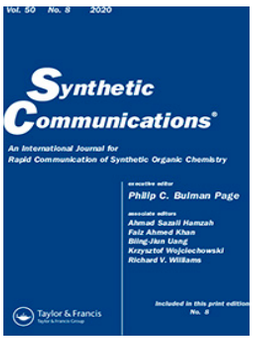

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Synthesis, DFT study, molecular docking and insecticidal evaluation of some pyrazole-based tetrahydropyrimidine derivatives

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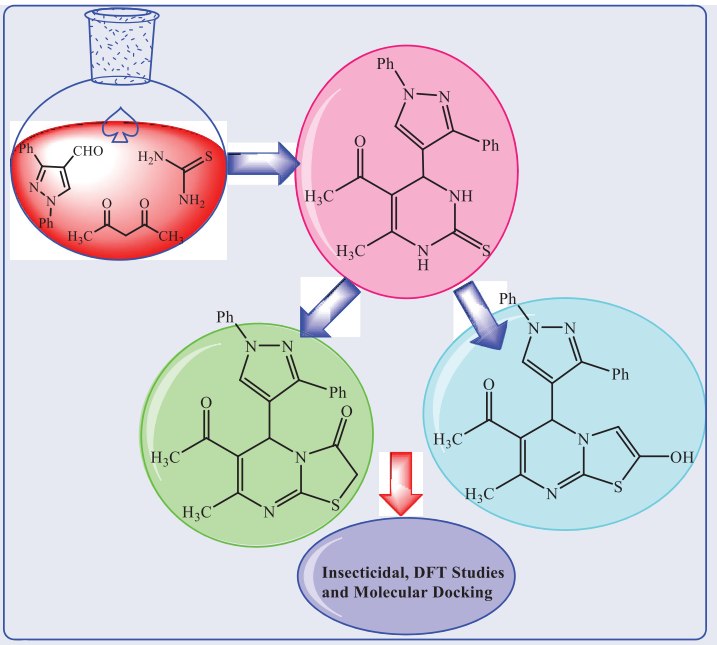
ABSTRACT

The building block synthon, 1-(4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one was efficiently synthesized by Biginelli reaction of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehdye, acetylacetone, and thiourea and submitted to react with ethyl chloroacetate and chloroacetyl chloride under different conditions to afford some *N*-heterocycles integrated with pyrazole scaffold. Hydrazinolysis of the pyrimidinethione was studied under different conditions. The insecticidal activity for these compounds, DFT calculations, and docking were run and discussed. Some of them exhibited 100% mortality against *Nilaparvata lugens* and *Mythimna separata*.

GRAPHICAL ABSTRACT



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Introduction

Tetrahydropyrimidinones and pyrazoles represent important classes of compounds due to their therapeutic and pharmacological properties such as antiviral, anti-inflammatory, antihypertension, anticancer, antidepressant, anti-tuberculosis, antioxidant, insecticidal, and antimicrobial activities.[1–14] The common synthetic routes to these compounds generally involve multi-step transformations that are essentially based on the Biginelli condensation methodology. Multicomponent reactions constitute major importance in organic synthesis because of its diversity, efficiency, and quick access to highly functionalized organic molecules which make them significant in drug discovery process.[2–5] In the past few years, the great interest of pyrazole derivatives has increased due to their proven usefulness as intermediates in the preparation of new pharmacological materials. Specifically, pyrazole derivatives have a long history of applications in the agrochemical industry as insecticides, herbicides, fungicides, and acaricides. The pyrazole ring exists in many agrochemically important compounds, such as the pesticides: fenpyroximate furametpyr,[15] cyantraniliprole,[16] cyenopyrafen,[17] tebufenpyrad,[18] and tolfenpyrad,[19] (Figure 1). Also, it was reported that the insecticidal activity of some pyrazole methanesulfonates against *Diabrotica undecimpunctata* Howardi, *Nilaparvata lugens*, and *Nephotettix cincticeps* displayed a very high level of activity against *D. undecimpunctata* Howardi, and *N. lugens*, *N. cincticeps*,[20] and a series of *N*-pyridylpyrazolecarboxamide derivatives exhibited excellent insecticidal activities against oriental armyworm (*Mythimna separata*) and diamondback moth (*Plutella xylostella*).[21]

Prompted by these observations and in continuation of our research group[7–14], we herein report the synthesis and reactions of tetrahydropyrimidinethione bearing pyrazole scaffold aiming to design some new pyrazolylpyrimidine derivatives to evaluate their insecticidal activity against *N. lugens* and *M. separata*. The DFT calculations and docking were discussed. This approach has been used for a variety of applications in organic synthesis and functional group transformations.

Results and discussion

Chemistry

Herein, tetrahydropyrimidinethione **2** was efficiently prepared *via* Biginelli cyclocondensation reaction of pyrazole aldehyde[22] **1**, acetylacetone and thiourea (Scheme 1) and utilized as a key building block synthon for construction of valuable *N*-heterocycles. The structure of pyrimidine **2** was established on the basis of its analytical and spectral data. Pyrimidine **2** could exist in three tautomeric structures (Scheme 1). DFT based on quantum chemical parameters was good agreement with three tautomeric structures in which highly conjugated 3,4-dihydropyrimidin-(1*H*)-thione **(2)** cause the lower in HOMO energy and increase the energy gap $\Delta E = E_{HOMO} - E_{LUMO}$. Due to the approximately 80% planarity of the pyrazole nucleus toward the pyrimidine moiety in the tautomer **2c** (Figure 2). Furthermore, increase the nucleophilicity of the pyrmidine **2** ($n = 1/\omega$) as outlined in Table 1 may be explained the reactivity of the pyrimidine **2** with different electrophilic reagent although the lower HOMO energy. One of interesting electrophilic reagents is ethyl chloroacetate or chloroacetyl chloride which has two electrophilic sites and reacted with nucleophiles *via* SN^2 or tetrahedral mechanism (THM)[5,23–25] dependent on the reaction conditions.

