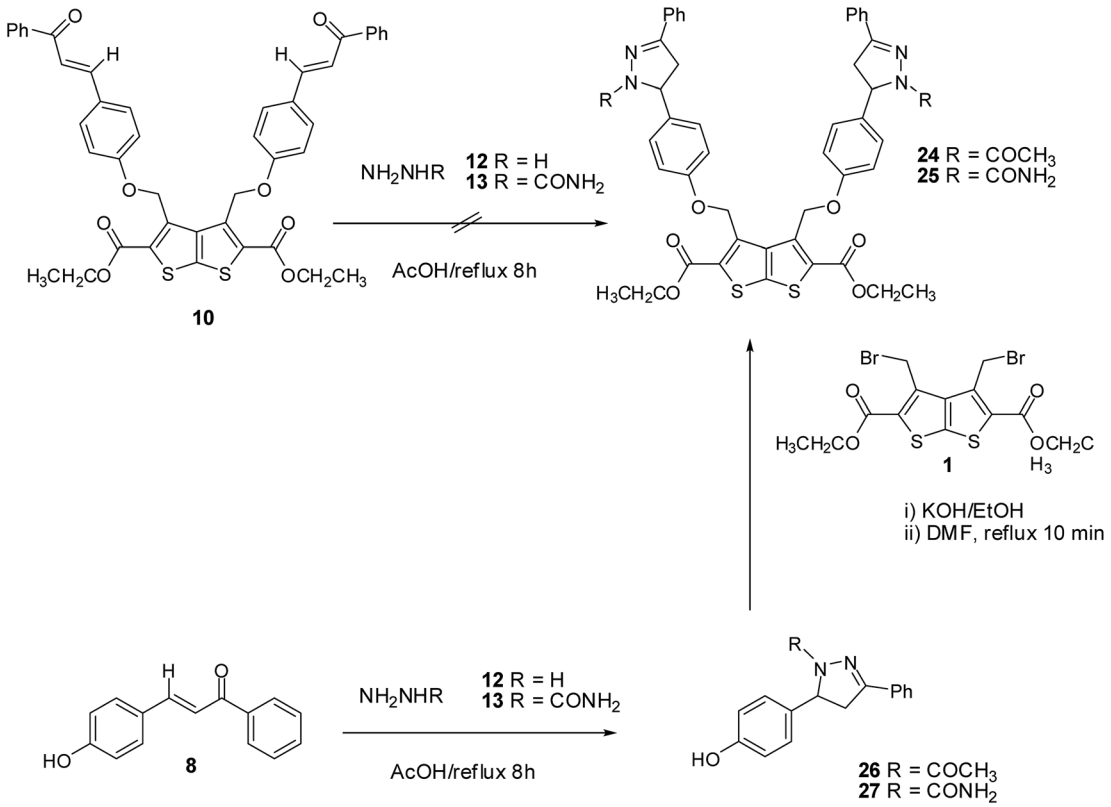
The chemical structures of the synthesized compounds were established by spectroscopic data (FTIR, ^{1}H NMR and ^{13}C NMR) and elemental analyses.

The IR spectra of bis-chalcones **7** and **10** reveal the presence of a strong bands at ν 1657 and 1658 cm^{-1}, respectively, assignable for the α,β-unsaturated C=O group.

^{1}H NMR spectra of compounds **7** and **10** exhibit each of the olefinic protons as a doublet signal at δ = 7.47–7.55 and 7.61–



Scheme 4 Reaction of bis(chalcone) **7** with different binucleophilic reagents.



Scheme 5 Synthesis of bis(dihydropyrazoles) **24** and **25**.

7.80 regions with a mutual coupling constant value $J = 15.2$ Hz. The large J value clearly reveals the *trans* geometry for the chalcones. All other protons were seen at the expected chemical shifts and integral values (*cf.* experimental part). The carbonyl carbon of the chalcones **7** and **10** appears at δ 187.60 and 189.34 ppm in their ^{13}C NMR spectra.

The IR spectra of dihydropyrazoles **16**, **17** and **25** reveal the presence of amino stretching vibration bands at ν 3423–3396 cm^{-1}. In addition, dihydropyrazoles **16** and **25** exhibit amidic carbonyl stretching vibration (at ν 1670–1664 cm^{-1}).

^{1}H NMR spectra of dihydropyrazoles **15–17**, **24** and **25** exhibit three signal sets each appears as a mutiplet assignable for nonmagnetically equivalent pyrazoline H_2C-4 (at δ 2.88–4.18, 3.64–4.30) coupled with each other and in turn with the vicinal methine proton HC-5 (at δ 5.38–6.25).

The IR spectrum of compound **20** showed an absorption band at (ν 3428 cm^{-1}) corresponding to the OH stretching frequency. On the other hand, the IR spectrum of compound **21** exhibited an absorption band at (ν 1448 cm^{-1}) corresponding to the C=S stretching frequency.

^{1}H NMR spectral features of dihydropyrimidines **20** and **21** are closely similar to those of **15–17** exhibiting non-magnetically equivalent methylene H_2C-5 as multiplet signals at δ 4.15–4.18 and 4.26–4.29 beside the multiplet dihydropyrimidine HC-6 at δ 6.22–6.26 ppm.

