Review

Biological Applications of Thiourea Derivatives: Detailed Review

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Abstract: Thiourea and its derivatives have become a significant focal point within the organic synthesis field, garnering attention for their diverse biological applications, including antibacterial, antioxidant, anticancer, anti-inflammatory, anti-Alzheimer, antituberculosis and antimalarial properties. My objective is to present a comprehensive and easily understandable analysis of recent advancements in the organic synthesis of thiourea derivatives. My focus is on the structure and activity of these derivatives over the past five years, highlighting the significant progress made in the field of organic synthesis. Additionally, I evaluate the current state of research in this area and provide an overview of the latest trends and future prospects. This review will prove to be beneficial for researchers, academics and industry professionals involved in drug development and organic synthesis.

Keywords: thiourea; antibacterial; antioxidant; anticancer; anti-inflammatory; anti-Alzheimer; antimalaria

1. Introduction

Thiourea is an organosulfur compound with a chemical formula of $SC(NH_2)_2$, and its structure is represented in Figure 1. Its structure is similar to that of urea ($H_2N-C(=O)-NH_2$), except the oxygen atom is replaced by a sulfur atom, indicated by the prefix "thio-" [1]. The term "thiourea" refers to a group of compounds with the formula (R_1R_2N) (R_3R_4N) C=S. Thiourea has two tautomeric forms: the thione form and the thiol form, as illustrated in Figure 2. The thione form is more prevalent in aqueous solutions, and the thiol form is also known as isothiourea.
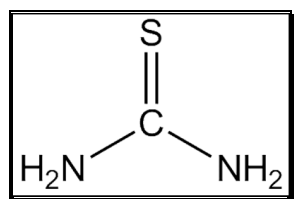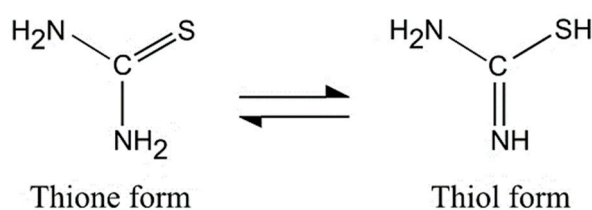
Figure 1. The chemical structure of thiourea.

Figure 2. Equilibrium between the tautomeric forms of thiourea.