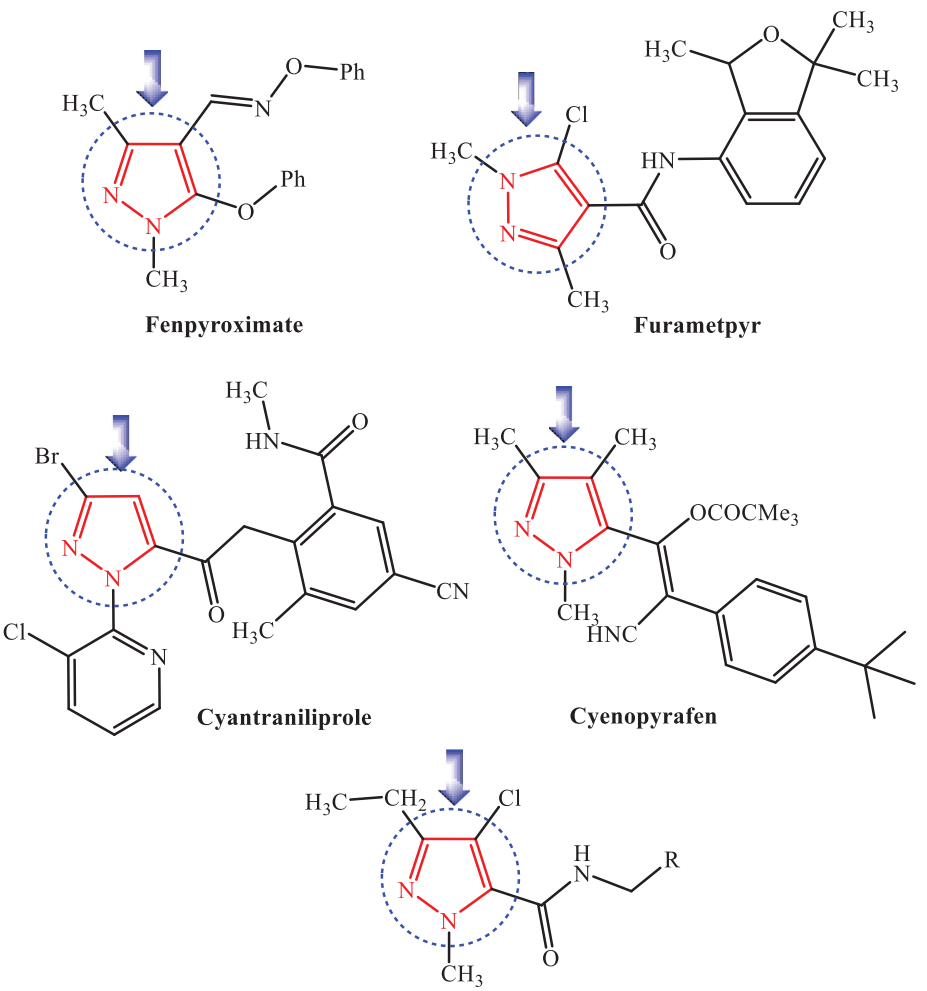
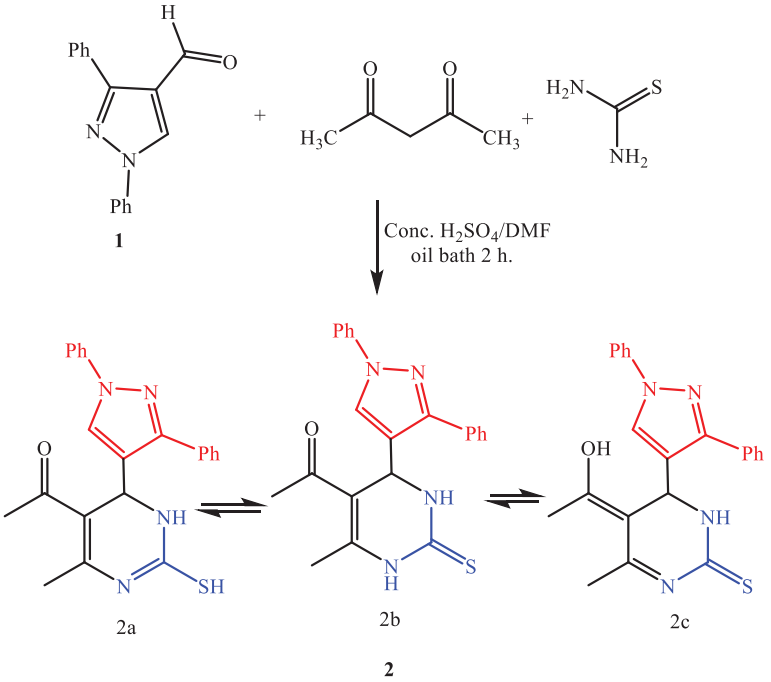


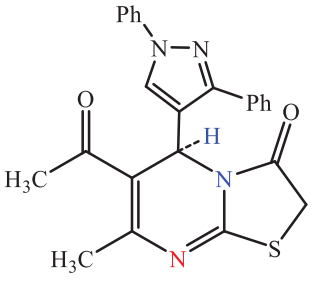
Figure 1. Agrochemical molecules containing pyrazole scaffold.

The reaction of pyrimidine **2** with ethyl chloroacetate under different conditions was studied and found to afford thiazolopyrimidine derivative **4** as a sole product (Scheme 2). The IR spectrum of compound **4** displayed the stretching absorption band for C=O of thiazolidinone ring at ν 1707 cm^{-1}. The ^{1}H-NMR spectrum exhibited singlet for methylene protons in the upfield region and was devoid of the triplet and quartet signals of ethyl ester group which exclude the open structure **3**. Furthermore, the mass spectrum evidenced the assigned structure by showing the correct molecular ion peak besides some interesting abundant peaks. The formation of compound **4** could be explained *via* formation of the *S*-alkylated product **3** in first followed by cyclization to eliminate ethanol molecule. Regioselective reaction of the pyrimidine **2** with ethyl chloroacetate takes place *via* SN^2 reaction proceeding *via* withdrawing Cl^- by the base (potassium carbonate or sodium acetate) to remove KCl followed by cyclization to afford 4-oxo-1,3-thiazole **4** rather than 5-oxo derivative.

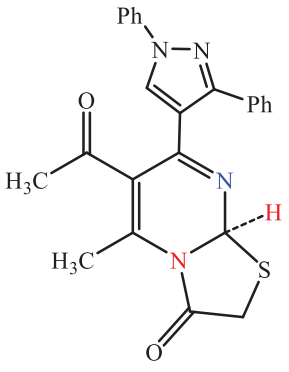


Scheme 1. Synthesis of tetrahydropyrimidinethione **2**.

