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Thiazole Derivatives: Synthesis Strategies, Structural Characterization, and Evaluation of their Functional Properties

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Abstract
Thiazole derivatives are a class of heterocyclic compounds that have gained significant attention in medicinal chemistry due to their diverse biological activities and therapeutic potential. This research article provides a comprehensive overview of the synthesis strategies, structural characterization, and evaluation of the functional properties of thiazole derivatives. The thiazole nucleus, a five-membered aromatic heterocycle composed of one nitrogen, one sulfur, and three carbon atoms, serves as a versatile scaffold for drug development. Thiazolo-pyrimidine derivatives were synthesized through one-pot condensation of substituted thiourea in alcoholic KOH, reacting with aromatic aldehyde and α-halo acid. The structure of 5,7-diphenyl-2H-thiazolo[3,2-a] pyrimidin-3(5H)-one was confirmed by FTIR and mass spectral data

Keywords: Heterocyclic, Thiazole, Derivatives, thiourea, onepot, Condensation

1. INTRODUCTION

2. Heterocyclic Chemistry

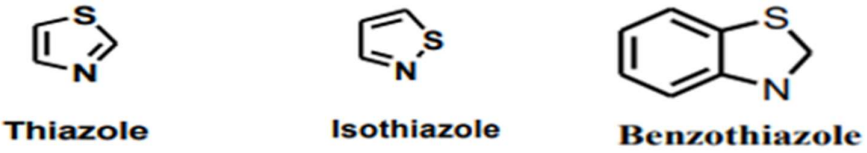
Heterocyclic chemistry, a complex and crucial branch of chemistry, focuses on compounds containing ring structures with at least one non-carbon atom. These compounds are prevalent in nature, particularly in plant products, and are renowned for their diverse biological activities. Due to their therapeutic potential, heterocyclic compounds are extensively used in pharmaceutical industries to combat various diseases and infections. However, natural sources alone cannot meet the growing demand for these compounds. Consequently, synthetic routes are employed to produce and optimize heterocyclic compounds based on structure-activity relationships, thereby fulfilling market needs and improving existing therapeutics [1].

Heterocyclic chemistry is a cornerstone of organic chemistry, encompassing two-thirds of all organic compounds. These cyclic structures contain carbon atoms and at least one heteroatom (typically sulfur, oxygen, or nitrogen) in their rings, which can be aromatic or non-aromatic. The most common heterocycles feature five- or six-membered rings with N, O, or S heteroatoms. Well-known examples include pyridine, pyrrole, furan, thiophene, pyrazole, thiazole, pyrimidine, and dioxane. Heterocyclic compounds are classified as aliphatic or aromatic, with aliphatic heterocycles being cyclic analogs of amines, ethers, thioethers, and amides. Ring strain significantly influences the properties of these compounds, particularly in aliphatic heterocycles [2]. Heterocyclic compounds typically feature small (3- and 4-membered) or common (5- to 7-membered) ring systems [3]. Key

examples include:
1. Pyridine: Six-membered ring with five carbon atoms and one nitrogen atom
2. Pyrrole, furan, and thiophene: Five-membered rings with four carbon atoms and one heteroatom (nitrogen, oxygen, or sulfur [4].

3. Thiazole

Thiazole, a heterocyclic compound containing sulfur and nitrogen atoms, plays a significant role in medicinal chemistry. This basic core scaffold is found in both natural compounds, such as Vitamin B1 (Thiamine), and various synthetic medicinal compounds. Thiazole is a crucial component of the penicillin nucleus and numerous derivatives with diverse pharmacological activities. These include antimicrobial agents (sulfazole, sulfasuxidine, sulfathiazole, and thiazolsulfone/Promizole), antiretroviral drugs (ritonavir), antifungals (abafungin), antihistamines, and antithyroid medications. Additionally, 2-Mercaptobenzothiazole (Mertax), a thiazole derivative, is used to accelerate rubber vulcanization [5]. Thiazole derivatives, including their reduced forms and condensed derivatives, have gained significant synthetic importance due to their expanding applications in medicine. These compounds have demonstrated efficacy as anthelmintics and anticancer agents (e.g., tiazofurin). The thiazole ring, when incorporated into cyanine dyes, serves as a photographic sensitizer. Furthermore, thiazole derivatives have exhibited a wide range of pharmacological activities, including anticonvulsant, antimicrobial, anti-inflammatory, anticancer, anti-HIV, antidiabetic, anti-Alzheimer, antihypertensive, and antioxidant properties [6-7].
The thiazole nucleus is a versatile scaffold in medicinal chemistry, prized for its diverse properties and functionalization potential. This five-membered aromatic heterocycle, composed of one nitrogen, one sulfur, and three carbon atoms, has proven instrumental in developing new leads and medications for various diseases. Thiazoles share similarities with oxazoles, featuring a basic nitrogen atom with an unshared electron pair. The thiazole ring structure is found in several marketed drugs, including febuxostat, dasatinib, ravuconazole, and actithiazic acid. The pharmacodynamic efficacy of these molecules has spurred chemists to explore new thiazole scaffolds with expanded applications. Additionally, the thiazole moiety is present in thiamine, a coenzyme essential for the oxidative decarboxylation of α-keto acids [8]. Thiazolidin-4-one derivatives of thiazole exhibit enhanced antibacterial activity [9]. The thiazolidine ring, a tetrahydro thiazole, is a key component of penicillin, a significant broad-spectrum antibiotic. Thiazole derivatives have demonstrated diverse biological activities, including treatment of allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections, as well as applications as hypnotics and analgesics. Thiazole is a pale-yellow liquid with the formula C3H3NS, possessing a pyridine-like odor. It has limited water solubility and boils at 116-118°C. Used as an intermediate in drug and dye synthesis, thiazole's planar, aromatic ring structure has numerous medicinal applications. Thiazoles (1,3-thiazoles) and isothiazoles (1,2-thiazoles) are part of the azole heterocyclic group, which includes imidazoles and oxazoles. Related structures include benzothiazole **and benzisothiazole [10-11].**



The thiazole moiety is a fundamental scaffold in numerous natural and synthetic compounds of medicinal importance. It is present in vitamin B1 (thiamine), a coenzyme crucial for the oxidative decarboxylation of α-keto acids. The thiazole nucleus is an essential component of bacitracin and penicillin, as well as various derivatives exhibiting diverse therapeutic properties. These include antimicrobial agents (sulfazole, sulfasuxidine, sulfathiazole, and promizole), antiretroviral drugs (ritonavir), antifungals (abafungin), antihistamines, and antithyroid medications. Synthetic thiazole derivatives have also demonstrated anthelmintic and anticancer (tiazofurin) activities. Furthermore, thiazole derivatives have shown potential in treating conditions such as epilepsy, inflammation, HIV, diabetes, Alzheimer's disease, and hypertension, as well as exhibiting antioxidant properties [12]. Prostaglandins containing a thiazole nucleus have demonstrated comparable binding to rat kidney prostaglandin receptors, specific effects on canine kidney vasculature, and the ability to increase renal blood flow. In medicinal chemistry, thiazole-containing compounds exhibit a wide range

of properties, including antioxidant, analgesic, antimicrobial, anti-inflammatory, antifungal, antiviral, anticonvulsant, and antitumor activities. Thiazole itself is the simplest member of the thiazole family. Thiazoles can be substituted at positions 2, 4, or 5 with hydroxyl, amino, or thio groups. These compounds react with alkyl halides to form corresponding thiazolium salts [13].

Thiazoles have medicinal significance as inhibitors of mitochondrial NADH dehydrogenase, specifically targeting NADH-ubiquinone reductase activity in mitochondrial membranes [14]. Benzothiazole (BT), a fusion of thiazole and benzene rings, exhibits diverse pharmacological properties, including antiviral, antibacterial, and fungicidal activities. BT derivatives also show potential as antiallergic, antidiabetic, antitumor, anti-inflammatory, anthelmintic, and anti-HIV agents [15]. The ongoing interest in thiazole derivatives stems from their broad spectrum of biological activities, which have applications in treating allergies, hypertension, inflammation, schizophrenia, bacterial and HIV infections. Additionally, these compounds have been explored as hypnotics and, more recently, for pain management [16].