Thiourea has a wide range of uses in organic synthesis reactions as intermediates, making it an incredibly versatile compound [2]. Additionally, it is utilized in many commercial products such as photographic films, dyes, elastomers, plastics and textiles [3]. However, the most significant and effective application of thiourea is in the realm of biology, as illustrated in Figure 3. Research has demonstrated that it possesses numerous beneficial properties, including antibacterial, antioxidant, anticancer, anti-inflammatory, anti-Alzheimer, antitubercular and antimalarial effects [4–9]. Several previous reviews have focused on the pharmacological activities of thiourea derivatives [10–12]. Here, this review presents an overview of state-of-the-art biomolecules derived from thiourea as well as diverse medicinal applications in this field over the last five years.
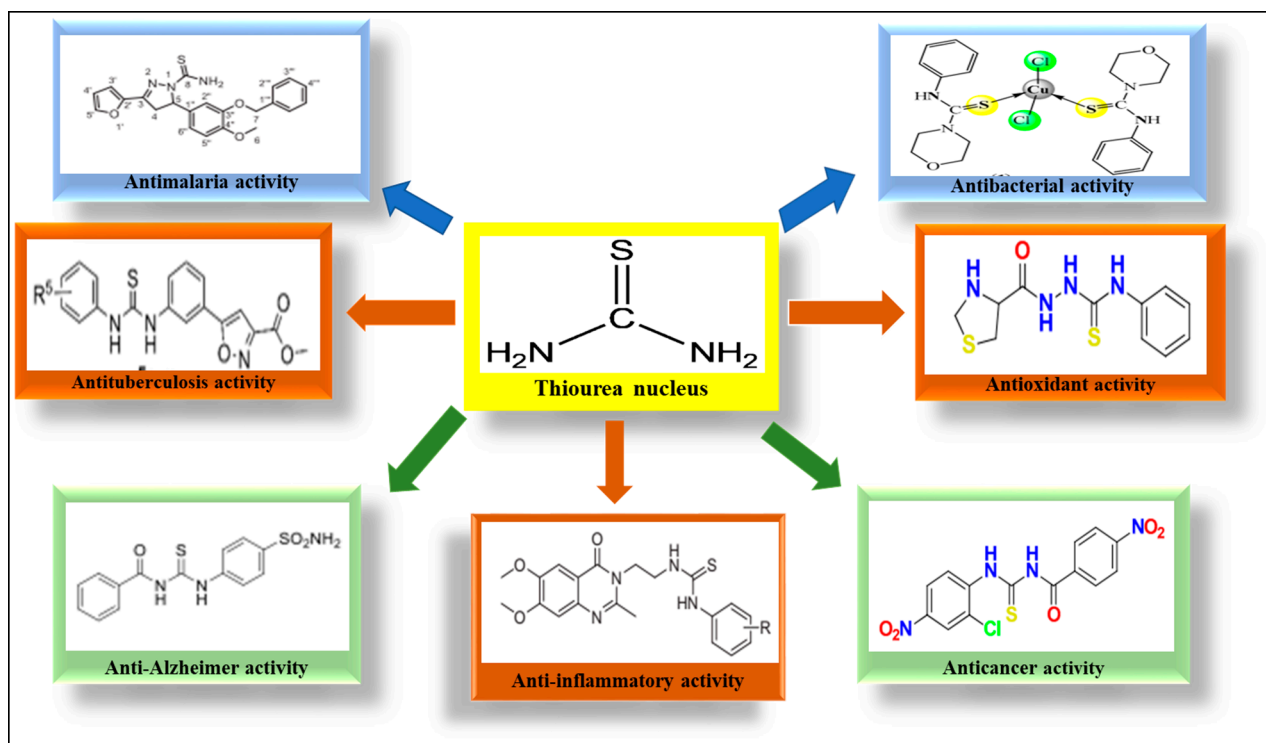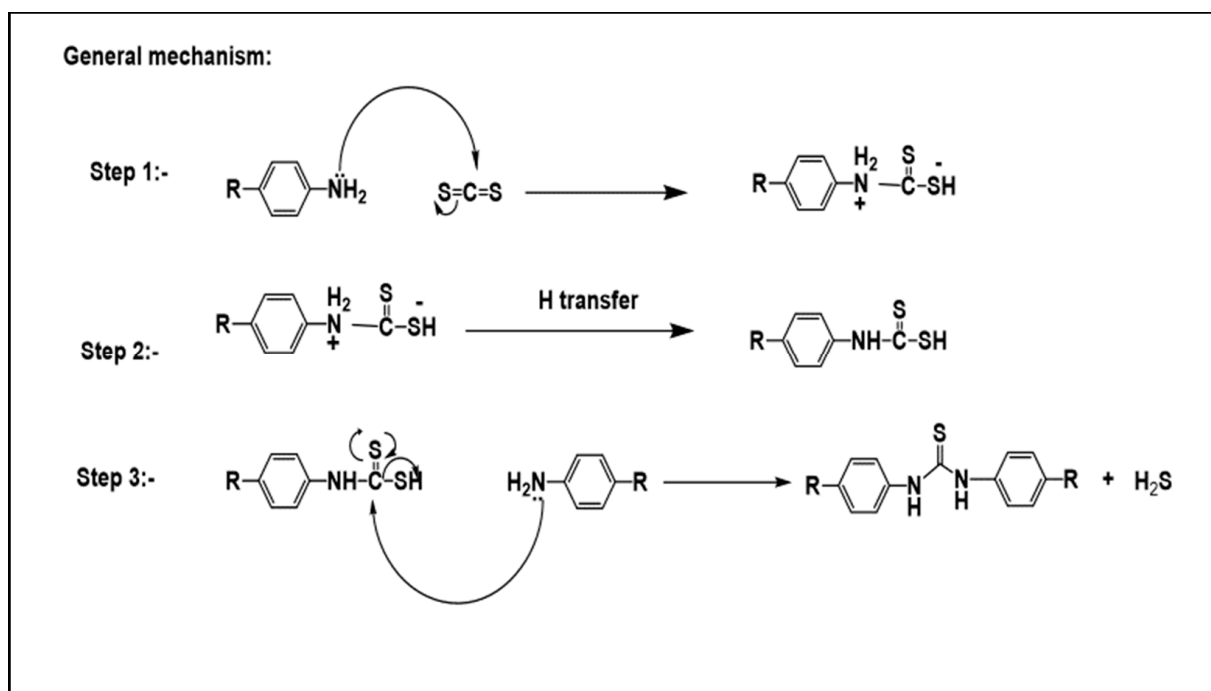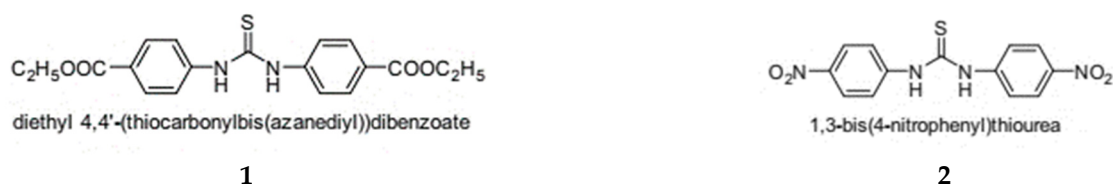

Figure 3. Different forms of biologically active thiourea derivatives.

2. Antibacterial Activity

The lack of new anti-infective drugs is a major concern for medicinal chemistry, as antimicrobial resistance poses a global threat. In response, Sumaira et al. [13] developed novel thiourea derivatives using amine derivatives as nucleophiles on the electrophilic carbon of CS2 to synthesize a thiocarbamate intermediate, as shown in Scheme 1. Both compounds **1** and **2** demonstrated antibacterial activity against *E. faecalis*, *P. aeruginosa*, *S. typhi* and *K. pneumoniae*. Compound **2** exhibited greater potency than that of compound **1**, with a minimum inhibitory concentration (MIC) against the tested organism ranging from 40 to 50 μg/mL. In comparison to the standard antibiotic, ceftriaxone, compound **2** showed comparable inhibition zone diameters. The inhibition zones of compound **2** against the tested organisms were 29, 24, 30 and 19 mm, respectively.