DFT optimization structure of the 4-oxo-1,3-thiazole **4** was cyclized *via* N_2 (blue color) rather than N_1 (red color) even though steric strain of the ring formation of 4-oxothiazole with diphenylpyrazole ring as in Figure 2 that outlined the electronic factor plays an important role in the stability of the product **4**. From DFT stimulation (Figure 3), the compound **4** has activation energy at $\Delta G = 31.509$ kcal/mol which is more proceeding than its Regio isomer **4'** that has activation energy at $\Delta G = 77.644$ kcal/mol as outlined in Figure 4. According to exact Arrhenius model,[26] it has calculated the pre-exponential factor, entropy, and Gibbs energy which have good agreement with the experimental ^{1}H-NMR spectrum of the compound **4** where it revealed the singlet signal of the proton (H) of C_4 pyrimidine nucleus at chemical shift δ 6.36 ppm that differ from proton (H) of its Regio isomer of thiazolopyrimidine **4'**.



Compound **4**



Compound **4'**

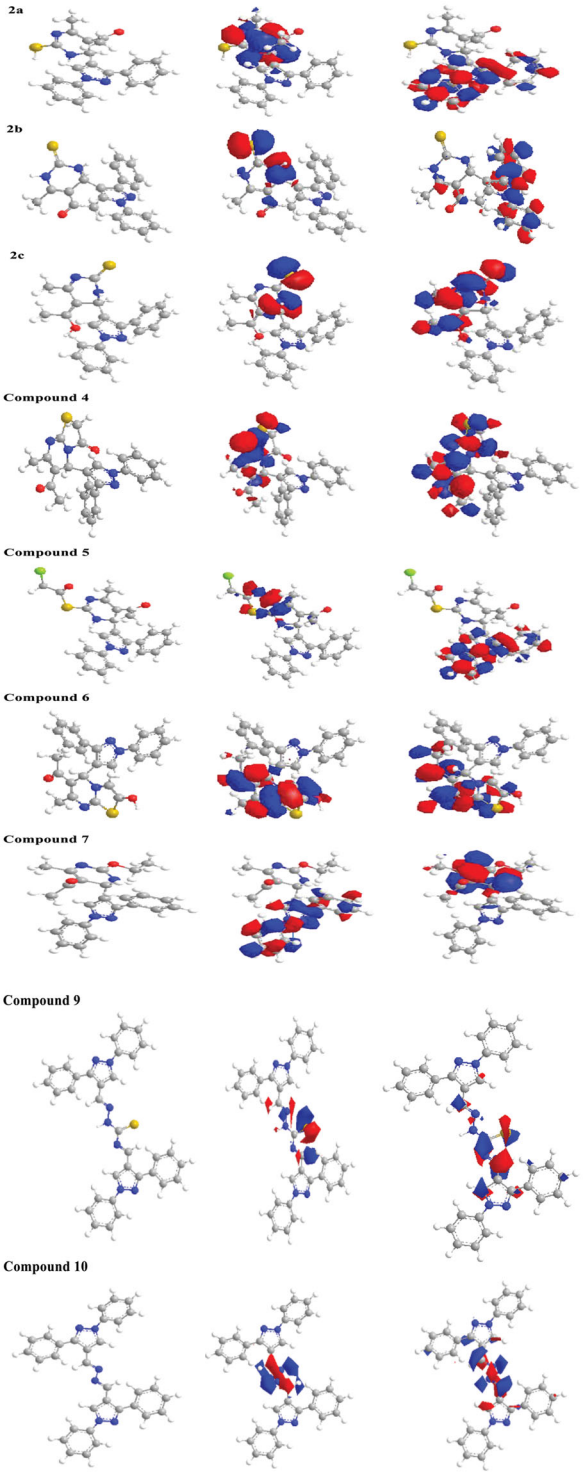
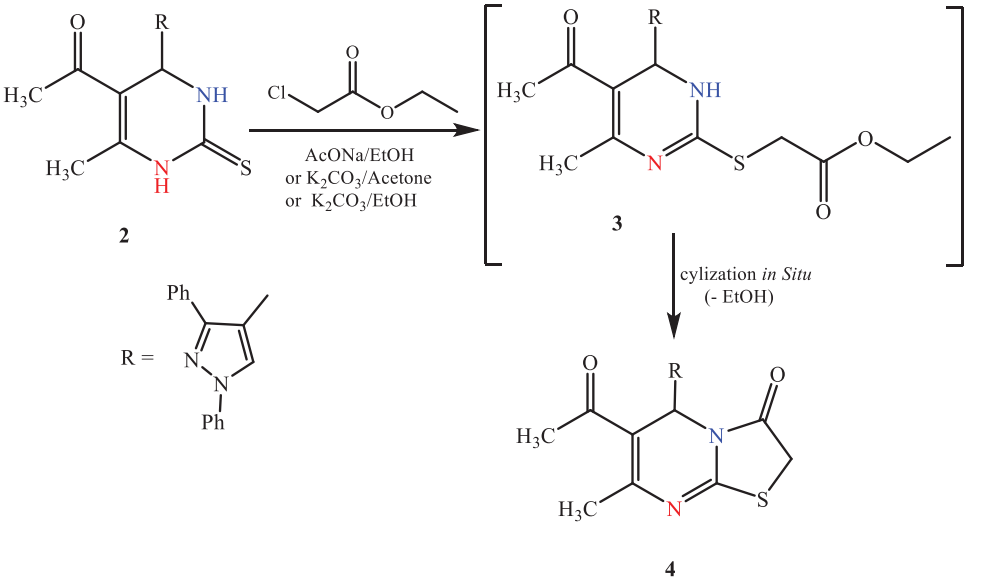


Figure 2. Optimized structures (left), HOMO (middle) and LUMO (right) for the potent insecticidal compounds. Color index: White H, Gray C, Blue N, Red O, yellow S and Green Cl.

Table 1. DFT parameters calculated for the synthesized compounds.

Comp. No.	E_{HOMO} (eV)	E_{LUMO} (eV)	$\Delta E_{(LUMO-HOMO)}$	Dipole moment, μ (Debye)	Hydration E (kcal/mol)	Surface area, A, (nm^2)	Electrophilicity, ω (eV)
2	−10.93	−0.886	9.664	−0.526	−20.691	1183.34	1.12
4	−7.42	−0.342	3.478	0.4520	−50.462	909.23	4.34
5	−7.75	−0.810	3.030	13.879	−55.453	1354.25	5.24
6	−7.85	−0.752	2.738	4.733	−59.942	1187.32	3.27
7	−8.17	−1.261	2.359	3.810	−29.331	1034.24	3.38
9	−2.271	−1.553	2.447	12.256	−53.272	1126.34	2.47



Scheme 2. Reaction of pyrimidinethione **2** with ethyl chloroacetate.