Moreover, compounds **15–17**, **20**, **21** and **23** also featured the methylene ether linkage OCH_2 as multiplet or two separate doublets signals at δ 4.89–5.94 regions although their precursors **7** and **10** exhibit singlet signals for these protons at $\delta = 5.67$ and 5.70 ppm, respectively. This suggests the generation of asymmetric centre (in the dihydropyrazole, dihydroisooxazole and dihydropyrimidine rings) and it is close enough to this CH_2 group to effect such splitting. Evidence from the ^{13}C NMR data for compound **16** indicate that it exists entirely as one stable conformer. On the other hand, the two methylene ether linkage OCH_2 resonance appears exceptionally as a singlet signal at $\delta = 5.57$ in compound **24**.

2.3. Molecular orbital calculations

DFT calculation at the B3LYP level of theory and 6-31G as a basis set can be used to explain why bis(chalcone) **7** reacted with hydrazine hydrate **12**, as representative example of binucleophilic reagents, to yield the corresponding bis(dihydropyrazole) **15** (88%). On the other hand, the cyclization of bis(chalcone) **10** with hydrazine hydrate did not lead to formation of pure sample of the corresponding bis(dihydropyrazole) **24**. Also, DFT calculation was employed to study the stability of the bis(dihydropyrazoles) **15** and **24**.

Bis(chalcones) **7** and **10** are π-isoelectronic molecules, both have thienothiophene core and oxyphenyl bridge, but they differ in the arrangement of the enone moiety (CH=CH–C=O) with respect to the oxyphenyl bridge. In case of bis(chalcone) **7** the C=O group is attached directly to the oxyphenyl bridge while for bis(chalcone) **10**, the C=C moiety is directly attached to the oxyphenyl bridge.

The optimized geometries (bond lengths, bond angles and dihedral angles) as well as ground state energies (total energy E_T, energy of highest occupied MO E_{HOMO}, energy of lowest unoccupied MO E_{LUMO}, energy gap E_g, dipole moment μ, and net charge on eneone moiety) of **7** and **10** using B3LYP/6-31G are presented in Tables 1–3 and Fig. 4 and 5.

From the results of Tables 1–3 and Fig. 4 and 5, the following conclusions were inferred:

(1) The optimized bond length of C=C in phenyl ring falls in the range from 1.393 to 1.428 Å which are in good agreement with the experimental data 1.411 Å,[47] for C=O bonds the optimized length obtained by B3LYP/6-31G is slightly shorter than the experimental value 1.229 Å.[47]

(2) The bond angles for DFT/6-31G reported in Tables 1 and 2 are slightly better than the HF-method compared to experimental results.

From the analysis of bond lengths and bond angles (paragraphs 1 and 2), we notice such differences between calculated and measured values. These discrepancies can be explained by the fact that the calculations assume an isolated molecule, where the intermolecular coulombic interactions with the neighboring molecules are absent.

(3) For both chalcones **7** and **10**, the two compounds are non-planar, where both the oxyphenyl bridges are out of the molecular plane of thienothiophene core.

(4) For chalcone **7**, the two oxyphenyl bridges are out of the molecular plane of thienothiophene core by 26.6° (C27 O28 C29 C34) and 178.0° (C19 O20 C21 C26), respectively, which allow the interaction with the appropriate binucleophilic reagents to afford the corresponding target molecule, compound **15** (88%).

(5) For chalcone **10**, the two oxyphenyl bridges are out of the molecular plane of thienothiophene core by 2° (C19 O20 C21 C22) and −32.7° (C27 O28 C29 C34), respectively, which may allow the interaction of chalcone moiety in one side only, and this should not lead to isolation of pure sample of **24**.

Table 1 Optimized bond length Å, bond angle degrees, and dihedral angle degrees of compound **7** using B3LYP/6-31G

Parameters of bond lengths	Å	Parameters of bond angles	Degrees
O20–C21	1.374	∠C19 O20 C21	117.0
C24–C49	1.487	∠C25 C24 C49	122.8
C49–O50	1.236	∠C24 C49 O50	120.4
C49–C51	1.481	∠O50 C49 C51	32.3
C51–C52	1.346	∠C49 C51 H77	117.1
C51–H77	1.090	∠C51 C52 H78	117.1
C51–H78	1.096	∠O28 C29 C30	115.3
O28–C29	1.380	∠C35 C59 C61	117.5
C32–C59	1.498	∠C32 C59 O60	121.2
C59–O60	1.226	∠C59 C91 H85	115.0
C59–C51	1.492	∠C61 C62 H84	119.8
C61–C62	1.338	∠C23 C24 C49 O50	24.1
C61–H85	1.095	∠O50 C49 C51 C52	−168.6
C62–H84	1.096	∠C25 C24 C49 C51	27.6
		∠C19 C20 C21 C26	2.4
		∠C33 C32 C59 C61	93.1
		∠C32 C59 C61 C62	103.8

Table 2 Optimized bond length Å, bond angle degrees, and dihedral angle degrees of compound **10** using B3LYP/6-31G