General mechanism:

Step 1:-

Step 2:-

H transfer

Step 3:-

Scheme 1. The general mechanism of thiourea derivative synthesis starting with carbon disulfide [13].

C_2H_5OOC —⟨ ⟩— N—C—N —⟨ ⟩— $COOC_2H_5$
diethyl 4,4'-(thiocarbonylbis(azanediyl))dibenzoate

1

O_2N —⟨ ⟩— N—C—N —⟨ ⟩— NO_2
1,3-bis(4-nitrophenyl)thiourea

2

A novel set of seven N-acyl thiourea derivatives, namely **3a–3g**, were developed by Roxana et al. [14]. Their synthesis method employed the condensation of acid chloride and ammonium thiocyanate in an anhydrous acetone solution. The resulting isocyanate was then allowed to react with a heterocyclic amine, with the amine undergoing a nucleophilic addition to the isocyanate, as shown in Scheme 2.

Scheme 2. The synthesis route of novel N-acyl thiourea derivatives **3a–3g** [14].

The synthesized compounds, **3a–3g**, were subjected to testing against various bacterial strains, including *S. aureus*, *E. faecalis*, *E. coli* and *P. aeruginosa*. The positive control used was Ciprofloxacin (5 μg/mL). The findings demonstrated that the tested drugs' MIC ranged from >5000 to 1250 μg/mL, which was considerably greater than the conventi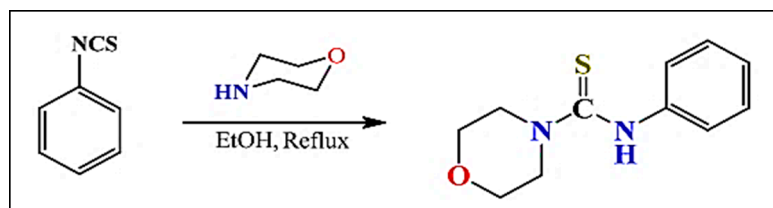onal antibiotic utilized. These compounds were found to be more potent than previously reported thiazole derivatives [14]. In addition, eight tris-thiourea derivatives, **4a–4h**, with symmetrical structures, were synthesized using benzoyl chloride and potassium thiocyanate with melamine under reflux conditions through a condensation reaction. The synthesis pathway is depicted in Scheme 3 [15].

Scheme 3. Synthesis pathway of tris-thiourea derivatives **4a–4h** [15].

Various Gram-positive and Gram-negative bacteria, including *S. aureus*, *B. cereus* and *E. coli*, were exposed to synthesized compounds **4a–4h**. The results revealed that compound **4a** (N, N,N-(((1,3,5-triazine-2,4,6-triyl)tris(azanediyl))tris-(carbonothioyl)) tribenzamid) was particularly effective against *E.coli*. Compound **4g** (N, N,N-(((1,3,5-triazine-2,4,6-triyl)tris(azanediyl))tris-(carbonothioyl)) tris(2-chlorobenzamide) exhibited the highest rate of microbicidal activity against *S. aureus*, and compound **4f** (N, N, N-(((1,3,5-triazine-2,4,6-triyl) tris(azanediyl))tris-(carbonothioyl))tris(2-methylbenzamide) was most effective at eliminating *B. cereus*.

Thiourea derivatives are highly effective in metal complexes due to the presence of nitrogen atoms, as well as lone pairs on sulfur and oxygen atoms, which serve as ligating centers and coordinate with a wide range of metal centers to produce stable metal complexes [16]. Ahmed et al. synthesized novel 1-morpholinyl 3-phenyl thiourea ligands and their corresponding metal complexes with the aim of developing new antimicrobial agents. The ligand N-Phenylmorpholine-4-carbothioamide (HPMCT) was prepared according to the procedure outlined in Scheme 4 [17].

Scheme 4. Preparation of N-Phenylmorpholine-4-carbothioamide (HPMCT) ligand [17].

In complexes **5–8**, the thiourea ligand coordinates through a sulfur atom as a monodentate, as demonstrated in Scheme 5 [17]. On the other hand, in complexes **9–15**, the

ligand coordinates with the central atom through N and S atoms as a bidentate, as shown in Scheme 6.

Scheme 5. The synthesis of complexes **5–8** of thiourea derivatives [17].

Scheme 6. Synthesis of complexes **9–15** of thiourea derivatives [17].

Three strains of bacteria "*E. coli*, *S. aureus*, and *K. pneumoniae*" were used to test each of the produced compounds, **5–15**. As seen in Figure 4 [17], all compounds exhibited strong antibacterial activity when compared to the ligand. Comparable to the common antibiotic tetracycline, compounds **5** and **9** had strong efficacy against *E. coli*. The several binding modes with the essential amino acid residues of the bacterial tyrosinase enzyme's active site are referred to as the antibacterial activity.