It was fortunate that reaction of pyrimidine **2** with chloroacetyl chloride was mainly dependent on the reaction conditions. Indeed, when the reaction was executed in triethylamine/dioxane at room temperature, the *S*-acylated product **5** was obtained (Scheme 3). The reaction in refluxing triethylamine/benzene afforded 2-hydroxythiazolopyrimidine **6** *via* tetrahedral mechanism (THM) reaction of thiol with the carbonyl precursors. The ^{1}H-NMR spectrum of compound **6** indicate the 2-hydroxy tautomer is approximately 80% more than 5-oxo-1,3-thiazolopyrimidine. While in refluxing compound **2** with chloroacetyl chloride in the presence of potassium hydroxide/ethanol, thiazolopyrimidine derivative **4** was obtained as a sole product. The chemical structures of all products were substantiated from their analytical and spectral data (cf. section "Experimental").

In turn, hydrazinolysis of pyrimidinethione **2** failed to give the expected hydrazinopyrimidine **8** and led to the formation of diheteryl hydrazine-1-carbothioamide **9** and diheteryl azine **10** when the reaction was executed in refluxing ethanol and in neat, respectively (Scheme 4). The spectral data were in a good agreement with the proposed chemical structures. Further, the structure of azine **10** was supported by an authentic sample prepared from condensation of the pyrazole aldehyde **1** with hydrazine hydrate in refluxing ethanol.[7] Formation of compounds **9** and **10** could be visualized to occur

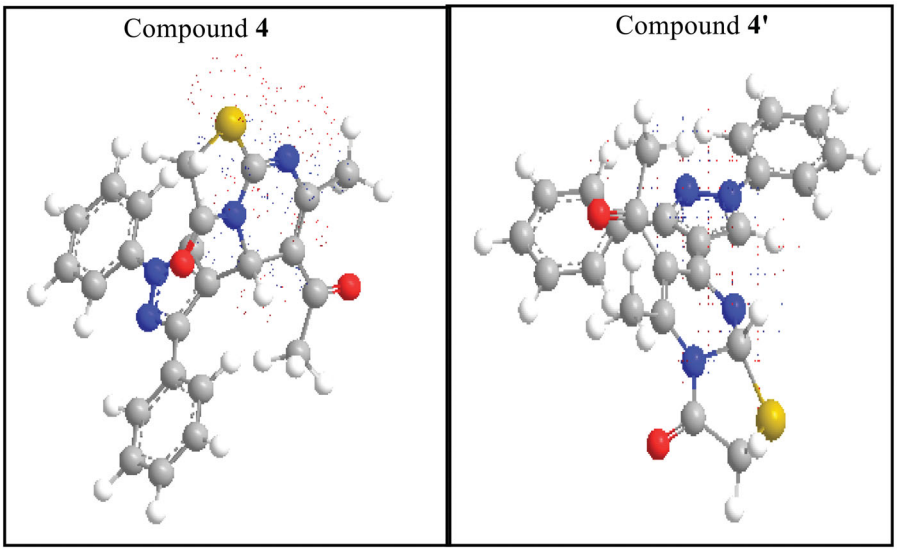


Figure 3. Outline the chemical and optimized structures of compounds **4** and **4′**.

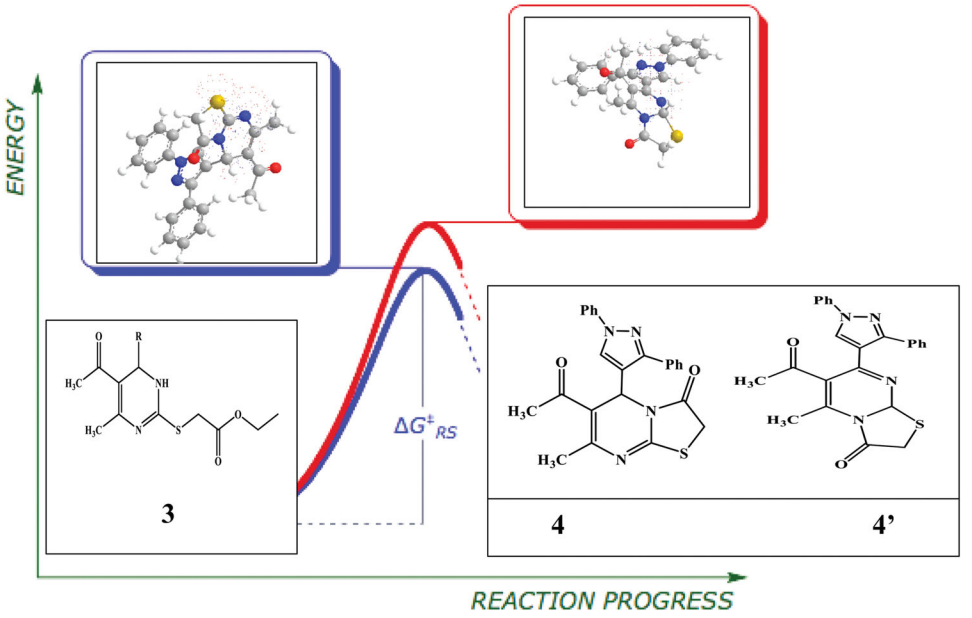
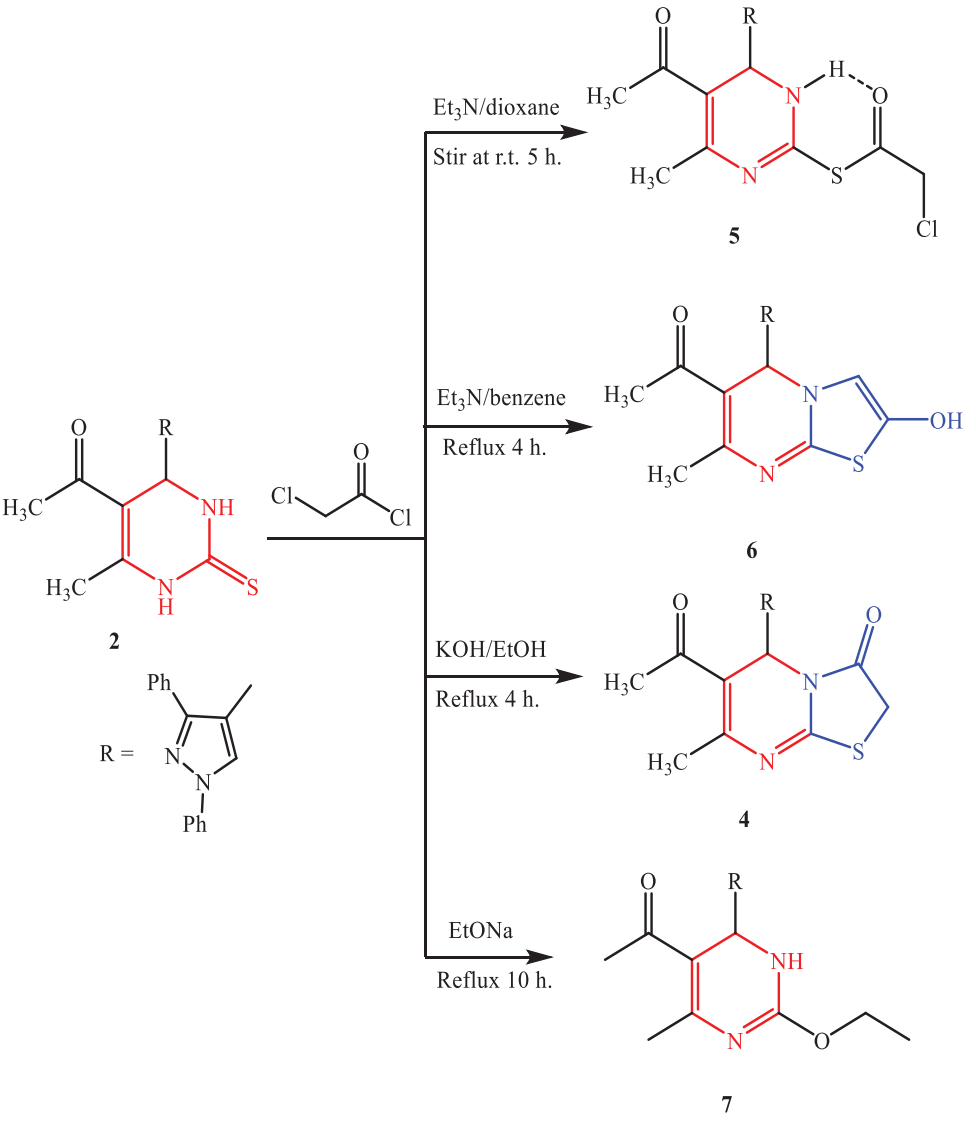