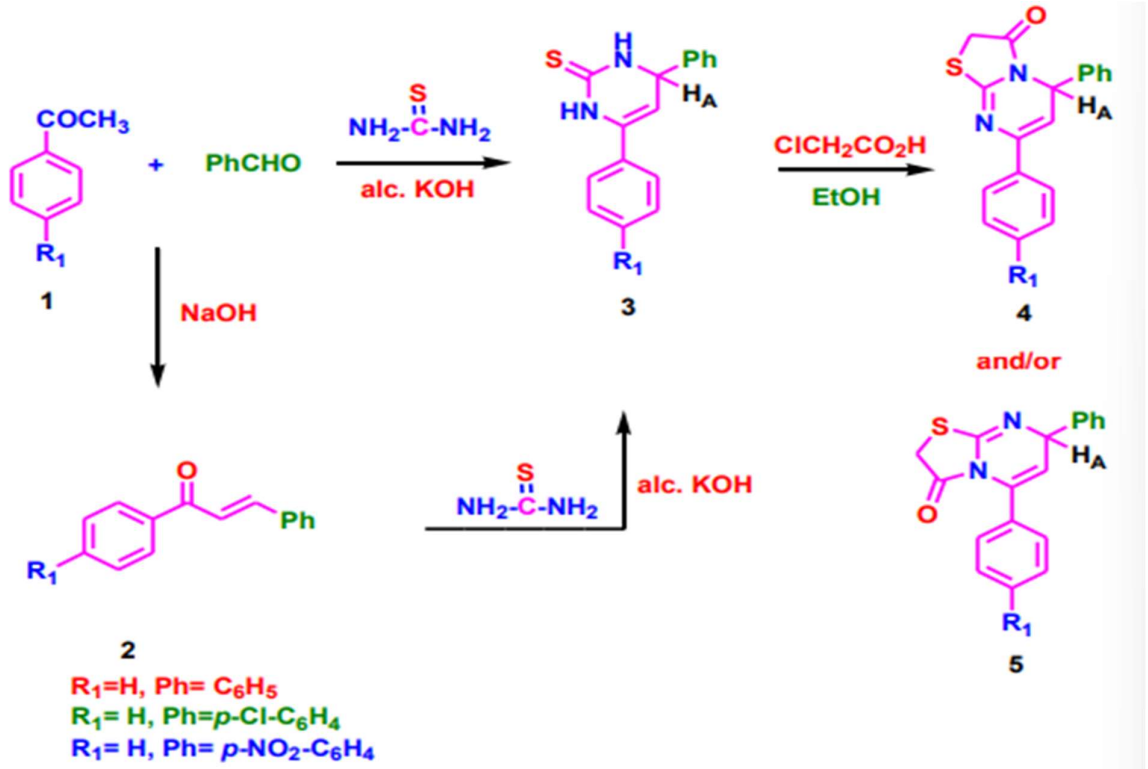
In drug design, derivatization of lead compounds' basic chemical structures is a widely accepted strategy to enhance pharmacokinetic and pharmacodynamic properties. The thiazole moiety, being highly significant, has undergone extensive derivatization methods as reported in literature. Thiazoles and their derivatives exhibit diverse structure-activity relationships and numerous medicinal applications, serving as precursors for biologically active compounds. Thiazoles demonstrate potent antitumor activity, particularly phenyl-substituted variants such as benzothiazoles. Additionally, 4-thiazolidinones and their derivatives have shown notable antiviral activity [17]. Derivatization of thiazole to thiazolidin-4-one enhances its antibacterial activity. 4-thiazolidinones and their derivatives demonstrate antimalarial properties. Reduced thiazoles are valuable in polypeptide and protein studies and occur as structural units in biologically important compounds. Thiazoles undergo various reactions through diverse routes and reagents, yielding useful heterocyclic compounds such as benzimidazole, benzodiazepine, and triazoles, which exhibit a range of activities. The extensive applications of thiazole-based derivatives as synthons in numerous biological compounds have provided significant momentum to research in this field [18-19].

Thiazoles and their substituted derivatives are an attractive pharmacophoric unit in drug design strategies, as they exhibit a wide range of pharmaceutical activities. In the present study, two different types of derivatives were synthesized: thiazolo-pyrimidine derivatives and pyrazole-carbothioamide derivatives.

The chemical characterization of the newly synthesized derivatives was analyzed through FTIR, 1H-NMR, 13C-NMR, and mass spectrometry. The structural parameters and regiochemistry of the cyclized products were established using spectral data and verified by Density Functional Theory (DFT) analysis.

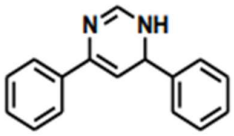
SYNTHESIS, CHARACTERIZATION AND EVLUATION OF THIAZOLOZOLO-PYRIMIDINE DERIVATIVES

In the present study, 5,7-diphenyl-2H-thiazolo[3,2-a] pyrimidin-3(5H)-one derivatives were synthesized from substituted thiones. During the synthesis of the thiazolo-pyrimidine system, a mixture of acetophenone 1, a substituted benzaldehyde, and thiourea in an alkaline medium was refluxed for 4 hours, resulting in the formation of thione 3. The characterization of the thione was based on spectral data. The unsymmetrical thione 3 on condensation with chloroacetic acid, followed by in situ cyclization, was likely to give either compound 4 or its isomer 5, or a mixture of both, depending on the mode of cyclization (Scheme 1) [20-24]. However, when thione 3 was treated with ethyl chloroacetic acid in the presence of anhydrous sodium acetate in absolute ethanol, a single product (TLC) 4 or 5 was obtained in 75% yield. Various reaction conditions, color, texture, percentage yield, and melting points of each derivative (1a, 1b, 1c, 2a, 2b, 2c) were recorded (Table 1).



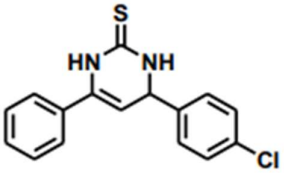
Scheme 1: Synthesis of 5,7-diphenyl-2H-thiazolo[3,2-a] pyrimidin-3(5H)-one from thiones

4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione (1a) [25]



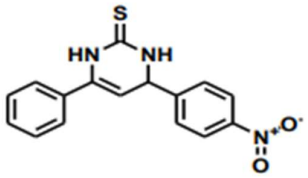
Property	Observation
Appearance	Yellow solid
Yield	85%
Melting Point	152-155°C
Literature Melting Point	158-160°C

4-(4-chlorophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione (1b) [25]



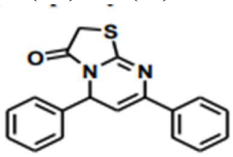
Property	Observation
Appearance	Yellow solid
Yield	85%
Melting Point	163-165°C
Literature Melting Point	158-160°C

4-(4-nitrophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione (1c) [25]



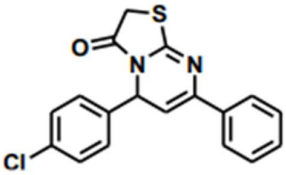
Property	Observation
Appearance	Yellow solid
Yield	85%
Melting Point	152-155°C
Literature Melting Point	158-160°C

5,7-diphenyl-2H-thiazolo[3,2-a] pyrimidin-3(5H)-one (2a)



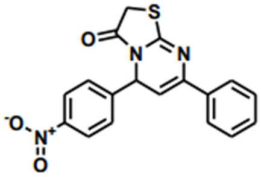
Property	Observation
Appearance	Yellow solid
Yield	62%
Melting Point	102-104°C
IR (cm-1)	1728 (C=O), 1589 (C=N)
Mass Spectrometry (MS)	m/z 307.1 (M+H+ ,60 %)
Elemental Analysis (Calculated %)	**C:** 70.56; **H:** 4.61; **N:** 9.14; **S:** 10.47
Elemental Analysis (Found %)	**C:** 70.67; **H:** 4.71; **N:** 9.24; **S:** 10.51.

5-(4-chlorophenyl)-7-phenyl-2H-thiazolo [3,2-a] pyrimidin-3(5H)-one (2b)



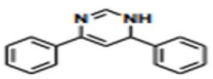
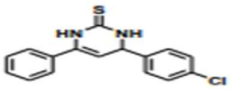
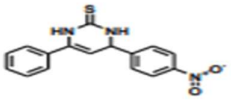
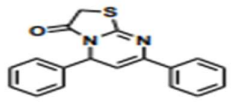
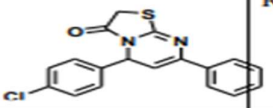
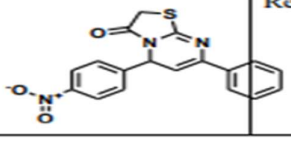
Property	Observation
Appearance	Yellow solid
Yield	62%
Melting Point	102-104°C
IR (cm-1)	1695 (C=O), 1665 (C=N)
Elemental Analysis (Calculated)	**C:** 63.43; **H:** 3.84; **N:** 8.22; **S:** 9.41
Elemental Analysis (Found)	**C:** 63.61; **H:** 3.71; **N:** 8.28; **S:** 9.51

3-(4-nitrophenyl)-7-phenyl-2H-thiazolo [3,2-a] pyrimidin-3(5H)-one (2c)



Property	Observation
Appearance	Yellow solid
Yield	62%
Melting Point	102-104°C
IR (cm-1)	1730 (C=O), 1639 (C=N)
Elemental Analysis (Calculated %)	**C:** 61.53; **H:** 3.73; **N:** 11.96; **S:** 9.13
Elemental Analysis (Found %)	**C:** 63.61; **H:** 3.71; **N:** 8.28; **S:** 9.5

Table 1. Reaction parameters for synthesis of 5,7-diphenyl-2H-thiazolo [3,2-a] Pyrimidin-3(5H)-one derivatives

Sample no.	Chemical structure of Derivatives	Reaction Condition	Time (Min)	Solvent	Colour/ Appearance	% Yield	Melting point
1a		Reflux	240	Ethanol	Yellow solid	85%	152-155°C
1b		Reflux	180	Ethanol	Yellow solid	85%	163-165°C
1c		Reflux	180-240	Ethanol	Yellow solid	85%	152-155°C
2a		Reflux	180-240	DMF-Ethanol	Yellow solid	62 %	102-04 °C
2b		Reflux	180-240	DMF-Ethanol	Yellow solid	62 %	102-04 °C.
2c		Reflux	180-240	DMF-Ethanol	Yellow solid	62 %	102-04 °C.