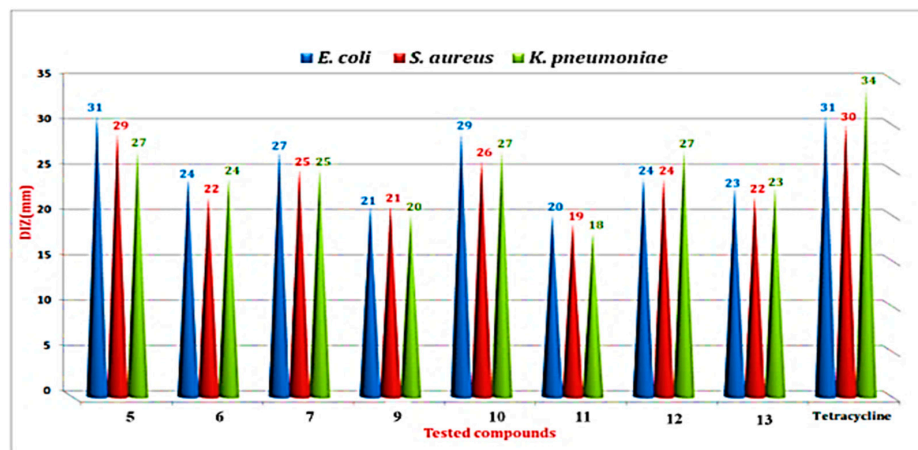**Figure 4.** The antibacterial activities of synthesized compounds **5–15** [17].

Five new Cu (II) complexes, **Cu16–Cu20**, with varied antimicrobial activities, were synthesized by Aleksandra et al. [18]. Five distinct ligands were produced and employed prior to complex formation. The particular groups of the ligands made of thiourea derivatives determine how copper complexes with them. Ligands **19** and **20** were halogen phenyl groups, and ligands **16–18** were alkylphenyl [19–21]. The method for synthesis is shown in Figure 5. The synthesized complexes were tested against a variety of bacterial and fungal strains, including *S. aureus* NCTC 4163, *S. aureus* ATCC 25923, *S. aureus* ATCC 6538, *S. aureus* ATCC 29213, *S. epidermidis* ATCC 12228, *S. epidermidis* ATCC 35984, *E. coli* NCTC 10538, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 15442, *P. aeruginosa* ATCC 27853, *C. albicans* ATCC 10231, *C. albicans* ATCC 90028 and *C. parapsilosis* ATCC 22019. With an MIC value of 4 µg/mL, the most active compound, **Cu20**, demonstrated strong activity against *Staphylococcus epidermidis* (MRSE) and methicillin-resistant *S. aureus* (MRSA) 537, 585 and 586 strains. The other complexes, however, exhibited minimal activity and were ineffective against other fungal species and Gram-negative strains of *E. coli*.
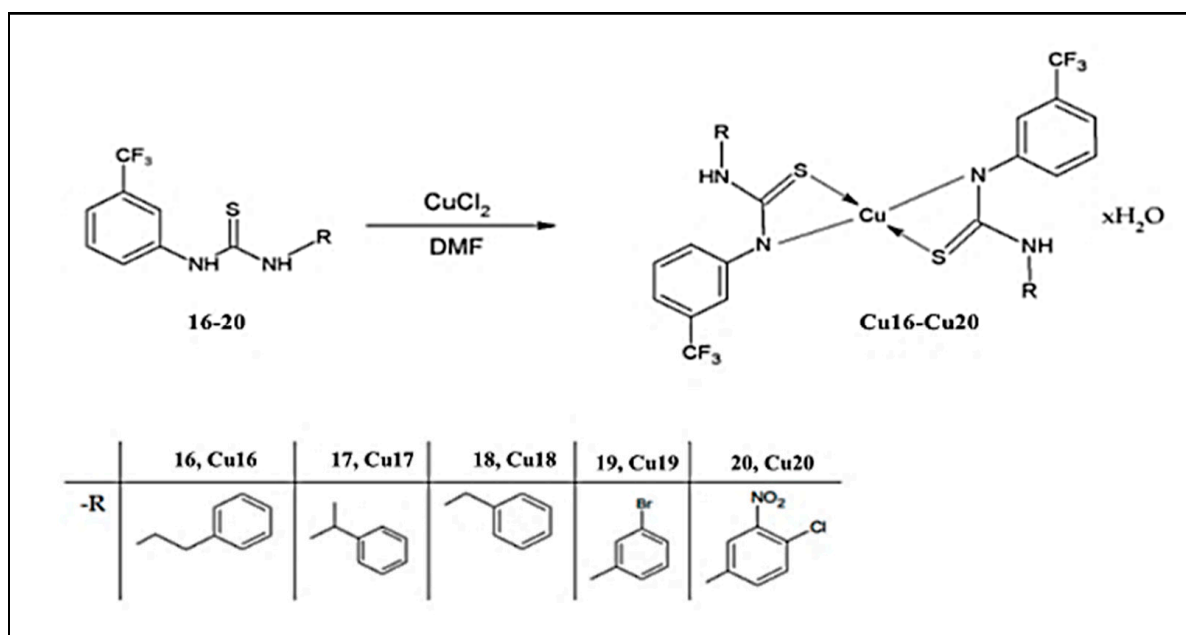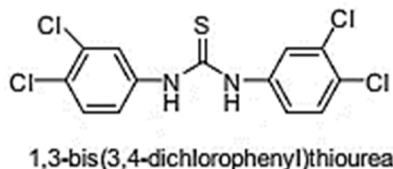