Figure 4. Energy diagram of the reaction progress outline the regioselectivity of the compound **4** than its Regio isomer **4′**.

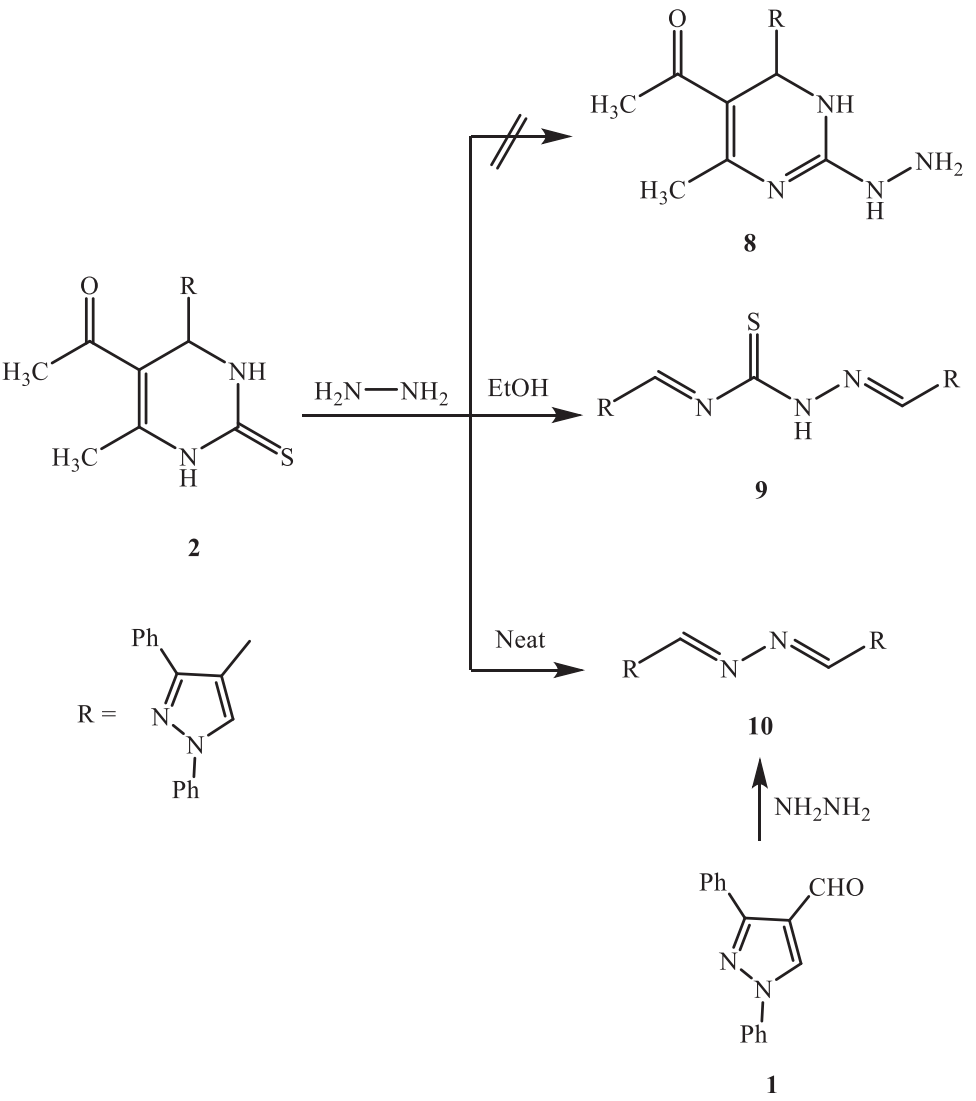
as depicted in Scheme 5. Presumably, the formation of diheteryl azine **10** involved condensation of the concerned substrate 2 with one equivalent of hydrazine to give the corresponding diheteryl hydrazine-1-carbothioamide **9** followed by nucleophilic attack of a second hydrazine molecule to C=N segment. Compelling evidence for the assigned structure was forthcoming by increase the % yield upon increase the molarity of the utilized hydrazine. Therefore, when the reaction was carried out using equimolar ratios of both the substrate **2** and the co-reactant hydrazine hydrate, the % yield of the azine **10**



Scheme 3. Behavior of pyrimidinethione **2** toward chloroacetyl chloride.

was only 42%. In turn, when the concentration of hydrazine hydrate is doubled relative to that of the substrate **2**, this resulted in an increase of the % yield to 71%.