Characterization

The characterization of organic compounds includes purity of organic compounds, determination of composition, functional groups present, physical properties, chemical structures of compounds and their spatial arrangement. The characterization of organic compounds involves several key aspects: determining the purity of the synthesized organic compounds, establishing the elemental composition of the compounds, identifying the functional groups present in the molecules, measuring the physical properties, such as melting point, boiling point, and solubility and determining the chemical structures of the compounds and their spatial arrangements. These characterization techniques provide comprehensive information about the identity, purity, and structural features of the synthesized organic compounds.

FTIR Analysis

Fourier-transform infrared (FTIR) spectroscopy is a technique used to obtain the infrared spectrum of absorption or emission from solid, liquid, or gaseous samples. This method is useful for identifying and characterizing unknown compounds based on the presence of different functional groups. The spatial positions of functional groups can be confirmed by their corresponding stretching and bending vibrational frequencies, which arise due to different chemical environments.

In general, the FTIR spectrum of thiazole-pyrimidine derivatives represents absorption bands in the range of 1625 cm-1 and 1183 cm-1, associated with C=N and C=S functionalities, respectively. A strong peak in the range of 785–540 cm-1 is observed due to C-Cl stretching vibrations in aliphatic chlorides. The absorption band at 1625 cm-1 corresponds to endocyclic C=N stretching vibrations, while the 1185-940 cm-1 range is attributed to

mixed vibrations of the -N-C=S moiety, with the 1183 cm-1 band due to the C=S group. The band at 3414 cm-1 is attributed to N-H stretching.

In the present study, the appearance of characteristic bands has been observed mainly for C=O and C=N groups. Additionally, C-N, NO2 stretching, and bending bands have also been observed.

In the 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione compound, the FTIR spectrum exhibits a characteristic peak at 1625 cm-1 associated with the C=N functionality and a peak at 1183 cm-1 corresponding to the C=S group. A strong peak observed in the range of 785-540 cm-1 is attributed to the C-Cl stretching vibrations in aliphatic chlorides.

The absorption band at 1625 cm-1 corresponds to the endocyclic C=N stretching vibrations. The 1185-940 cm-1 range is associated with the mixed vibrations of the -N-C=S moiety, while the 1183 cm-1 band is specifically due to the C=S group. The band at 3414 cm-1 is attributed to the N-H stretching (**Figure 1**) In the compound 5,7-diphenyl-2H-thiazolo [3,2-a] pyrimidin-3(5H)-one (2a), the FTIR spectrum exhibits a characteristic peak at 1728 cm-1, which can be attributed to the carbonyl (C=O) group. This peak is indicative of the carbonyl functionality formed during the cyclization process. Additionally, a characteristic peak at 1589 cm-1 is observed, corresponding to the stretching vibrations of the endocyclic C=N groups. (**Figure 2**). The compound 5-(4-chlorophenyl)-7-phenyl-2H-thiazolo [3,2-a] pyrimidin-3 (5H)-one (2b) exhibits several characteristic infrared (IR) absorption bands. The strong band at 1730 cm-1 is attributed to the carbonyl (C=O) group, which is formed as a result of the cyclization process. The peak at 1665 cm-1 corresponds to the Amide-I band, which arises due to the (C=N) stretching vibrations. Additionally, an absorption band at 1589 cm-1 is observed, which corresponds to the endocyclic C=N stretching vibrations. Furthermore, a strong peak in the range of 785–540 cm-1, which in this case appears at 714 cm-1, is attributed to the C-Cl stretching vibrations in the aliphatic chlorides (**Figure 3).** The compound 3-(4-nitrophenyl)-7-phenyl-2H-thiazolo [3,2-a] pyrimidin-3(5H)-one (2c) exhibits the following characteristic infrared (IR) absorption bands. A strong band at 1730 cm-1 is attributed to the (C=O) stretching vibrations. A peak at 1639 cm-1 corresponds to the Amide-I band, which is due to the (C=N) stretching vibration. An absorption band at 1599 cm-1 corresponds to the endocyclic C=N stretching vibrations. Peaks in the region of 1550–1490 cm-1 appear as a result of the asymmetric (strong) and symmetric (strong) stretching vibrations of the nitro group. Additionally, a vibrational band in the range of 1355–1315 cm-1 has been observed, which is due to the presence of the nitro group in the derivative (**Figure 4)**. The compounds 2a-2c exhibit several characteristic infrared (IR) absorption bands related to their chemical structures. Generally, stretching bands in the range of 1350–1250 cm-1 are observed, which correspond to the CN stretching of the heteroaromatic systems. Additionally, complex bands in the region of 3300 cm-1 and a weaker band at around 3100 cm-1 are attributed to the secondary amides present in the compounds. These bands are a result of the Fermi resonance overtone of the 1550-cm-1 band.

Mass Analysis

Mass spectrometry is an analytical technique that measures the mass-to-charge ratio of ions. The generation of ions during the ionization process determines the fragmentation and dissociation patterns of a complex molecule. The intensity of the base ion peak helps to interpret the primary route of dissociation for an organic compound. The mass spectrum is a plot of the signal intensity as a function of the mass-to-charge ratio (m/z) of the analyte. In the mass spectrum of the TLC-purified product, the presence of a quasimolecular ion peak at m/z 307.1 (M+H+, 60%) suggests the formation of the thiazolidinone 4 or 5 **(Figure 5)**. The IR and mass spectral data alone were inconclusive in determining the structure as either 4 or 5. However, based on the DFT (Density Functional Theory) studies, the structure 4 was finally assigned as the preferred cyclization product over structure 5.

Computational Studies/DFT analysis of 5,7-diphenyl-2H-thiazolo [3,2-a] Pyrimidin-3(5H)-one derivatives

Density Functional Theory (DFT) is a computational modeling method that has been widely used in physics and chemistry for the past 35 years to study the electronic structure of various atoms and molecules. DFT is a versatile and important technique employed in computational physics and computational chemistry, particularly for the structure validation of cyclized compounds. In the present case, computational studies of compound 4 and its corresponding regioisomer 5 were carried out using the DFT method. The molecular geometry optimization was executed with the Gaussian 09 W software package, utilizing the B3LYP (Becke three-parameter Lee-Yang-Parr) exchange-correlation functional, which combines the hybrid exchange functional of Becke with the gradient-correlation functional by Lee, Yang, and Parr [26-29]. The 6-31G (d) basis set was used for the DFT

studies on the isomeric pair 4 and 5. The optimized configurations of compounds 4 and its isomer 5, along with their atom numbering schemes, are shown in Figure 4.6. Density Functional Theory (DFT) is a computational modeling method that has been widely used in physics and chemistry for the past 35 years to study the electronic structure of various atoms and molecules. DFT is a versatile and important technique employed in computational physics and computational chemistry, particularly for the structure validation of cyclized compounds. In the present case, computational studies of compound 4 and its corresponding regioisomer 5 were carried out using the DFT method. The molecular geometry optimization was executed with the Gaussian 09 W software package, utilizing the B3LYP (Becke three-parameter Lee-Yang-Parr) exchange-correlation functional, which combines the hybrid exchange functional of Becke with the gradient-correlation functional by Lee, Yang, and Parr. The 6-31G (d) basis set was used for the DFT studies on the isomeric pair 4 and 5. The optimized configurations of compounds 4 and its isomer 5, along with their atom numbering schemes, are shown in **Figure 6**. The optimized bond lengths and bond angles obtained from the geometry optimization of structures 4 and 5 are reported in **Table 2**. In the case of structure 4, the optimized bond lengths of the C=O and C-S bonds in the thiazolidinone ring are 1.214 Å and 1.814 Å, respectively, which are close to the actual bond lengths. The optimized bond angles for O-C-N and S-C-N were observed to be 123.62° and 122.95°. For structure 5, the optimized bond lengths of the C=O and S-C bonds in the thiazolidinone ring are 1.19 Å and 1.838 Å, respectively. The optimized bond angles for C-N-C and S-C-N were observed to be 115.63° and 121.33°. It is important to note that the slight differences in the bond parameters are attributed to the fact that the theoretical calculations have been carried out for isolated molecules in the gaseous phase. The total energies obtained for the optimized structures 4 and 5 are -801,330.19 kcal/mol and -801,320.1 kcal/mol, respectively. This indicates that structure 4 is more stable than the isomeric structure 5.