Figure 5. Synthetic pathway of **Cu16–Cu20** complexes with the following formulas: Cu (**16**)2H$_2$O, Cu (**17**)2·0.75H$_2$O, Cu (**18**)2·0.5H$_2$O, Cu (**19**)2·0.5H$_2$O and Cu (**20**)2·H$_2$O. DMF—dimethylformamide [18].
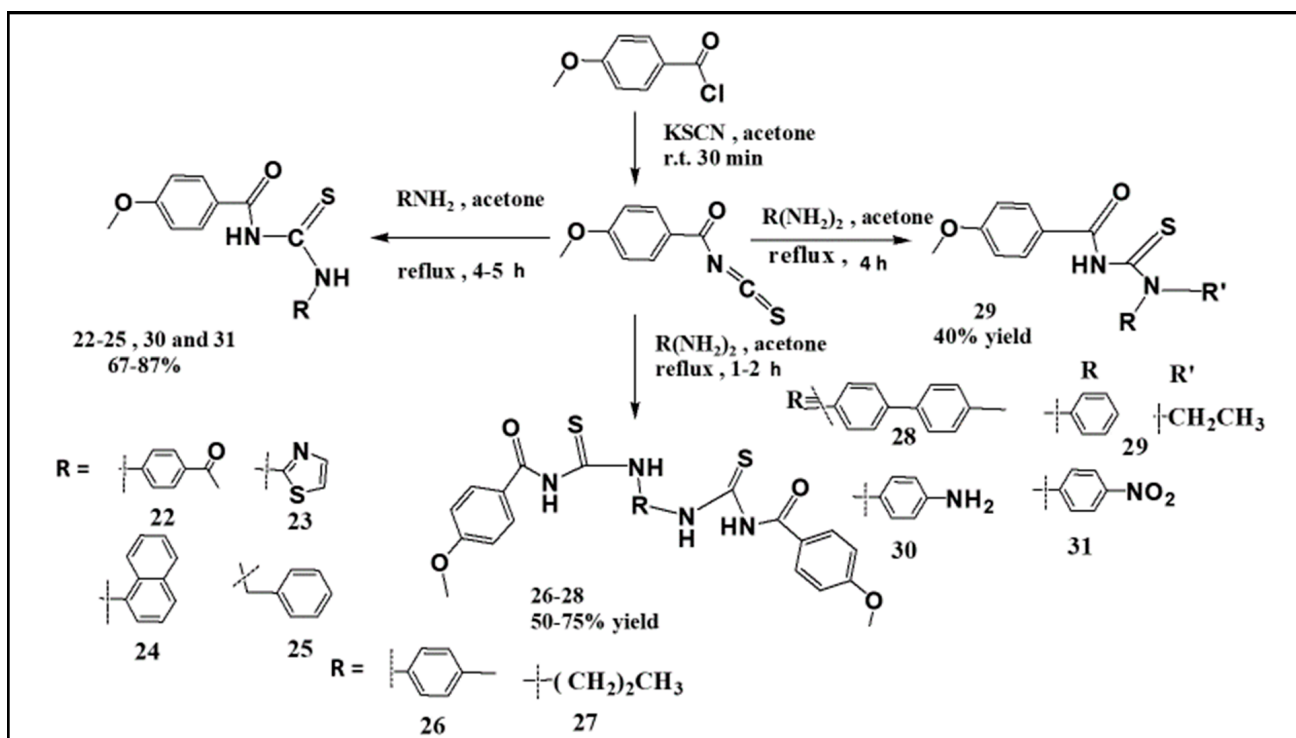
3. Antioxidant Activity

Thiourea derivatives such as 1-(2-aminoethyl) thiourea, N, N'-(iminodiethane-2,1-diyl) bis(thiourea) and 1-[1-methyl-2-(phenylamino)ethyl] thiourea were prepared by Sudzhaev et al. [22]. Additionally, 1,3-bis(3,4-dichlorophenyl) thiourea **21**, a new thiourea derivative, was synthesized by Sumaira et al. [23] and demonstrated strong antioxidant activity. This derivative had a high reducing potential when tested against ABTS free radicals, with an IC_{50} of 52 µg/mL and a DPPH assay value of 45 µg/mL.