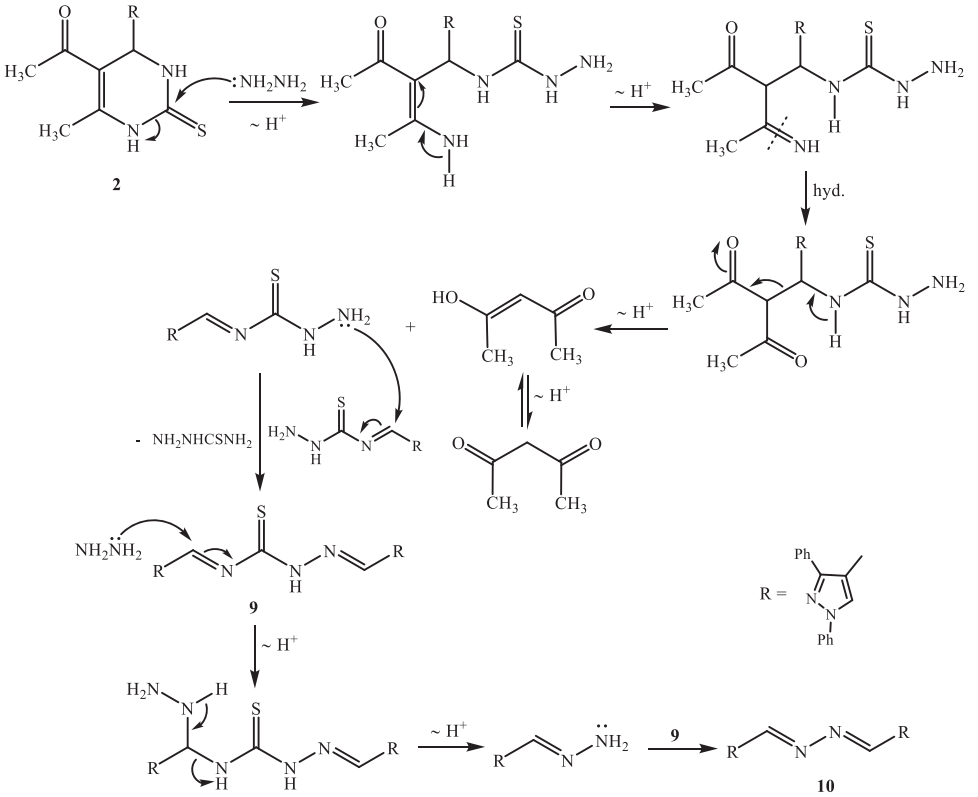
Presumably, hydrazinolysis in boiling ethanol afforded product **9** due to the presence of protic solvent e.g., ethanol can be competitive and weaken the nitrogen nucleophile e.g., hydrazine hydrate that is preferred to attack the reactant molecule **2** than product **9**. Moreover, the solvation of product **9** with ethanol affords more stability of the Schiff base **9** because of the presence of four sites to form intermolecular hydrogen bond with ethanol. Nevertheless, in neat hydrazine hydrate, DFT simulation approach the reactivity of LUMO of the thiosemicabazone derivative **9** to the HOMO of hydrazine is lower in energy gap than LUMO of the pyrimidine thione **2**. So, in the neat hydrazine hydrate, it preferred to complete the reaction *via* the true intermediate **9** to afford azine derivative **10** (see more in Scheme 5).



Scheme 4. Hydrazinolysis of pyrimidine **2**.

Computational studies (DFT methods)

DFT studies were carried out for the pyrimidine and thiazolopyrimidine compounds using Materials Studio 6.0 (MS 6.0) software from Accelrys, Inc. DMol3 module was used to perform the DFT calculations using Perdew and Wang LDA exchange-correlation functional and DND basis set. The calculated parameters involved the electron density, dipole moment, and Frontier molecular orbitals and the molecular surface area. Frontier molecular orbitals include the highest occupied molecular orbitals (HOMOs) and the lowest unoccupied molecular orbitals (LUMOs).[27,28] The molecular structures of the synthesized compounds are superior to be formed to a stable geometry is known as optimization. Such the energy of the structure is transported to a stationary point, the geometry of pyrimidine derivatives is gradually optimized, and its energy is



Scheme 5. Plausible pathways for the formation of compounds **9** and **10**.

continuously decreased until the fluctuations in the molecule energy are minimized. Frontier molecular orbitals possess the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) (Figure 2). The regions of highest electron density (HOMO) characterizes the electrophilic-attacking sites, while the LUMO imitates the nucleophilic-attacked sites.[29,30] The quantum chemical computation could be exploited this reaction at the different conditions afforded different products **2–10** (Table 1).

Insecticidal activity

The insecticidal activities of compounds **2–10** were measured against *M. separata* and *N. lugens* according to the standard test[31] with a slight modification. The test analogs were dissolved in DMF and serially diluted with water containing Triton X-80 (0.1 mg/L) to obtain the required concentrations. The insects were reared at 25 (±1)°C and groups were transferred to glass Petri dishes. All experiments were carried out in three replicates for the purpose of statistic requirements. Assessments of mortality were calculated 72 h by the number and size of the live insects relative to those in the negative control. Evaluations were based on a percentage scale of (0 = no activity and 100 = complete eradication). The mortality rates were subjected to probity analysis.[32] Phenytoin and carbamazepine were used as positive control while water containing

Table 2. Insecticidal activity of the synthesized compounds against *Mythimna separata* and *Nilaparvata lugens*.

Comp.	Insecticidal activities at different concentrations (μg/mL) (mortality, %)									
	Mythimna separata					*Nilaparvata lugens*				
	500	200	100	50	25	500	200	100	50	25
2	92.9	87.2	73.8	73.8	66.9	92.2	78.1	75.2	74.5	67.9
4	96.6	92.3	69.1	65.3	63.2	91.3	86.4	77.5	73.2	69.2
5	60	57.2	43.7	33.7	24.1	65.2	63.1	57.2	51.0	42.8
6	44.6	29.8	14.3	9.0	6.2	45.2	23.5	11.4	9.8	2.3
7	95.2	94.2	83.8	84.5	75.2	89.4	87.9	85.1	81.2	76.7
9	99.4	96.2	85.1	83.8	79.6	98.7	87.6	82.0	79.8	71.9
10	70	60.0	56.4	53.7	37.1	78	75.0	73.2	60.4	57.8
Phenytoin	100	100	100	98	93	–	–	–	–	–
Carbamazepine	–	–	–	–	–	100	100	100	91	85

Table 3. LC_{50} values of compounds **2, 4, 7** and **9** with phenytoin and carbamazepine against *Mythimna separata* and *Nilaparvata lugens*, respectively.