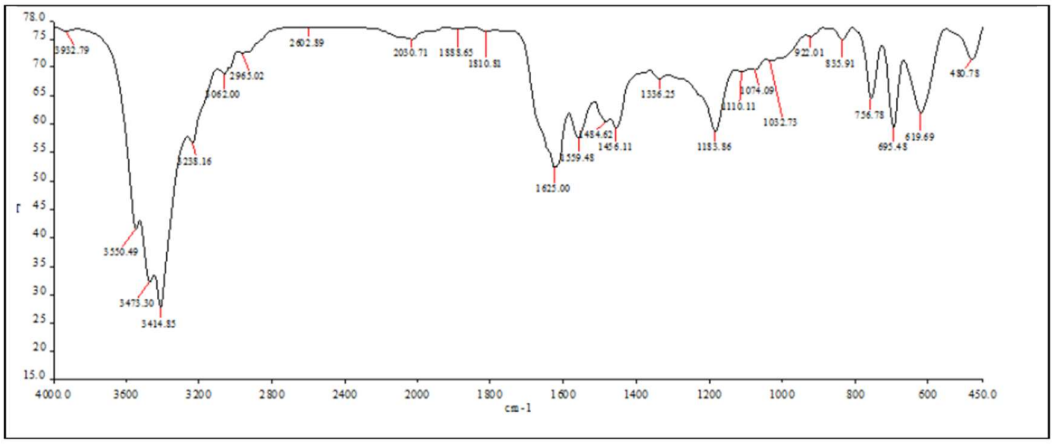


Figure 1: FTIR spectrum of 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)- thione (1)

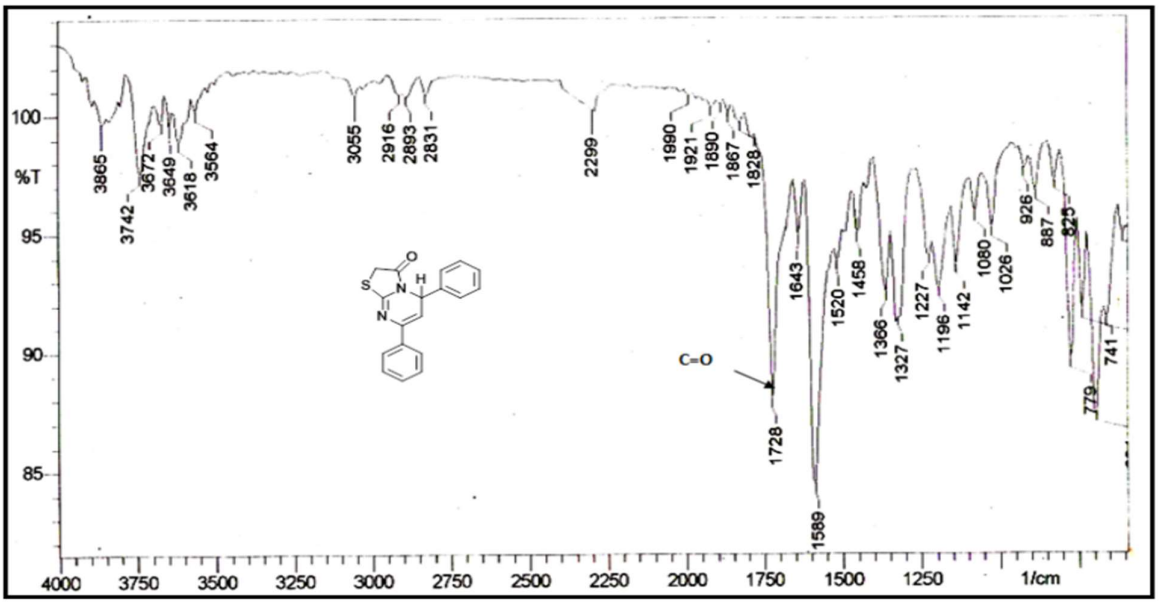


Figure 2: FTIR spectrum of 5,7-diphenyl-2H-thiazolo[3,2-a] pyimidin-3(5H)- one (2a).

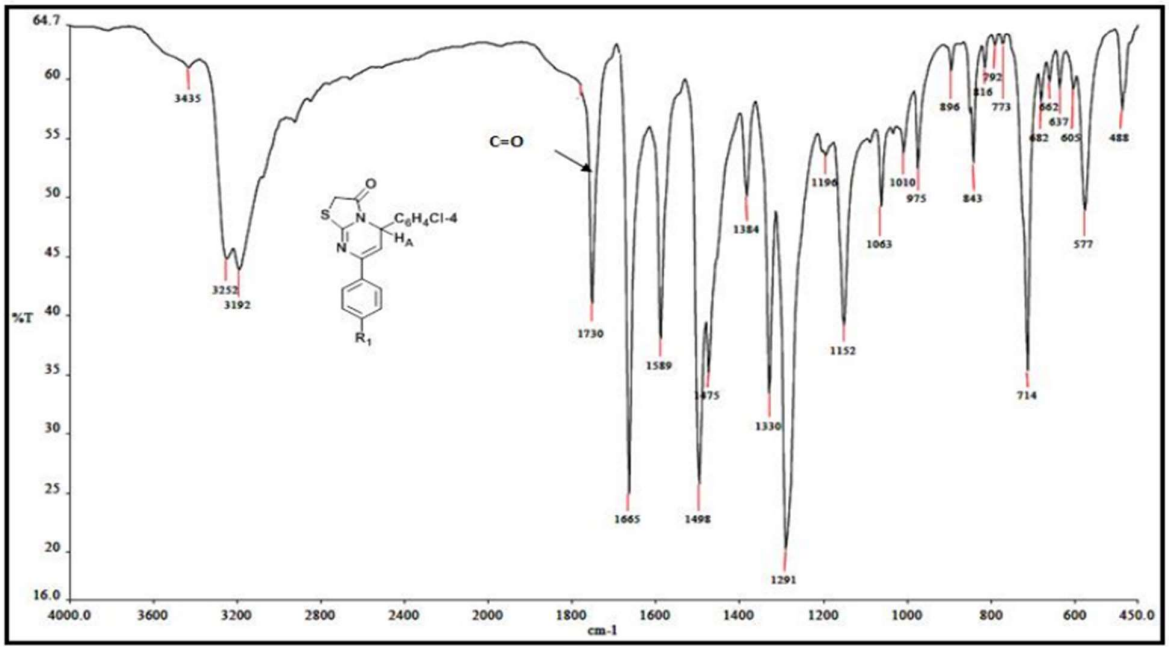


Figure 3: FTIR spectrum of [5-(4-chlorophenyl)-7-phenyl-2H-thiazolo [3,2- a] pyrimidin-3(5H)-one (2b).

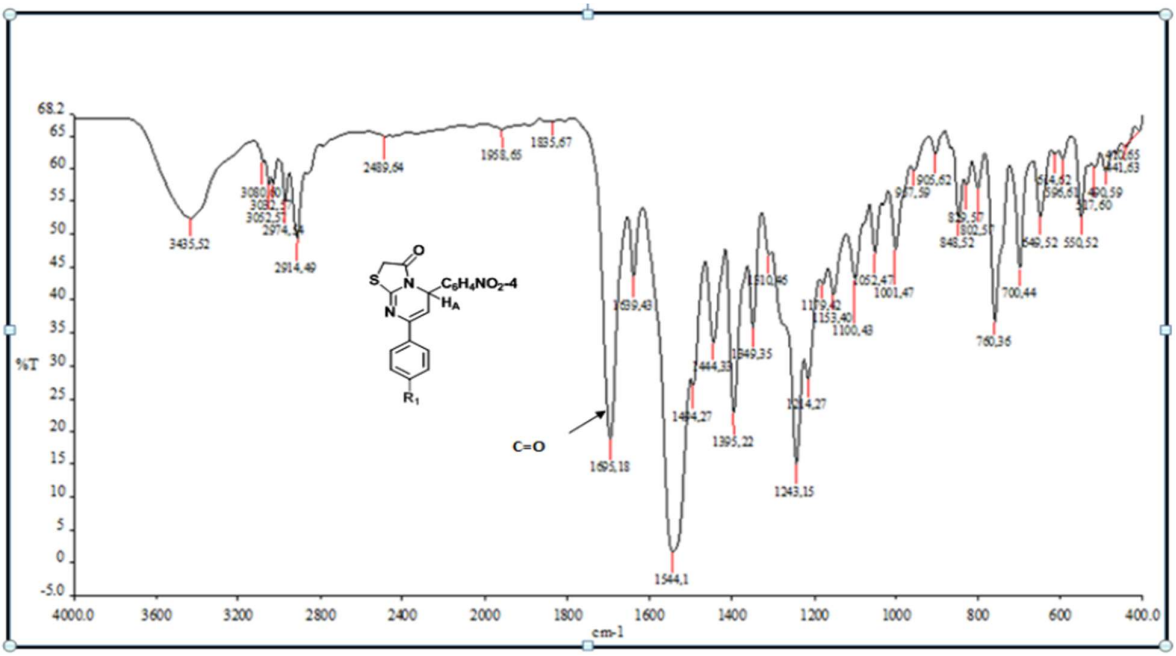


Figure 4: FTIR spectrum of 5-(4-nitrophenyl)-7-phenyl-2H-thiazolo [3,2- a] pyrimidin-3(5H)-one (2c).