1,3-bis(3,4-dichlorophenyl)thiourea

21

Ten novel thiourea derivatives, **22–31**, were recently synthesized by reacting potassium thiocyanate with 4-methoxy benzoyl chloride using the nucleophilic addition–elimination mechanism to form an isothiocyanate derivative, as shown in Scheme 7 [24]. The final ten compounds were produced by reacting this derivative with various amines in accordance with the amine's nucleophilic addition mechanism to the isothiocyanate. The DPPH radical scavenging activity method was used to describe these compounds and assess their antioxidant potential. Compounds **29**, **27** and **24** demonstrated good antioxidant activity with IC_{50} values of 5.8, 42.3 and 45 µg/mL, respectively, when compared to normal ascorbic acid, which had an IC_{50} value of -33.22 µg/mL. The other drugs' IC_{50} values varied between 89 and 245 µg/mL.
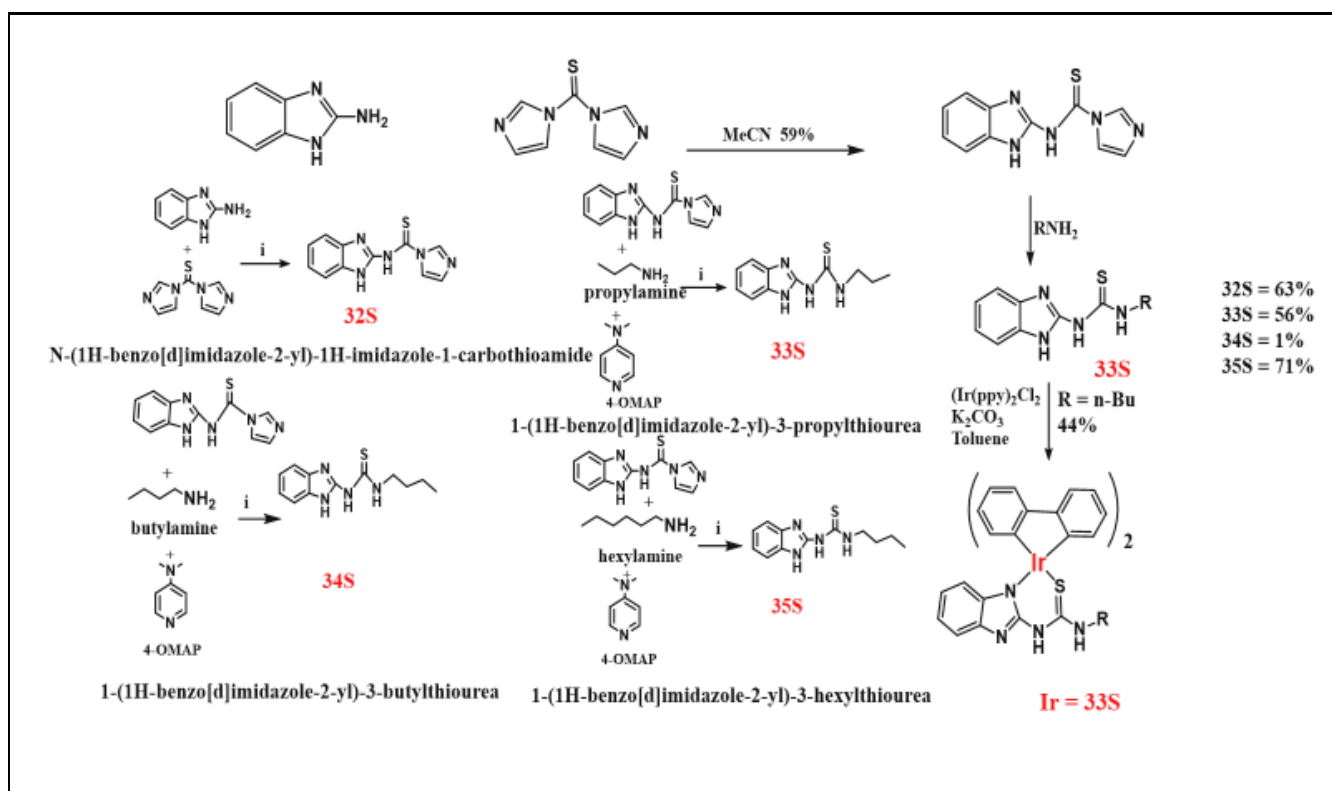

Scheme 7. Synthesis of new thiourea derivatives **22–31** through nucleophilic addition–elimination mechanism [24].

4. Anticancer Activity

In the fight against cancer, thiourea derivatives have demonstrated great promise. Studies conducted recently have demonstrated that these compounds can inhibit the growth

of several cancer cell lines and reverse treatment resistance in cancer cells [25–30]. A variety of human cell lines, including those from breast and lung malignancies, were evaluated against non-metal-containing thiourea derivatives in earlier research. Low LC_{50} values, spanning from 7 to 20 μM, were demonstrated by the findings [31]. Furthermore, it has been discovered that thiourea derivatives target particular molecular pathways involved in the development of cancer, such as those that limit angiogenesis and alter cancer cell signaling pathways [32–34]. With IC_{50} values ranging from 3 to 14 μM, derivatives of phosphonate thiourea demonstrated encouraging responses when evaluated against cell lines related to pancreatic, prostate and breast cancer [35]. The treatment of human leukemia cell lines with the bis-thiourea structure also demonstrated efficacy, with IC_{50} values as low as 1.50 μM [36]. Lung, liver and breast malignancies demonstrated positive LC_{50} values of less than 20 μM for aromatic derivatives of thiourea produced using indole molecules [37].