Parameters of bond lengths	Å	Parameters of bond angles	Degrees
O20–C21	1.384	∠C24 C49 H88	115.3
C24–C49	1.464	∠C24 C49 C50	126.2
C49–H88	1.094	∠C49 C50 H87	121.3
C49–C50	1.341	∠C50 C51 O75	121.1
C50–H87	1.091	∠C32 C58 H89	114.9
C50–C51	1.484	∠C32 C58 C59	124.9
C51–O75	1.234	∠C58 C59 H90	121.4
C51–C52	1.502	∠C58 C59 C60	27.3
O28–C29	1.398	∠C59 C60 O81	26.4
C32–C58	1.474	∠O20 C21 C22 H67	−1.0
C58–H89	1.095	∠C25 C24 C49 C50	19.8
C58–C59	1.335	∠C23 C24 C49 C50	−161.3
C59–H90	1.092	∠C24 C49 C50 C51	179.0
C59–C60	1.496	∠C28 C29 C34 C33	175.0
C60–O81	1.231	∠C31 C32 C58 C59	134.9
C60–C61	1.491	∠C32 C58 C59 C60	170.8
		∠C58 C59 C60 O81	24.9
		∠H90 C58 C60 O81	−84.2
		∠C60 C59 C58 CH89	175.2

(6) For chalcone **7**, the frame work at which the addition occurs are (C29 O60 C61 C62) and (C49 O50 C51 C52). The active centers for electrophilic attack are C59, C62, C49, and C52. The above two moieties are out of the molecular plane of oxyphenyl by 27.6° and 93.1°, respectively, [Tables 1–3 and Fig. 4 and 5].

(7) For chalcone **10**, where no products obtained, the frame work moieties are (C59 O60 C61 C62) and (C49 O50 C51 C52). Two moieties are out of the molecular plane of oxyphenyl by 24.9° and 134.9°, respectively [Tables 1–3, Fig. 4 and 5].

From the above results (3–7), it is clear that as the eneone moiety (CH=CH–C=O) comes close to the molecular plane of the oxyphenyl moiety the addition process occurs and pure sample of the corresponding target products could be isolated as in chalcone **7**. On the other hand, as the two enone moieties go far from the molecular plane of the oxyphenyl moiety, by increasing its dihedral angles, no pure products would be expected from the addition reaction as in case of chalcone **10**.

(8) The two π-isoelectronic structures **7** and **10** are of nearly the same order of stability, even though chalcone **10** seems a little bit more stable than chalcone **7** by 0.27 eV (≈6 kcal).

(9) From the calculations of the energy gap, E_g, which measure the chemical activity, chalcone **10** was found to be more reactive than chalcone **7** by 5.3 kcal.

(10) The polarity or charge separation over the molecule, which is measured by the dipole moment μ, showed that μ of chalcone **10** > μ of chalcone **7** by 3.5 D.

From the above results (8–10), one can conclude that although the total energy (E_T) of chalcone **7** is less than that of **10** by a factor of 6 kcal together with the fact that polarity as well as reactivity of compound **10** are more than that of **7**, experimental results showed that chalcone **7** reacted easily with

Table 3 Ground state properties and net charges on active centers of **7** and **10** using B3LYP/6-31G[a]

	Compound **7**				Compound **10**			
E_T (au)	−3079.890				3079.920			
E_{HOMO} (au)	−0.2193				0.2111			
E_{LOMO} (au)	−0.0725				−0.0727			
E_g (eV)	3.99				3.76			
μ (D)	3.654				7.167			
Net charges	C49	0.384	C59	0.294	C49	0.0944	C58	0.0606
	O50	−0.478	O60	−0.384	C50	−0.0691	C59	−0.0137
	C51	−0.067	C61	0.0005	C51	0.398	C60	0.364
	C52	0.093	C62	0.045	O75	−0.0483	O81	−0.443

[a] $E_g = E_{LOMO} - E_{HOMO}$.

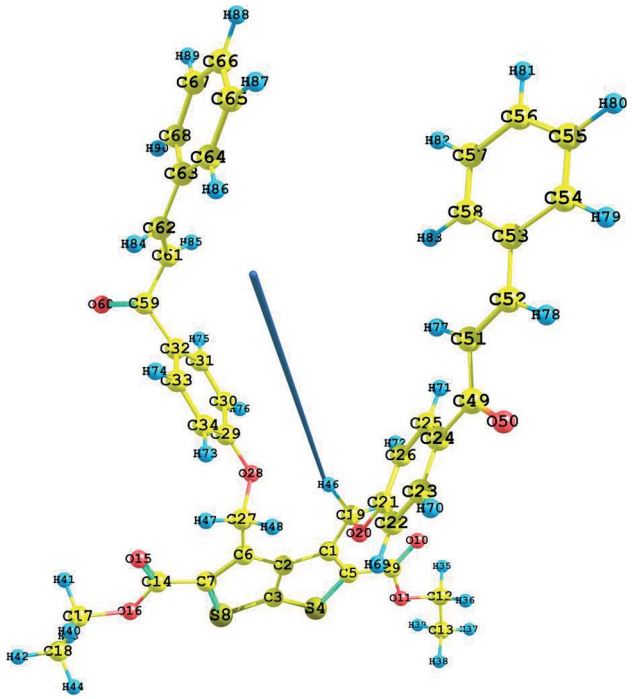


Fig. 4 The optimized geometry, numbering system, the vector of the dipole moment and moiety of addition of **7** using B3LYP/6-31G.

hydrazine hydrate to give the corresponding cyclic product **15** while compound **10** cannot do that, this may confirm that the geometry of the enone moiety is the most effective factor in the formation of pure sample of **15** or **24**.