Insects	Compd.	LC_{50} (mg/L)	$y = a + bx$	Toxic ratio
Mythimna separata	**2**	4.856	$y = 3.1852 + 1.0493x$	0.980
	4	5.587	$y = 2.35527 + 1.59130x$	0.943
	7	6.732	$y = 2.15892 + 1.2746x$	0.927
	9	5.774	$y = 2.09929 + 1.7009x$	0.869
	Phenytoin	7.643	$y = 3.732 + 1.46x$	0.992
Nilaparvata lugens	**2**	5.865	$y = 2.3643 + 1.5001x$	0.974
	4	1.768	$y = 2.6981 + 1.1224x$	0.980
	7	7.103	$y = 3.4268 + 0.8336x$	0.936
	9	5.294	$y = 2.3290 + 1.4716x$	0.915
	Carbamazepine	3.562	$y = 2.2280 + 1.3748x$	0.994

Triton X-80 (0.1 mg/l) was used as negative control. The results listed in Table 2 indicated that most of the title compounds showed weakly insecticidal activity against the two pests. However, some of the compounds displayed good insecticidal activities. For example, compounds **4** and **9** showed approx. 100% activities at 500 μg/mL and 50% activities at 50 μg/mL against both *M. separata* and *N. lugens*, whereas they exhibited 93.1% and 95.0% activity, respectively, against *N. lugens* at 500 μg/mL. In addition, compounds **2, 7** and **9** also showed good insecticidal activities, the mortalities of them against *M. separata* were 92.9, 95.2, and 90.4%, respectively (500 μg/mL), and with 200 μg/mL concentration, the activity of compound **7** against *M. separata* was still 94.2%. Furthermore, the activities of compound **2** against *N. lugens* at 200 μg/mL were 78.1% and 77.6% for compound **9**.

The LC_{50} of compounds **2, 4, 7** and **9** were further evaluated and the results listed in (Table 3). The LC_{50} values of such compounds on *M. separata* were much lower than that of Phenytoin which indicated that the activities of these compounds on *M. separata* are better than standard reference. On the other hand, The LC_{50} value of compound **4** on *M. separata* was much lower than that of Carbamazepine which indicated that its activity on *N. lugens* is better than standard reference. Toxic ratio is defined as the ratio of the imidacloprid's LC_{50} value for base line toxicity and the compounds' LC_{50} value. DFT based on the dipole moment (μ) is a promising measurable parameter for the molecular polarity, it is clearly evident from Table 3 that compounds **2, 4** and **9** exhibit high polarities and the possibility of binding with insecticidal Tyr69A and Arg192A

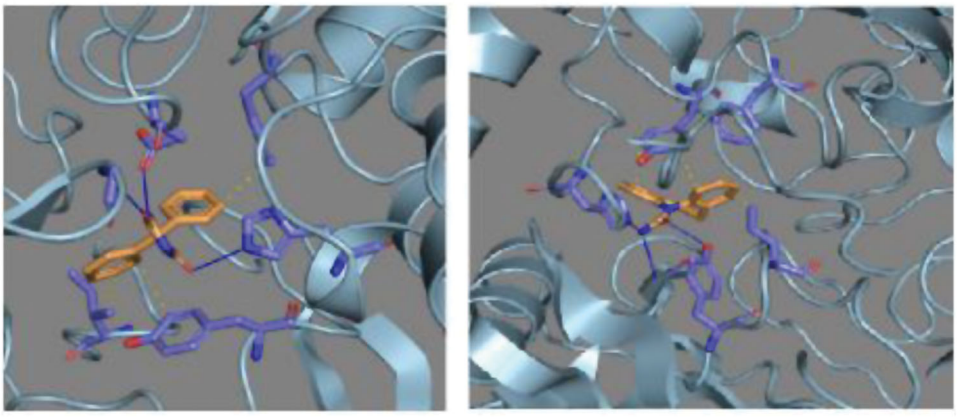


Figure 5. Binding interaction poses of phenytoin and carbamazepine with GABA-AT receptor (PDB ID: 1OHW). Compounds represented as tube, H-bonding as blue line and hydrophobic interactions as yellow dashed lines.

which in turn favored. So, they are most potent insecticidal activity. The hydration energy can be echoed the more solvated parts of synthesized compounds that be contributed to attack the insect resulting in most potent activity for such compounds (Table 1). For more confirmation, the nucleophilicity index (ω) as well as the surface area, follow the order: **9 > 2 > 4 > 5** are in conformity to insecticidal activity. Accordingly, the DFT data run in harmony with the previous obtained results (cf. Tables 1–3).

Molecular docking

Chem-bioinformatics studies speed up target arrangement and rational drug design[33–35] convenience of 3 D coordinates of the receptor besides facilitating the process and techniques like molecular docking can be used to study the binding of drug to receptor enzyme. To understand the molecular basis of insecticidal activity of the newly designed of pyrimidine derivatives **(2–10)** and to discover the binding mechanisms of these molecules, the authors docked these molecules into the active site of GABA-AT receptor that is a homo-tetramer and the active site is present at the interface of two monomers that extracted the coordinates corresponding to chain A and B. The active site residues consist of chain A (His44A, Tyr69A, Ile72A, Gly136A, Ser137A, Phe189A, Arg192A, Lys203A, Ile205A, His206A, Glu265A, Ser269A, Glu270A, Glu298A, Val300A, Lys329A, Arg422A, Asn423A, Ile426A, Gly438A, Gly440A) and chain B (Tyr348B, Phe351B, Thr353B). In our docking study, first, we evaluated following available antiepileptic drugs: Phenytoin (4.1 kcal/mol) showed three H-bonds with Gly440A, Glu270A, and His206A. Likewise, carbamazepine (4.2 kcal/mol) showed three H-bonds with His44A, Tyr69A and Gly438A (Figure 5). The docking score (in kcal/mol) of all newly synthesized pyrimidine analogs range was better than the available standard drugs. Docking results (docking score, non-covalent interactions: H-bonds, p-cation, p-stacking, halogen bonds, and salt bridges) of all molecules in GABA-AT active site are