Also, Samuel et al. [38] conducted a thorough screening of several thiourea derivatives for toxicity in ovarian cancer cell lines, including those that showed cisplatin treatment resistance. Three molecules of luminescence iridium complexes based on a 2-aminobenzimidazole unit were produced by the researchers. Through a substoichiometric 2-aminobenzimidazole reaction in acetonitrile, 1,1′-thiocarbonyldiimidazole was mono-substituted efficiently. When compounds **32S**–**35S** were purified, they had a 63–81% yield. This was due to a series of amines replacing the second imidazoyl unit in the presence of dimethylaminopyridine (DMAP) in dimethylformamide. Scheme 8 shows how iridium complexes based on these systems were subsequently created by reacting **33S** with [Ir(ppy)2Cl]2 in toluene with potassium carbonate present. The result was bright yellow powders, or **Ir-33S**, in a 53% yield.

Scheme 8. Synthesis of thiourea compounds and their iridium complexes [38].

Different human ovarian cancer cell lines, such as EFO-21, EFO-27 and COLO-704, as well as their cisplatin-resistant sublines, EFO-21rCDDP2000 and EFO-27rCDDP2000, were evaluated against a variety of unmetalled chemicals. With IC_{50} values in the low micromolar range, these substances demonstrated toxicity in every cell line tested. Thioureas **32S**, **33S**

and **35S** were the most active compounds among those examined; their average IC$_{50}$ values were 1.29, 1.26 and 2.96 μM in all cell lines. In drug-resistant cell lines, the series **32S**–**35S** exhibited a negligible decline in efficacy, but **Ir-33S** was found to be more effective in one resistant subline.

Targeting molecules different from cisplatin, gold complexes are another kind of chemical with anticancer effects. Gold compounds primarily target enzymes that include thiols, especially those that are located in mitochondria, like cyclooxygenases, glutathione reductase and thioredoxin reductase [39–41]. The kind of ligand that is employed determines how stable gold complexes are in a biological setting. In the past 20 years, thiolate [42–45], phosphine [46–51] and N-heterocyclic carbene ligands, which are depicted in Figure 6, have all been widely employed and have demonstrated positive biological effects.

Figure 6. Gold complexes with interesting ligands [52].

Because silver complexes are less toxic, they are useful in the therapy of cancer. Their principal mode of action is binding to proteins that contain thiols and DNA [53]. Through a 1:1 reaction between the respective isothiocyanate a and b and 2-(diphenylphosphino) ethylamine (c), Guillermo et al. synthesized metal complex thioureas **36** and **37**. Thioureas **36** (80% yield) and **37** (85% yield) were synthesized as shown in Scheme 9 [52].

Scheme 9. Synthesis of thioureas **36** and **37** [52].

The synthesis of Ag(I) and Au(I) complexes from compounds **36** and **37** was carried out as shown in Schemes 10 and 11 [52].

Three cancer cell lines, HeLa (human cervical carcinoma), A549 (human lung carcinoma) and Jurkat (leukaemia), were used to assess the toxicity of each synthesized complex. The toxicity test findings are shown in Tables 1 and 2.

Very low IC$_{50}$ values were discovered for the gold complexes in the complexes containing thiourea **36**; however, all of the complexes with thiourea **37** showed improved cytotoxicity.

Scheme 10. Synthesis of metal complexes **C36a–e** derived from **36** [52].

Scheme 11. Synthesis of metal complexes **C37a–c** derived from **37** [52].

Coordinators containing sulfur atoms frequently form metal complexes with thiourea derivatives, especially in complexes of transitional elements [54]. A tetrahedron is the shape of copper, whereas the majority of these metal complexes are octahedral in shape [55,56]. Five compounds of thiourea benzamide derivatives, shown in Scheme 12 [57], were synthesized by Yaqeen et al. These included ligands L1, L2, L3, L4 and L5 and their metal complexes, **38–42**. Benzoyl chloride and ammonium thiocyanate were reacted to produce thiourea benzamide ligands, which were then used to synthesize the ligands. These ligands were subsequently used to create complex compounds **38–42** by reacting with Cu (II) ions in methanol and acetone. Using the MTT cytotoxicity assay against the MCF7 breast cancer cell lines, all of the produced compounds were evaluated. With IC_{50} values of 4.03 and 4.66 μg/mL, respectively, complexes **38** and **39** were extremely effective, whereas the ligands had variable anti-cancer efficacy. Compounds **38** and **39** target the PR and Akt

proteins of breast cancer cell lines (MCF-7), as demonstrated in Figure 7, based on the molecular docking of these compounds with target proteins 4OAR and 5KCV.

Table 1. Antitumor activity expressed in IC_{50} values of complexes **C36a–e** compared with that of thiourea **36** as the standard [52].

Compound	IC$_{50}$(µM) Values for Cell Lines [a]		
	Hela	**A549**	**Jurkat**
36	>25	13.89 ± 4.0	>25
[**36**-Ag-PPh$_3$]OTf (**C36a**)	10.17 ± 1.74	7.06 ± 1.95	3.89 ± 0.19
[**36**-Au-PPh$_3$]OTf (**C36c**)	2.09 ± 0.17	>25	0.62 ± 0.03
[**36**-Au-**36**]OTf (**C36b**)	0.25 ± 0.12	>25	0.70 ± 0.06
[**36**-Au-Cl]OTf (**C36d**)	>25	>25	19.80 ± 0.46
[**36**-Au-SR]OTf (**C36e**)	4.52 ± 0.23	5.98 ± 1.18	2.57 ± 0.15
Cisplatin	55 ±9 [b]	114.2 ± 9.1 [c]	10.8 ±1.2 [c]

[a] Each value represents the mean ± standard deviation from three independent experiments. [b] Cisplatin dissolved in DMSO. [c] Cisplatin dissolved in H_2O.