(11) As outlined in Scheme 5, compound **24** can be obtained using alternative pathway. DFT calculations at the same level of theory B3LYP/6-31G for both π-isoelectronic structures **15** and **24** were performed. The geometry and ground state energies of both structures are presented in Table 4 and Fig. 6. The results of DFT calculations predicted that structure **15** is more stable than structure **24** by only ≈24 kcal. It is also found that the structure **15** is more chemically active than structures **24** by only ≈3 kcal. This implies that the two structures have almost the same order of stability, reactivity and both can chemically exist.

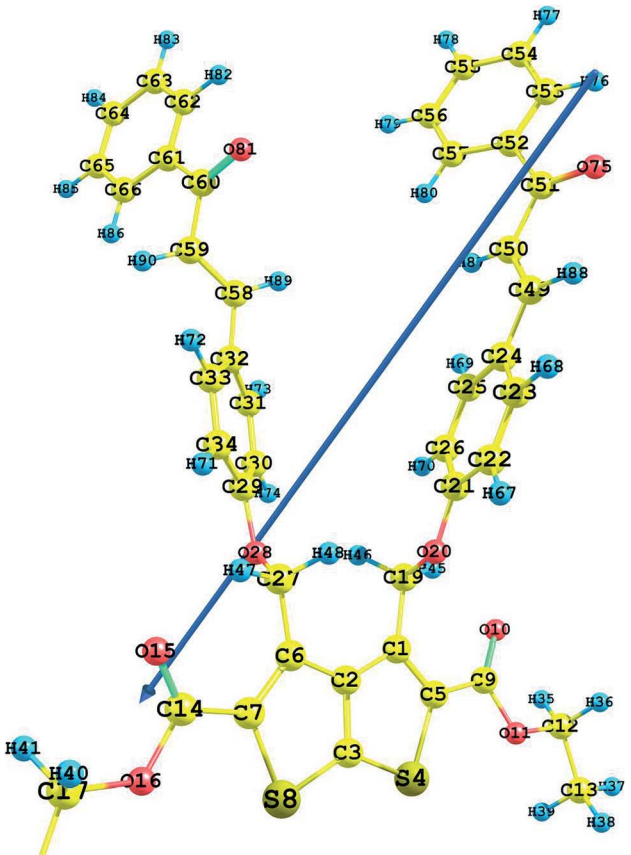
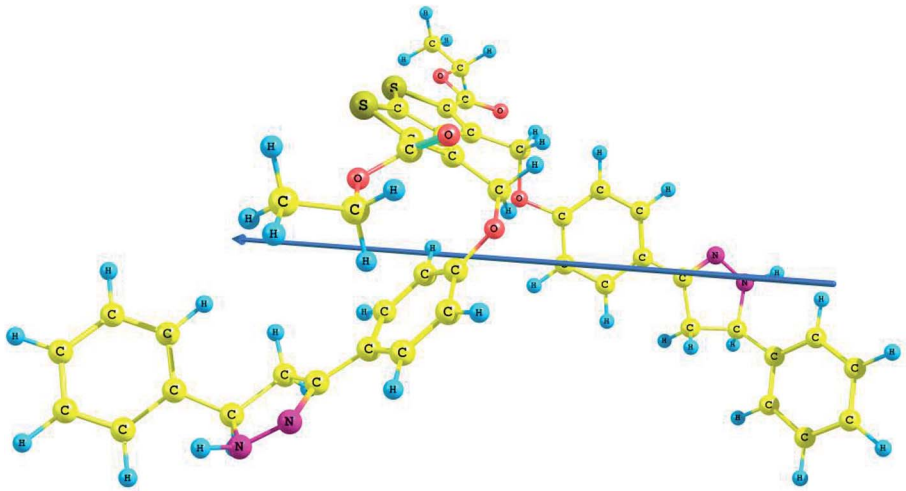


Fig. 5 The optimized geometry, numbering system, the vector of the dipole moment and the moiety of addition of **10** using B3LYP/6-31G.