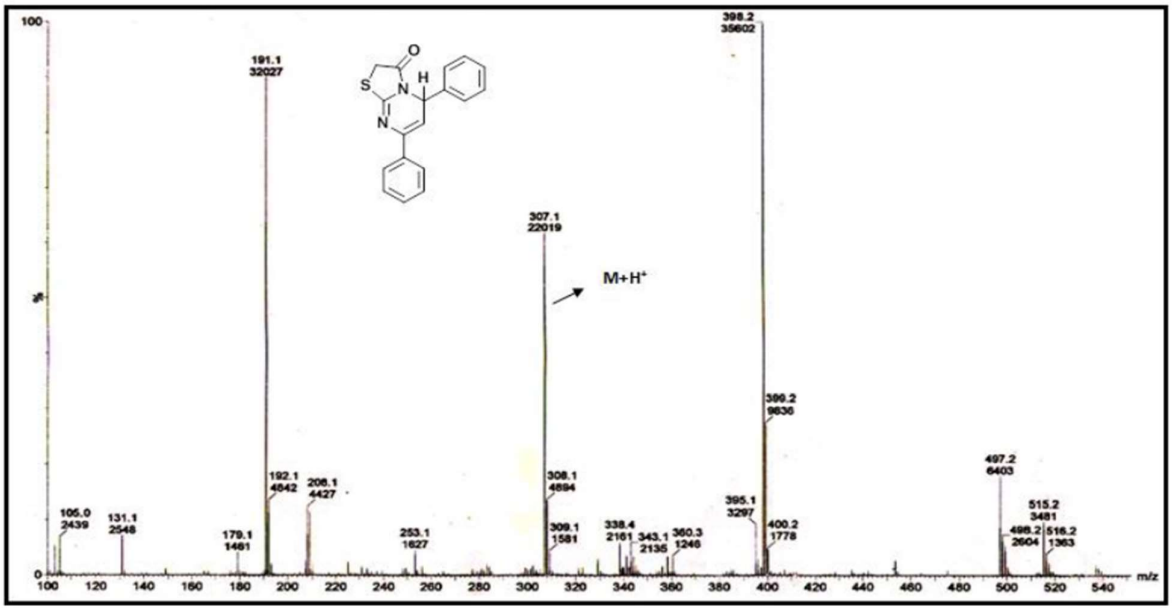


Figure 5: Mass spectrum of 5,7-diphenyl-2H-thiazolo[3,2-a] pyimidin3(5H)-one

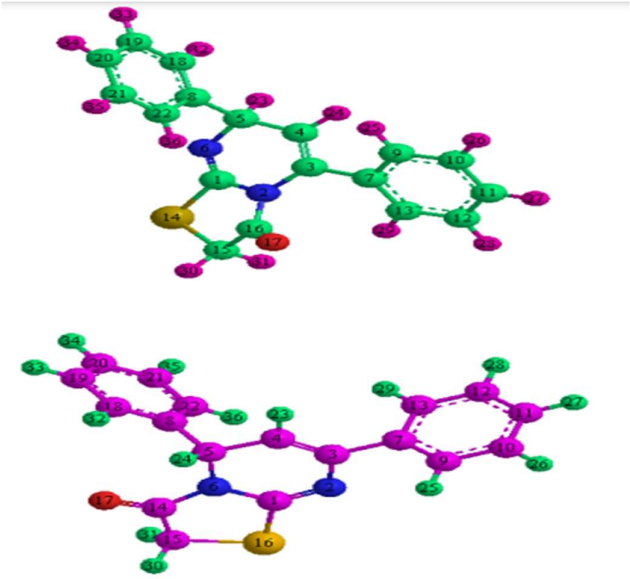


Figure 6: Optimized structures of 7-diphenyl-2H-thiazolo [3,2-a] Pyrimidin3(5H)-one derivative (compound 4 and its regio-isomer 5) by DFT analysis.

Table 2: Selected calculated bond parameters obtained by geometry optimization of 5,7-diphenyl-2H-thiazolo [3,2-a] Pyrimidin-3(5H)-one derivative (compound 4 and its regio-isomer 5) by DFT analysis.

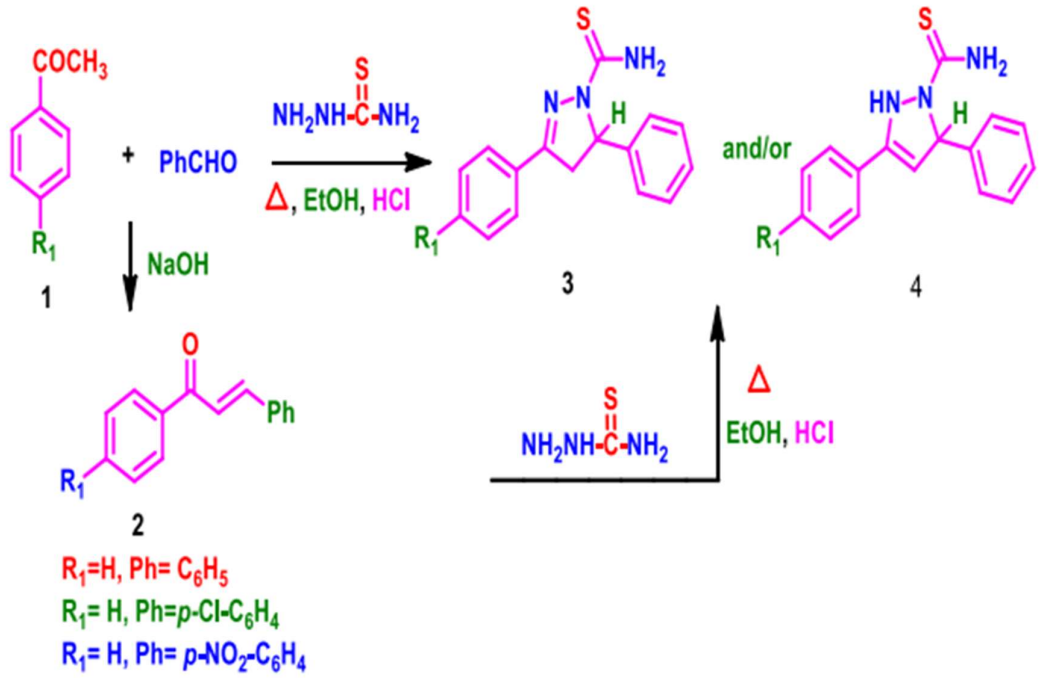
Bond lengths(Å)			
S(16)-C(1)	1.8140	C(15)-S(14)	1.8712
C(1)-N(6)	1.3882	N(2)-C(1)	1.4125
C(15)-S(16)	1.8681	C(1)-S(14)	1.8384
C(1)-N(2)	1.2554	N(6)-C(1)	1.2377
C(14)-O(17)	1.2149	C(16)-O(17)	1.2080
C(14)-N(6)	1.3717	N(2)-C(3)	1.4368
N(2)-C(3)	1.4252	C(16)-N(2)	1.3924
C(5)-H(24)	1.0798	C(5)-H(23)	1.0827
C(9)-C(10)	1.3845	C(5)-N(6)	1.4783
C(7)-C(9)	1.3926	C(7)-C(9)	1.3909

Bond Angles (°)			
S(16)-C(1)-N(2)	122.95	C(15)-S(14)-C(1)	89.55
S(16)-C(1)-N(6)	111.04	S(14)-C(15)-C(16)	107.27
N(2)-C(1)-N(6)	125.98	N(2)-C(16)-C(15)	110.57
C(1)-S(16)-C(15)	90.591	N(2)-C(16)-O(17)	125.97
H(31)-C(15)-S(16)	109.84	C(15)-C(16)-O(17)	123.39
H(30)-C(15)-S(16)	110.20	C(1)-N(6)-C(5)	120.04
S(16)-C(15)-C(14)	107.05	N(6)-C(5)-C(4)	111.33
O(17)-C(14)-C(15)	123.29	N(6)-C(5)-H(23)	106.39
O(17)-C(14)-N(6)	123.62	N(6)-C(5)-C(8)	111.46
C(15)-C(14)-N(6)	113.07	C(4)-C(3)-N(2)	117.21
C(1)-N(6)-C(14)	117.61	S(14)-C(1)-N(2)	111.04
C(1)-N(6)-C(5)	121.57	C(3)-N(2)-C(16)	127.70
C(14)-N(6)-C(5)	120.6898	N(2)-C(1)-N(6)	127.59
C(1)-N(2)-C(3)	118.1086	S(14)-C(1)-N(6)	121.33

SYNTHESIS, CHARACTERIZATION OF PYRAZOLE-CARBOTHIOAMIDE DERIVATIVES

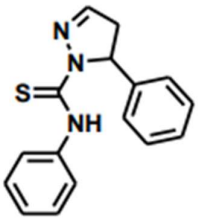
Synthesis of 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1) derivatives.