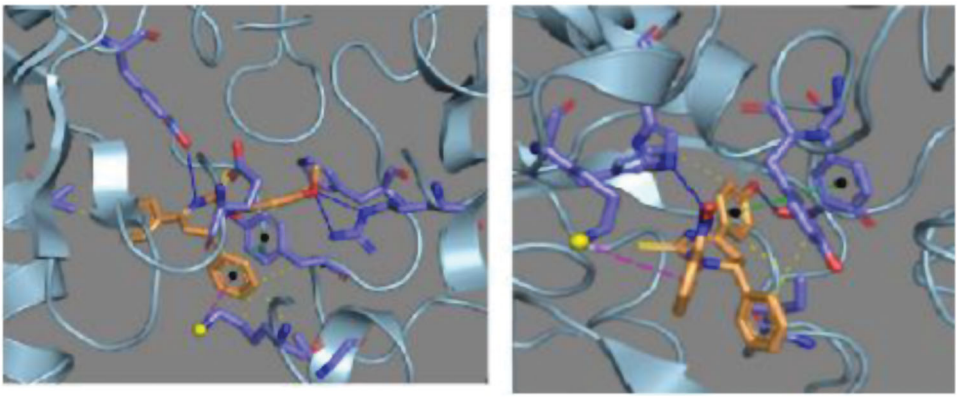


Figure 6. Binding interaction poses of compounds **4** and **9** with GABA-AT receptor (PDB ID: 1OHW). Compounds represented as tube, H-bonding as blue line, p–p interactions as green dashed line, p-cation interactions as magenta dashed line, and hydrophobic interactions as yellow dashed lines.

shown in Figures 5 and 6. Among all, the best three scoring molecules are **2** (5.6 kcal/mol), **4** (5.6 kcal/mol), and **9** (5.4 kcal/mol). Compounds **2** and **4** showed similar interactions: two H-bonds (His206A and Thr353B), one p-stacking interaction (Phe351B) and one p-cation interaction (Lys203A) (Figure 6). Thiosemicarbazone derivative **9** made three H-bonds with Tyr69A and Arg192A (two H-bond). It also showed a p-stacking with Tyr348B and a p-cation interaction with Lys203A (Figure 6). The substituted 5,6-dihydropyrimidine-2(1*H*)-thione analogs showed characteristic features to make H-bonds, p-cation, p-stacking and halogen bonds with GABA-AT. N-3 (of pyrimidine ring) made H-bond with Tyr69A and His206A.

Conclusion

A 1-(4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one was synthesized by Biginelli reaction of 1,3-diphenyl-1*H*-pyrazole-4-carbaldehdye, acetylacetone and thiourea and submitted to react with ethyl chloroacetate and chloroacetyl chloride under different conditions to construct some *N*-heterocycles bearing 1,3-diphenylpyrazole scaffold. Hydrazinolysis of the pyrimidinethione was also studied under different conditions to produce thiosemicarbazone and azine derivatives. The explanation of insecticidal activity for these newly synthesized compounds was discussed *via* DFT-based quantum calculations and molecular docking.

Experimental

Chemistry

All melting points were measured on a GALLENKAMP electric melting point apparatus and are uncorrected. All chemicals and solvents used were obtained from commercial sources and used as received or dried by standard procedures. The IR spectra (ν, cm^{-1})

were recorded using potassium bromide disks on Fourier Transform Infrared Thermo Electron Nicolet iS10 Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA) at the Central Laboratory of Faculty of Science, Ain Shams University. The 13C and ^{1}H-NMR spectra (δ_H, ppm) were run at 100 and 400 *MHz* on BRUKER NMR Spectrometer (BRUKER, Manufacturing & Engineering Inc., Anaheim, CA, USA) using tetramethyl silane (TMS) as internal standard in deuterated dimethylsulfoxide (DMSO-d_6) at Faculty of Pharmacy, Ain Shams University. The mass spectra (MS) were recorded on Shimadzu GC-MS-QP-1000 EX mass spectrometer (Shimadzu Scientific Instruments, Inc., USA) operating at 70 eV at the Regional Center for Mycology and Biotechnology (RCMB) of Al-Azhar University, Nasr City, Cairo, Egypt. The reactions were monitored by thin layer chromatography (TLC) using Merck Kiesel gel 60 F_{254} analytical sheets obtained from Fluka, Switzerland. The starting aldehyde, namely 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(1)**, was prepared according to the literature procedure *via* the Vilsmeier–Haack reaction of acetophenone phenylhydrazone.[22]

General procedure for the synthesis of pyrimidinethione 2

An equimolar mixture of pyrazole aldehyde **1**, thiourea, and acetylacetone (5 mmol) in *N,N*-dimethylformamide (10 mL) containing 2-drops of concentrated sulfuric acid was heated on oil bath at 140–150 °C for 2 h. After cooling, the reaction mixture was poured onto ice-cold water. The separated solid was filtered off, dried and recrystallized from benzene to afford pyrimidinethione **2**.

1-(4-(1,3-Diphenyl-1H-pyrazol-4-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)ethan-1-one (2)

Brown crystals, mp. 210–212 °C, yield 81%. Anal. Calcd. for $C_{22}H_{20}N_4OS$ (388.49): C, 68.02; H, 5.19; N, 14.42. Found: C, 67.88; H, 4.98; N, 14.29%. IR (KBr, ν, cm^{-1}): 3377, 3223 (2 NH), 1682 (C=O), 1622 (C=N), 1185 (C=S). 13C-NMR (100 MHz, DMSO-d_6, δ, ppm): 195.0 (C=O), 174.3 (C=S), 150.8 (C=C), 144.4 (C=N), 139.7, 133.2, 130.0, 129.0, 128.9, 128.5, 128.4, 126.9, 125.0, 124.0, 119.0, 118.9 (Ar-C), 111.7 (C=C), 46.1 (CH), 30.7 ($\underline{CH_3}$C=O), 19.8 (CH_3). ^{1}H-NMR (400 MHz, DMSO-d_6, δ, ppm): 10.24 (br.s, 1 H, NHCS, exchangeable), 9.73 (br.s, 1 H, NH, exchangeable), 8.31 (s, 1 H, C_5-H pyrazole), 7.88–7.31 (m, 10 H, Ar-H), 5.48 (s, 1 H, C_4-H pyrimidine), 2.37 (s, 3 H, CH_3CO), 2.02 (s, 3 H, CH_3). EIMS (70 eV, *m/z*, %): 390 ([M^++2], 22), 388 (M^+, 55), 335 (25), 130 (33), 125 (100), 104 (73), 91 (51), and 77 (81).

Full experimental details, tables, figures and spectroscopic data can be found in Supplemental files.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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