Table 4 Energetics of the ground state of **7** and **10** using B3LYP/6-31G

	Chalcone **7**	Chalcone **10**
E_T (au)	−3150.363	−3150.325
E_{HOMO} (au)	−0.1836	−0.1923
E_{LOMO} (au)	−0.0698	−0.0742
E_g (eV)	3.09	3.21
μ (D)	2.722	4.372



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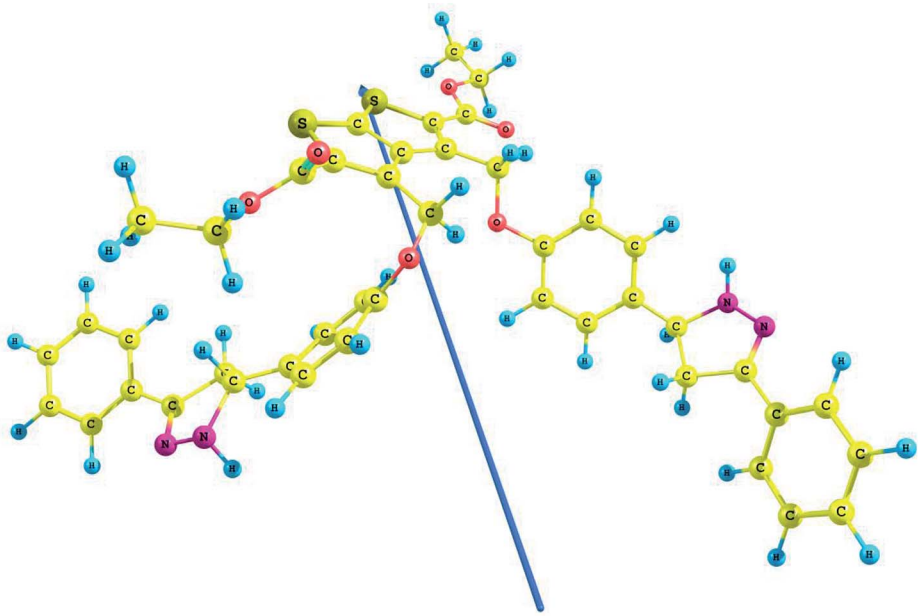

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Fig. 6 The optimized geometry, numbering system and the vector of the dipole moment of **15** and **24** using B3LYP/6-31G.

3. Conclusions

We developed a straightforward strategy for the synthesis of some novel bis(chalcones) and highlighted the significance of this class of compounds as versatile synthons for novel bis(dihydroisoxazoles), bis(dihydropyrazoles) and bis(dihydropyrimidines) *via* simple reactions. Due to the mild reaction conditions, good yields as well as easily accessible starting material we think that the synthetic approaches discussed here should provide access for novel bis(functionalized) heterocycles.

The new synthesized compounds are interesting both in their own right as unusual molecules as well as for their promising pharmacological and biological activities. This forecast depends on a large volume of research papers and review articles which reported the use of chalcones and bis-heterocycles as potent and efficient drugs for the treatment of several dreadful diseases. Full characterization of these compounds is reported.

DFT calculations at B3LYP/6-31G predicted that the dihedral angles of (eneone) moiety of both π-isoelectronic structures **7** and **10** are mainly responsible for the addition reaction. The presence of both enone moieties of **7** near the molecular plane of the oxyphenyl bridge enables the nucleophile to attack the electrophilic centers leading to the formation of the target molecules. However, in chalcone **10** the two eneone moieties are

far from the molecular plane of the oxyphenyl bridge and hence no pure samples of the corresponding bis(azoles) could be isolated. Also, DFT calculations predicted that the products **15** and **24** are of the same order of stability and reactivity and both can chemically exist.

4. Experimental

4.1. General

Melting points were determined in open glass capillaries with a Gallenkamp apparatus and were not corrected. The infrared spectra were recorded in potassium bromide disks on a PyeUnicam SP 3-300 and Shimadzu FTIR 8101 PC infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were determined on a Varian Mercury VX 300 NMR spectrometer using TMS as an internal standard and DMSO-d_6 as a solvent. Mass spectra were measured on a GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were carried out at the Microanalytical Center of Cairo University, Giza, Egypt.

4.2. Synthesis of bis(chalcone) compounds 7, 10

4.2.1. General procedure. To a solution of each of 1-(4-hydroxyphenyl)-3-phenylprop-2-en-1-one **8** or 3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one **11** (10 mmol) in ethanol (10 mL), KOH (0.56 g, 10 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. The solvent was removed *in vacuo* and the remaining materials were dissolved in DMF (15 mL) and the appropriate dibromides **5** (5 mmol) was added. The reaction mixture was refluxed for 5 min during which potassium chloride was separated. The solvent was then removed *in vacuo* and the remaining materials were washed with water and purified by crystallization from acetic acid to give bis(chalcones) **7** and **10** as off-white crystals.

4.2.1.1. Diethy-3,4-bis((4-(3-phenylacryloyl)phenoxy)methyl) thieno[2,3-b]thiophene-2,5-dicarboxylate (7). Yield (82%), mp 230–232 °C; IR (cm^{-1}): 1715, 1657 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6 Hz), 4.34 (q, 4H, CH_2CH_3, J = 6 Hz), 5.70 (s, 4H, OCH_2), 6.95 (d, 4H, ArH, J = 9 Hz), 7.37–7.78 (m, 14H, ArH and CH=CH–), 7.93 (d, 4H, ArH, J = 9 Hz);^{13}C NMR (DMSO-d_6): δ 14.45, 61.42, 62.24, 114.68, 122.154, 127.50, 128.64, 129.16, 129.47, 130.77, 131.08, 135.76, 136.19, 143.50, 145.85, 146.22, 161.51, 161.98, 187.60; MS: m/z 756 (M^+, 1.25%); $C_{44}H_{36}O_8S_2$: anal. calcd: C, 69.82; H, 4.79; S, 8.47. Found: C, 69.70; H, 4.50; S, 8.50%.