In the present work, the synthesis of pyrazole-carbothioamide derivatives was carried out. The reaction involved the use of benzaldehyde or substituted benzaldehydes and thiosemicarbazide in ethanol, in the presence of concentrated hydrochloric acid (HCl), under reflux conditions for 3 hours. After the completion of the reaction, the reaction mixture was kept overnight, and a yellow-colored product was obtained, which was then isolated and recrystallized. During the synthesis of the pyrazole-carbothioamide derivatives, the first step was the synthesis of the arylidene 2 compound. This was achieved by the condensation of acetophenone and substituted aromatic aldehydes in the presence of 5% sodium hydroxide (NaOH) in an aqueous medium, following a reported procedure with minor modifications [30]. In a one-pot condensation system, acetophenone 1, thiosemicarbazide, and substituted aromatic aldehydes were combined in the presence of anhydrous ethanol and 1-2 drops of concentrated HCl, which afforded the corresponding 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide 1d-f, as outlined in Scheme 2. According to the reaction scheme, there was a possibility of the formation of two regioisomers. In this case, the formation of compound 3 was favored over the regioisomer 4, as suggested by the DFT (Density Functional Theory) analysis, which indicated the preferential formation of the hydrazone. The various reaction parameters, including the appearance/texture, percentage yield, and melting point of each derivative (1a, 1b, 1c) have been recorded (Table 3).



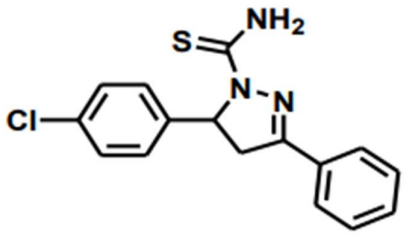
Scheme 2: Synthesis of substituted pyrazole-carbothioamide derivatives.

3, 5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1a)



Property	Observation
Appearance	Yellow solid
Yield	62%
Melting Point	90-92°C
IR (cm-1)	3443, 3263 (NH2), 1590 (C=N), 1347 (C=S)
Mass Spectrometry (MS)	m/z 281.1 (M+, 20 %)
Elemental Analysis (Calculated %)	**C:** 68.30; **H:** 5.37; **N:** 14.93; **S:** 11.40
Elemental Analysis (Found %)	**C:** 68.47; **H:** 5.41; **N:** 14.64; **S:** 11.57

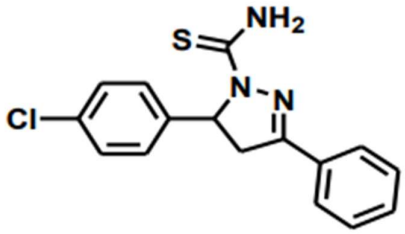
5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1b)



Property	Observation
Appearance	White solid
Yield	7%

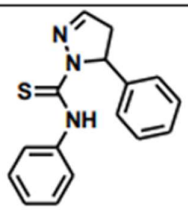
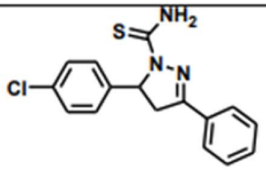
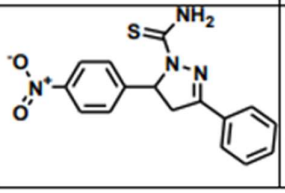
Melting Point	90-92°C
IR (cm-1)	427, 3262 (NH2), 1595 (C=N), 1374 (C=S)
Mass Spectrometry (MS)	m/z 281.1 (M+, 20 %)
Elemental Analysis (Calculated %)	**C:** 60.85; **H:** 4.47; **N:** 13.31; **S:** 10.15
Elemental Analysis (Found %)	**C:** 60.47; **H:** 4.61; **N:** 13.64; S: 10.27

5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1c)



Property	Observation
Appearance	Brown solid
Yield	68 %
Melting Point	154-56 °C
IR (cm-1)	3427, 3262 (NH2), 1595 (C=N), 1374 (C=S)
Elemental Analysis (Calculated %)	**C:** 58.88; **H:** 4.32; **N:** 17.17; **S:** 9.82
Elemental Analysis (Found %)	**C:** 58.47; **H:** 4.61; **N:** 17.44; **S:** 10.17

Table 3: Reaction parameters for synthesis of pyrazole-carbothioamide derivatives

Sample no.	Chemical structure	Reaction Condition	Time (Min)	Solvent	Colour/ Appearance	% Yield	Melting point
1a		Reflux	180-240	Ethanol	Yellow solid	62	90-92 °C
1b		Reflux	180	Ethanol	White solid	7	105-07 °C
1c		Reflux	180	Ethanol	Brown solid	68	154-56 °C

4.2.2. Characterization

The characterization of organic compounds involves the assessment of their purity, determination of composition, identification of functional groups, evaluation of physical properties, and elucidation of the molecular structure and its spatial arrangement. In the case of compounds 3d-f, the structural features have been established through the use of spectroscopic methods, such as Fourier Transform Infrared (FTIR) spectroscopy, elemental analysis, and mass spectrometry.

4.2.2.1. FTIR analysis

In the FTIR analysis of substituted pyrazole-carbothioamide derivatives, characteristic absorption bands for C=S and C=N functional groups were observed. Additionally, bands corresponding to C-N, NH_2, NO_2, and symmetrical and asymmetrical stretching and bending vibrations were also detected.

Three consistent bands appeared in the regions of 1570-1397 cm-1, 1420-1260 cm-1, and 1140-940 cm-1, attributed to mixed vibrations of the –N-C=S moiety. Medium to strong intensity bands were observed at 1650 to 1380 cm-1, corresponding to the three ring stretching bands of the pyrazole nucleus. A stretching band in the range of 1350–1250 cm-1 was attributed to C-N stretching of aromatic systems.

The observed bands are attributed to a Fermi resonance resulting from N-H stretching and the overtone of the 1550 cm-1 bending band. In 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1a), characteristic peaks due to the –N-C=S moiety were recorded at 1567.18, 1490, 1473, 1451, 1363, 1347, 1206, 1075, and 947 cm-1, corresponding to symmetrical and asymmetrical stretching and bending vibrations. The three ring stretching bands of the pyrazole nucleus in 3a overlapped with peaks from the –N-C=S moiety (Figure 7a).

The presence of carbothioamide amino stretching vibration bands at 3443 and 3263 cm-1 is attributed to N-H stretching. A characteristic peak at 1589 cm-1 is due to (C=N) stretching of endocyclic C=N vibrations, while the peak at 1347 cm-1 indicates the presence of the C=S group. In 5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1b), characteristic peaks were recorded at 1535, 1485, 1374, 1354, 1269, 1183, and 998 cm-1, corresponding to symmetrical and asymmetrical stretching and bending vibrations of the –N-C=S moiety. The ring stretching bands of the pyrazole nucleus in 3b were observed at 1646 and 1618 cm-1, as well as overlapping vibrations with the –N-C=S moiety.

A characteristic peak at 1595 cm-1 was attributed to the (C=N) stretching of endocyclic C=N vibrations. Strong and broad bands in the region of 3340-2500 cm-1 (specifically at 3262, 3151, 2945, and 2651 cm-1) were recorded due to N-H stretching vibrations.

In 5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1b), a strong peak at 757 cm-1 was observed due to C-Cl stretching vibrations, typically occurring in the range of 785–540 cm-1 (Figure 7b).

For 5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1c), medium intensity peaks appeared at 1445 and 1415 cm-1, corresponding to the three ring stretching bands of the pyrazole nucleus. Peaks at 1309, 1251, 1185, and 1150 cm-1 were attributed to symmetrical and asymmetrical stretching and bending vibrations of the –N-C=S moiety. A characteristic band at 1499 cm-1 was due to (C=N) stretching of endocyclic C=N vibrations. Broad bands at 3427 and 3262 cm-1 were recorded due to N-H stretching vibrations. The nitro group was observed through peaks in the region of 1550–1490 cm-1 (asymmetric stretch, strong) and 1355–1315 cm-1, with the symmetric stretch (strong) occurring at 1499 cm-1 (Figure 7c).

4.2.2.2. Mass and NMR analysis

In the present study, mass analysis was carried out for the derivative 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (1a). The mass spectrum of 3d showed an [M+] peak at m/z 281 (20%), confirming its structure. The proposed structure of 3a was further validated by DFT studies. Similarly, the structures of 1e and 1f were established using analytical and spectral data (Figure 8).

The ^{1}H NMR spectrum showed two multiplets at δ 7.32 and δ 7.35, each integrating for five protons, corresponding to the protons on the phenyl rings (Figure 9). The ^{13}C NMR spectrum revealed peaks at δ 165.2 ppm and δ 162.5 ppm, attributed to the C=O and C=N carbons, respectively (Figure 10).

4.2.2.3. Computational Studies/DFT analysis of pyrazole carbothioamide Derivatives (compound 3 and its isomer 4)

The molecular geometry optimization was performed using the Gaussian 09 W software package [31], employing Density Functional Theory (DFT) methods with the B3LYP (Becke three-parameter Lee-Yang-Parr) exchange-correlation functional. This functional combines Becke's hybrid exchange functional [32] with the gradient-correlation functional of Lee, Yang, and Parr [33]. The 6-31G (d) basis set was utilized for DFT studies on the isomeric pair 3/4. Figure 11 displays the optimized configurations of compounds 3 and its isomer 4, including their atom numbering schemes. The optimized bond lengths and bond angles obtained from the geometry optimization of structures 3 and 4 are reported in Table 4. In structure 3, the optimized bond lengths in the pyrazoline ring are 1.2639 Å for C (7) = N (11), 1.41 Å for N(10)-N(11), and 1.3472 Å for C(19)-N(10), which closely match actual bond lengths. The optimized bond angles are 114.3389˚ for N (11)-C (7)-C (8), 109.5076˚ for C(7)-N(11)-N (10), and 119.4961˚ for N(11)-N(10)-C(19). For structure 4, the optimized bond lengths in the

pyrazoline ring are 1.4526 Å for C (7)-N (11), 1.4590 Å for N (11)-N (10), and 1.3337 Å for C(19)-N(10). The optimized bond angles are 111.8633˚ for N (11)-C (7)-C (8), 103.4375˚ for C(7)-N(11)-N(10), and 112.2371˚ for N(11)-N(10)-C(9). Slight differences in bond parameters are attributed to theoretical calculations being performed for isolated molecules in the gaseous phase.

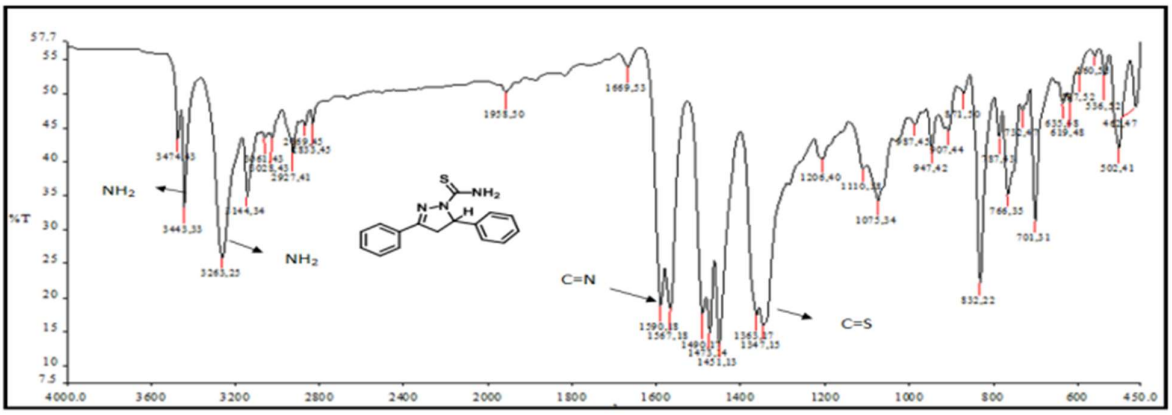


Figure 7a: FTIR spectrum of 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1- carbothioamide (1a)

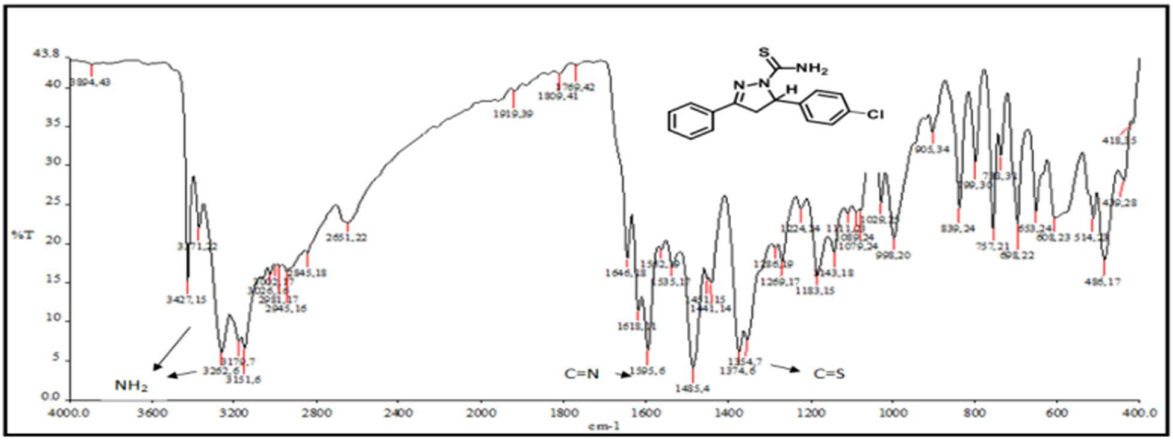


Figure 7b: FTIR spectrum of 5-(4-chlorophenyl)-3-phenyl-4,5-dihydro-1Hpyrazole-1-carbothioamide (1b).

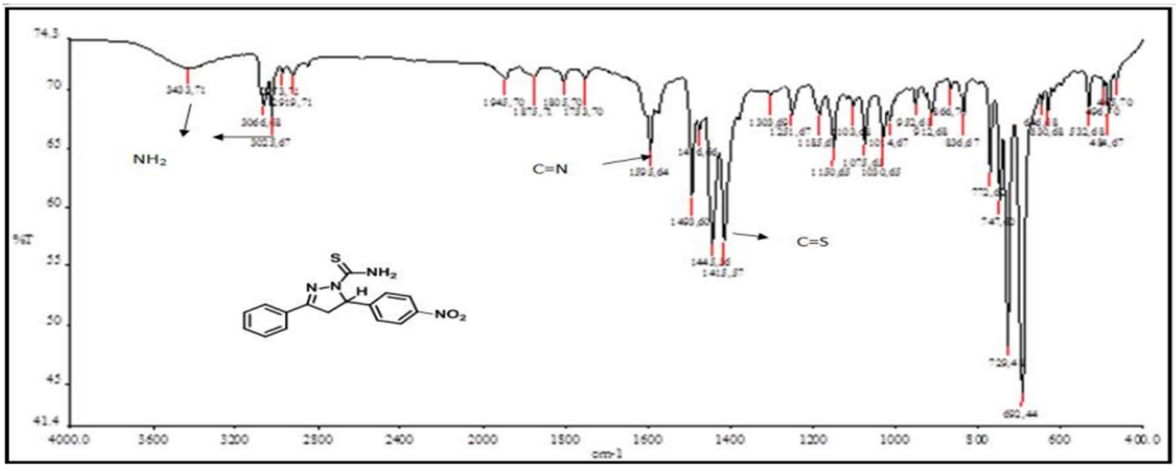


Figure 7c: FTIR spectrum of 5-(4-nitrophenyl)-3-phenyl-4,5-dihydro-1Hpyrazole-1-carbothioamide (1c).

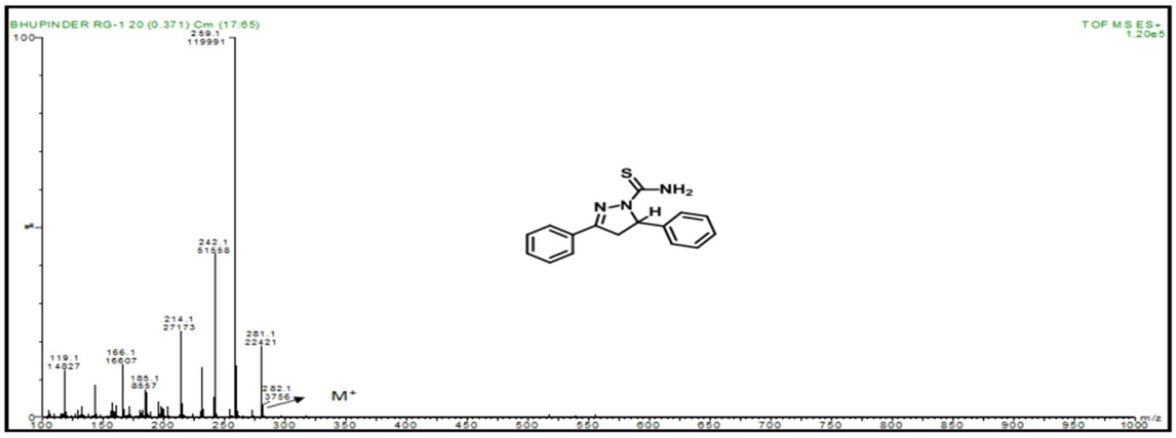


Figure 8: Mass spectrum of 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1- carbothioamide(1a)