*4.2.1.2. Diethyl-3,4-bis((4-(3-oxo-3-phenylprop-1-enyl)phenoxy)-methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**10**).* Yield (75%), mp 160–162 °C; IR (cm^{-1}): 1712, 1658 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, CH_2CH_3, J = 6 Hz), 4.34 (q, 4H, CH_2CH_3, J = 6 Hz), 5.67 (s, 4H, OCH_2), 6.93 (d, 4H, ArH, J = 9 Hz), 7.46–7.71 (m, 14H, ArH, –CH=CH–), 8.02 (d, 4H, ArH, J = 9 Hz); ^{13}C NMR (DMSO-d_6): δ 14.43, 61.26, 62.22, 115.25, 120.11, 128.14, 128.80, 129.09, 131.13, 132.08, 133.44, 135.21, 136.31, 144.29, 145.80, 146.23, 160.20, 161.72, 189.34; MS: m/z 756 (M^+, 1.48%); $C_{44}H_{36}O_8S_2$: anal. calcd: C, 69.82; H, 4.79; S, 8.47. Found: C, 69.73; H, 4.85; S, 8.41%.

4.3. Synthesis of bis(pyrazole) derivatives 15–17

4.3.1. General procedure. To a solution of the appropriate bis(chalcone) **7** (0.01 mol) in acetic acid (20 mL), hydrazine hydrate (**12**), semicarbazide (**13**) or thiosemicarbazide (**14**) (0.02 mol) was added. The reaction mixture was heated under reflux for 5 h (in case of compounds **15** and **16**) and 8 h (in case of compound **17**). The reaction mixture was then cooled and poured onto crushed ice. The solid residues were collected by filtration and recrystallized from the proper solvent to give the corresponding bis(pyrazole) derivatives **15–17** as off-white crystals.

*4.3.1.1. Diethyl-3,4-bis((4-(1-acetyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**15**).* Methanol, yield (88%), mp 131–133 °C; IR (cm^{-1}): 1710, 1663 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6 Hz), 2.25 (s, 3H, CH_3CO), 2.26 (s, 3H, CH_3CO), 3.01–3.07 (m, 2H, pyrazole-4-CH), 3.64–3.73 (m, 2H, pyrazole-4-CH), 4.33 (q, 4H, CH_2CH_3, J = 6 Hz), 5.43–5.47 (m, 2H, pyrazole-5-CH), 5.64–5.68 (m, 4H, OCH_2), 6.93 (d, 4H, ArH, J = 7.5), 7.13–7.33 (m, 10H, ArH), 7.57 (d, 4H, ArH, J = 7.5); ^{13}C NMR (DMSO-d_6): δ 14.38, 22.11, 42.52, 59.82, 61.21, 62.28, 115.07, 124.41, 127.95, 128.63, 129.11, 131.03, 135.20, 136.52, 142.91, 145.79, 146.15, 154.26, 159.79, 161.73, 167.59; MS: m/z 868 (M^+, 1.77%); $C_{48}H_{44}N_4O_8S_2$: anal. calcd: C, 66.34; H, 5.10; N, 6.45; S, 7.38. Found: C, 66.29; H, 5.01; N, 6.56; S, 7.31%.

*4.3.1.2. Diethyl-3,4-bis((4-(1-carbamoyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**16**).* Acetic acid, yield (85%), mp 333–335 °C; IR (cm^{-1}): 3423 (br) (NH_2), 1709, 1663 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6 Hz), 4.15–4.30 (m, 4H, pyrazole-4-CH), 4.35 (q, 4H, CH_2CH_3, J = 6 Hz), 4.98 (d, 2H, OCH_2, J = 9.9 Hz), 5.65 (m, 4H, NH_2), 5.91 (d, 2H, OCH_2, J = 9.9 Hz), 6.23–6.25 (m, 2H, pyrazole-5-CH), 6.96 (d, 4H, ArH, J = 8.4), 7.21–7.36 (m, 10H, ArH), 7.78 (d, 4H, ArH, J = 8.4); ^{13}C NMR (DMSO-d_6): δ 14.38, 42.21, 50.28, 61.28, 62.21, 117.20, 127.11, 127.47, 128.85, 129.07, 129.89, 132.75, 135.45, 135.78, 142.60, 145.62, 146.82, 154.17, 161.53, 162.01; MS: m/z 870 (M^+, 0.23%); $C_{46}H_{42}N_6O_8S_2$: anal. calcd: C, 63.43; H, 4.86; N, 9.65; S, 7.36. Found: C, 63.50; H, 4.75; N, 9.58; S, 7.30%.