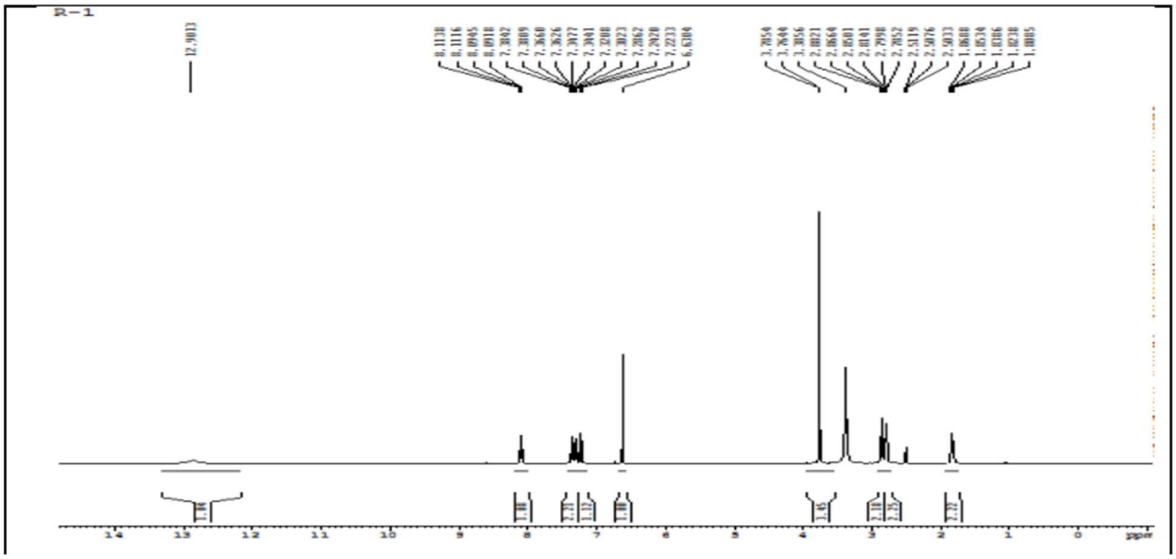


Figure 9: [1]H NMR spectrum of 3,5-diphenyl-4,5-dihydro-1H-pyrazole-1- carbothioamide

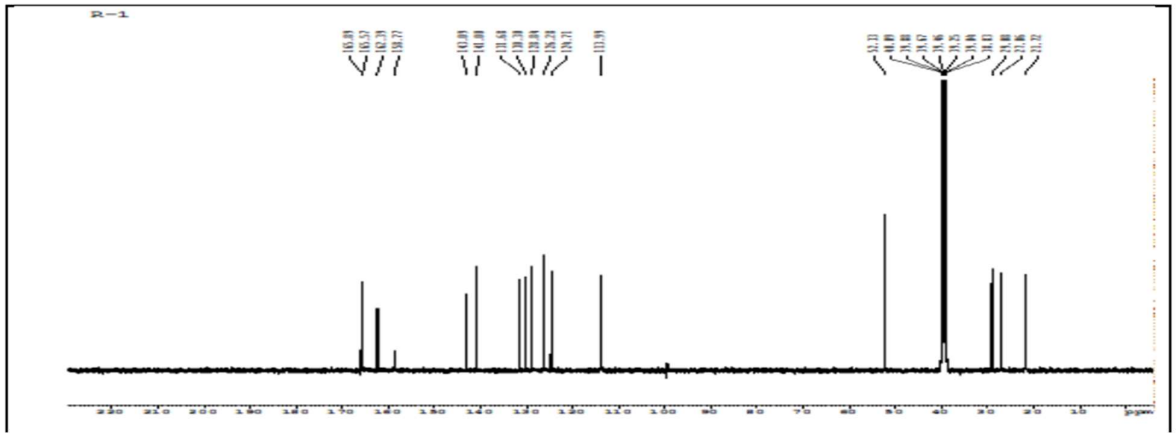


Figure 10: [13]C NMR spectrum of 3, 5-diphenyl-4,5-dihydro-1H-pyrazole-1- carbothioamide

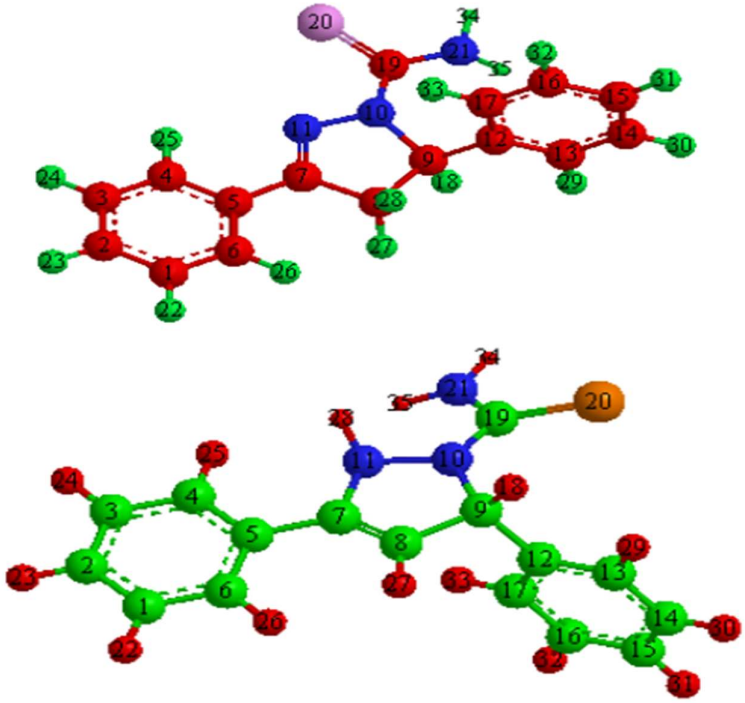


Figure 11: Optimized structures of pyrazole carbothioamide Derivatives (compound 3 and its isomer 4) by DFT analysis.

Table 4: Selected Calculated bond parameters of pyrazole carbothioamide Derivatives (compound 3 and its isomer 4) by DFT analysis

Parameters	Calculated	Parameters	Calculated
Bond lengths(Å)			
N(21)-H(35)	0.9977	N(21)-H(35)	1.0011
N(21)-H(34)	0.9971	N(21)-H(34)	0.9938
N(10)-C(9)	1.4958	N(11)-H(28)	1.0155
N(11)-N(10)	1.4189	N(11)-C(7)	1.4526
C(7)-N(11)	1.2639	N(10)-C(9)	1.4836
C(19)-N(21)	1.3358	N(11)-N(10)	1.4590
C(19)-S(20)	1.7448	C(19)-N(21)	1.3326
N(10)-C(19)	1.3472	C(19)-S(20)	1.7472
C(5)-C(7)	1.4681	N(10)-C(19)	1.3337
C(8)-C(7)	1.5185	C(5)-C(7)	1.4724

Bond Angles (°)			
H(35)-N(21)-H(34)	118.8901	H(35)-N(21)H(34)	120.48
H(35)-N(21)-C(19)	123.0625	H(35)-N(21)C(19)	120.15
H(34)-N(21)-C(19)	117.0139	H(34)-N(21)C(19)	118.56
N(21)-C(19)-S(20)	119.3872	N(21)-C(19)-S(20)	121.25
N(21)-C(19)-N(10)	116.0490	N(21)-C(19)N(10)	116.17
S(20)-C(19)-N(10)	124.5595	S(20)-C(19)-N(10)	122.50
N(10)-N(11)-C(7)	109.5076	H(28)-N(11)-C(7)	110.39
C(9)-N(10)-N(11)	111.1961	H(28)-N(11)N(10)	106.65
C(9)-N(10)-C(19)	128.1766	C(7)-N(11)-N(10)	103.43
N(11)-N(10)-C(19)	119.4961	C(9)-N(10)-N(11)	112.23
C(8)-C(9)-N(10)	101.5476	N(11)-N(10)C(19)	119.62
N(10)-C(9)-H(18)	107.8881	C(8)-C(9)-N(10)	99.81
N(10)-C(9)-C(12)	113.6141	N(10)-C(9)-H(18)	110.48
N(11)-C(7)-C(5)	121.4687	N(10)-C(9)-C(12)	112.32

The total energy obtained for optimized structures 3 and 4 are -733675.1976 Kcal/Mol and Total Energy = -733666.8498 Kcal/Mol respectively. This shows structure 3 is more stable than isomer 4.

CONCLUSION

This research article focuses on synthesizing thiazole-based derivatives. Two types were produced: thiazolo-pyrimidine and pyrazole-carbothioamide derivatives. Thiazolo-pyrimidine derivatives were synthesized through one-pot condensation of substituted thiourea in alcoholic KOH, reacting with aromatic aldehyde and α-halo acid. The structure of 5,7-diphenyl-2H-thiazolo[3,2-a] pyrimidin-3(5H)-one was confirmed by FTIR and mass spectral data. DFT analysis verified the final regioisomers. Pyrazole-carbothioamide derivatives were synthesized from substituted benzaldehyde and thiosemicarbazide under reflux conditions in ethanol with concentrated HCl. These were characterized by FTIR, H^1-NMR, C^{13}-NMR, and mass spectra. DFT analysis confirmed structural parameters and regiochemistry.

Conflict of Interest

None declared.

Financial support and sponsorship

Nil

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