*4.3.1.3. Diethyl-3,4-bis((4-(1-carbamothioyl-5-phenyl-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**17**).* Acetic acid, yield (80%), mp 325–327 °C; IR (cm^{-1}): 3437 (br) (NH_2), 1710, 1664 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6 Hz), 4.14–4.27 (m, 4H, pyrazole H-4), 4.33 (q, 4H, CH_2CH_3, J = 6 Hz), 4.98 (d, 2H, OCH_2, J = 10.2 Hz), 5.67 (m, 4H, NH_2), 5.90 (d, 2H, OCH_2, J = 10.2 Hz), 6.22–6.25 (m, 2H, pyrazole-5-CH), 6.96 (d, 4H, ArH, J = 7.9 Hz), 7.21–7.34 (m, 10H, ArH), 7.78 (d, 4H, ArH, J = 7.9); MS: m/z 902 (M^+, 0.31%); $C_{46}H_{42}N_6O_6S_4$: anal. calcd: C, 61.18; H, 4.69; N, 9.31; S, 14.20. Found: C, 61.25; H, 4.60; N, 9.21; S, 14.27%.

4.4. Synthesis of bis(isoxazole) compound 23

4.4.1. General procedure. To a solution of the appropriate bis(chalcone) compound **7** (0.01 mol) in acetic acid (20 mL), hydroxyl amine hydrochloride **22** (0.02 mol) and sodium acetate (0.02 mol) were added. The reaction mixture was heated under reflux for 6 h. The solid obtained upon cooling was collected by

filtration and recrystallized from acetic acid to give **23** as off-white crystals.

*4.4.1.1. Diethyl-3,4-bis((4-(5-phenyl-4,5-dihydroisoxazol-3-yl) phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**23**).* Yield (68%), mp 336–338 °C; IR (cm^{-1}): 1709 (CO) ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 7.2 Hz), 4.15 (d, 2H, isoxazole-4-CH, J = 6.9 Hz), 4.15–4.28 (m, 4H, isoxazole-4-CH), 4.33 (q, 4H, CH_2CH_3, J = 6.9 Hz), 4.98 (d, 2H, OCH_2, J = 10.2 Hz), 5.90 (d, 2H, OCH_2, J = 10.2 Hz), 6.23–6.25 (m, 2H, isoxazole-5-CH), 6.96 (d, 4H, ArH, J = 8.7 Hz), 7.21–7.35 (m, 10H, ArH), 7.78 (d, 4H, ArH, J = 8.7 Hz); MS: m/z 786 (M^+, 0.31%); $C_{44}H_{38}N_2O_8S_2$: anal. calcd: C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 67.27; H, 4.80; N, 3.50; S, 8.20%.

4.5. Synthesis of bis(dihydropyrimidin) derivatives 20, 21

4.5.1. General procedure. To a solution of the bis(chalcone) **7** (0.01 mol) in DMF (3 mL), urea **18** or thiourea **19** (0.02 mol) and potassium hydroxide (0.02 mol) in ethanol (25 mL) were added. The reaction mixture was heated under reflux for 6 h. The reaction mixture was then cooled and poured onto crushed ice acidified with few drops of conc. HCl. The solid residue was collected by filtration and recrystallized from acetic acid to give the corresponding bis(dihydropyrimidine) derivatives **20** and **21** as off-white crystals.

*4.5.1.1. Diethyl-3,4-bis((4-(2-hydroxy-6-phenyl-5,6-dihydro-pyrimidin-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**20**).* Acetic acid, yield (70%), mp 272–274 °C; IR (cm^{-1}): 3428 (br) (OH), 1709 (CO); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6.9 Hz), 4.14–4.29 (m, 4H, prymidin-5-CH), 4.33 (q, 4H, CH_2CH_3, J = 6.9 Hz), 4.94–4.99 (m, 2H, OCH_2), 5.89–5.94 (m, 2H, OCH_2), 6.22–6.25 (m, 2H, prymidin-6-CH), 6.96 (d, 4H, ArH, J = 8.7), 7.19–7.26 (m, 10H, ArH), 7.78 (d, 4H, ArH, J = 8.7 Hz); MS: m/z 840 (M^+, 0.22%); $C_{46}H_{40}N_4O_8S_2$: anal. calcd: C, 65.70; H, 4.79; N, 6.66; S, 7.63. Found: C, 61.30; H, 4.55; N, 9.30; S, 14.30%.

*4.5.1.2. Diethyl-3,4-bis((4-(2-mercapto-6-phenyl-5,6-dihydro-pyrimidin-4-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**21**).* Acetic acid, Yield (72%), mp 320–325 °C; IR (cm^{-1}): 1701 (CO), 1448 (C=S); ^{1}H NMR (DMSO-d_6): δ 1.28 (t, 6H, CH_2CH_3, J = 6.9 Hz), 4.15–4.29 (m, 4H, pyrimidin-5-CH), 4.33 (q, 4H, CH_2CH_3, J = 6.9 Hz), 4.98 (d, 2H, OCH_2, J = 10.2 Hz), 5.90 (d, 2H, OCH_2, J = 10.2 Hz), 6.22–6.26 (m, 2H, pyrimidin-6-CH), 6.96 (d, 4H, ArH, J = 7.9 Hz), 7.20–7.76 (m, 10H, ArH), 7.78 (d, 4H, ArH, J = 9 Hz); ^{13}C NMR (DMSO-d_6): δ 14.4, 40.62, 50.09, 61.37, 62.20, 114.72, 122.20, 127.54, 128.99, 129.25, 129.79, 130.77, 131.0, 135.18, 142.56, 143.46, 161.75, 162.05, 163.44, 187.62; MS: m/z 873 (M^+, 0.57%); $C_{46}H_{40}N_4O_6S_4$: anal. calcd: C, 63.28; H, 4.62; N, 6.42; S, 14.69. Found: C, 61.30; H, 4.65; N, 9.40; S, 14.6%.

4.6. Synthesis of bis(pyrazole) derivatives 24, 25

4.6.1. General procedure. To a solution of each of 1-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)ethan-1-one **26** or 5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide **27** (10 mmol) in ethanol (10 mL), KOH (0.56 g, 10 mmol) was added. The reaction mixture was stirred at room temperature for 10 min. The solvent was removed *in vacuo* and the remaining material was dissolved in DMF (15 mL) and the dibromo compound **1** (5 mmol) was then added. The reaction mixture was refluxed for 5 min during which potassium chloride was separated. The solvent was then removed *in vacuo* and the remaining materials were washed with water and purified by crystallization from the proper solvent to give bis(pyrazole) derivatives **24** and **25** as off-white crystals.

*4.6.1.1. Diethyl-3,4-bis((4-(1-acetyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**24**).* Benzene, yield (65%), mp 130–133 °C; IR (cm^{-1}): 1711, 1664 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.24 (t, 6H, CH_2CH_3, J = 9.6 Hz), 2.27 (s, 6H, CH_3CO), 3.24–3.28 (m, 2H, pyrazole-4-CH), 3.66–3.84 (m, 2H, pyrazole-4-CH), 4.30 (q, 4H, CH_2CH_3, J = 9.6 Hz), 5.38–5.50 (m, 2H, pyrazole-5-CH), 5.57 (s, 4H, OCH_2), 6.77 (d, 4H, ArH, J = 7.8), 7.00–7.78 (m, 12H, ArH); MS: m/z 869 (M^+, 0.77%); $C_{48}H_{44}N_4O_8S_2$: anal. calcd: C, 66.34; H, 5.10; N, 6.45; S, 7.38. Found: C, 66.29; H, 5.20; N, 6.40; S, 7.31%.

*4.6.1.2. Diethyl-3,4-bis((4-(1-carbamoyl-3-phenyl-4,5-dihydro-1H-pyrazol-5-yl)phenoxy)methyl)thieno[2,3-b]thiophene-2,5-dicarboxylate (**25**).* Ethanol, yield (72%), mp 192–195 °C; IR (cm^{-1}): 3476, 3396 (NH_2), 1700, 1675 (2 CO); ^{1}H NMR (DMSO-d_6): δ 1.27 (t, 6H, CH_2CH_3, J = 6.9 Hz), 2.88–3.04 (m, 2H, pyrazole-4-CH), 3.64–3.88 (m, 2H, pyrazole-4-CH), 4.31 (q, 4H, CH_2CH_3, J = 6.9 Hz), 5.24–5.38 (m, 2H, pyrazole-5-CH), 5.24–5.40 (m, 4H, OCH_2), 6.44 (s, 4H, NH_2), 6.76–7.80 (m, 18H, ArH); MS: m/z 871 (M^+, 0.52%); $C_{46}H_{42}N_6O_8S_2$: anal. calcd: C, 63.43; H, 4.86; N, 9.65; S, 7.36. Found: C, 63.51; H, 4.92; N, 9.57; S, 7.30%.

4.7. Synthesis of pyrazole compound 27

4.7.1. General procedure. To a solution of chalcone **8** (0.01 mol) in acetic acid (20 mL), semicarbazide **13** (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h. The solid obtained upon cooling was collected by filtration and recrystallized from ethanol to give pyrazole derivative **27** as colorless crystals.

*4.7.1.1. 5-(4-Hydroxyphenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide (**27**).* Ethanol, yield (82%), mp 270–275 °C; IR (cm^{-1}): 3400–3255 (br) (OH, NH_2), 1663 (CO); ^{1}H NMR (DMSO-d_6): 3.30 (dd, 1H, pyrazole-4-CH, J = 5.1, 17.7 Hz), 3.75 (dd, 1H, pyrazole-4-CH, J = 12, 17.6 Hz), 5.31 (dd, 2H, pyrazole-5-CH, J = 4.8, 11.7 Hz), 6.42 (s, 2H, NH_2), 6.68–7.79 (m, 9H, ArH), 9.27 (s, 1H, OH); MS: m/z 281 (M^+, 2.23%); $C_{16}H_{15}N_3O_2$: anal. calcd: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.35; H, 5.41; N, 15.1%.

4.8. Computational method

Calculations have been performed using Khon–Sham's DFT method subjected to the gradient-corrected hybrid density functional B3LYP.[48] This function is a combination of the Becke's three parameters non-local exchange potential with the non-local correlation functional of Lee *et al.*[49] For each structure, a full geometry optimization was performed using this function and the 6-311G bases set[50] as implemented by Gaussian 09 package.[51] All geometries were visualized either using GaussView 5.0.9 [52] or chemcraft 1.6 [53] software packages. No symmetry constrains were applied during the geometry optimization. Subsequently, to locate stationary point and validate the optimized structures as true minimums, the

vibrational spectrum was determined to confirm that no imaginary frequency exists.

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