Table 2. Antitumor activity expressed in IC_{50} values of complexes **C36a–e** compared with that of thiourea **37** as the standard [52].
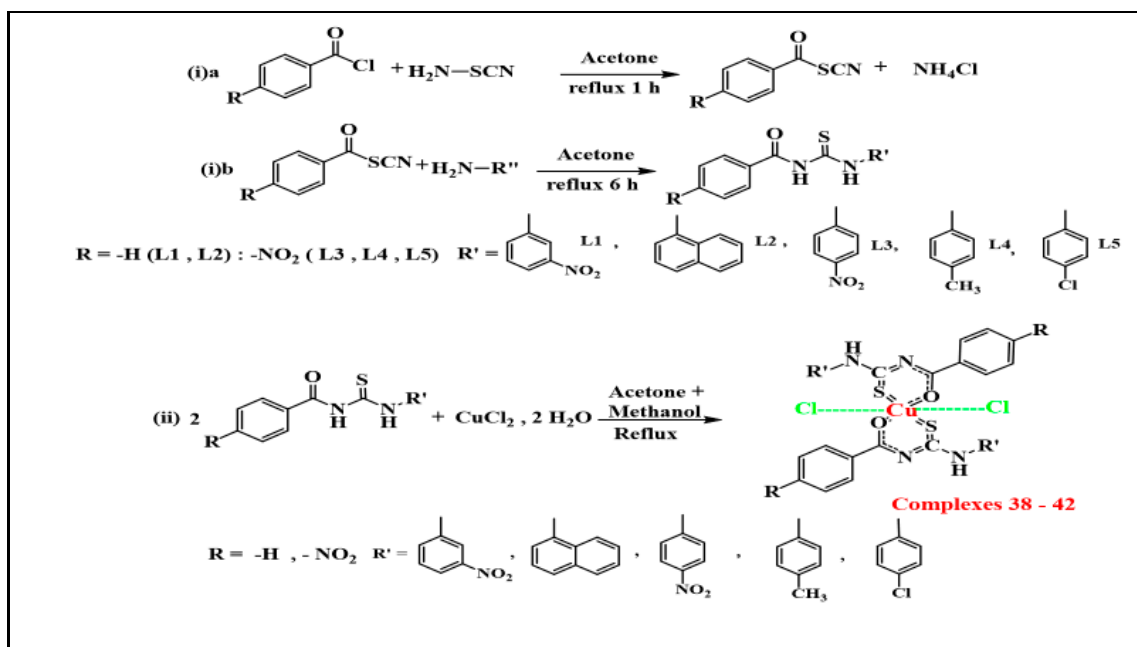
Compound	IC$_{50}$(µM) Values for Cell Lines [a]		
	Hela	**A549**	**Jurkat**
37	8.16 ± 0.15	>25	14.20 ± 0.72
[**37**-Ag-PPh$_3$]OTf (**C37a**)	0.87 ± 0.06	0.79 ± 0.04	0.64 ± 0.04
[**37**-Au-PPh$_3$]OTf (**C37b**)	1.48 ± 0.15	4.91 ± 0.23	5.15 ± 0.32
[**37**-Ag-**37**]OTf (**C37c**)	1.52 ± 0.09	0.58 ± 0.02	1.53 ± 0.31

[a] Each value represents the mean ± standard deviation from three independent experiments.

Scheme 12. Reparation pathway of ligand and metal complexes [57].

Figure 7. Two-dimensional and three-dimensional forms. (**a**) Complex **38** with target proteins 4OAR; (**b**) Complex **39** with target proteins 4OAR; (**c**) Complex **38** with target proteins 5CVK; (**d**) Complex **39** with target proteins 5CVK [57].

Cancer has been treated with symmetrical and unsymmetrical bis-thioureas. For example, at nanomolar concentrations, phenyl-bis phenylthiourea Figure 8a demonstrated cytotoxicity against numerous malignant cell lines [58]. Furthermore, alkylated bis-thiourea's polyamine analog (Figure 8b) demonstrated anticancer efficacy by acting as a lysine-specific demethylase inhibitor [59].
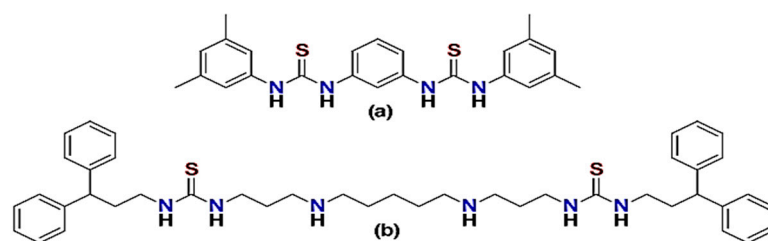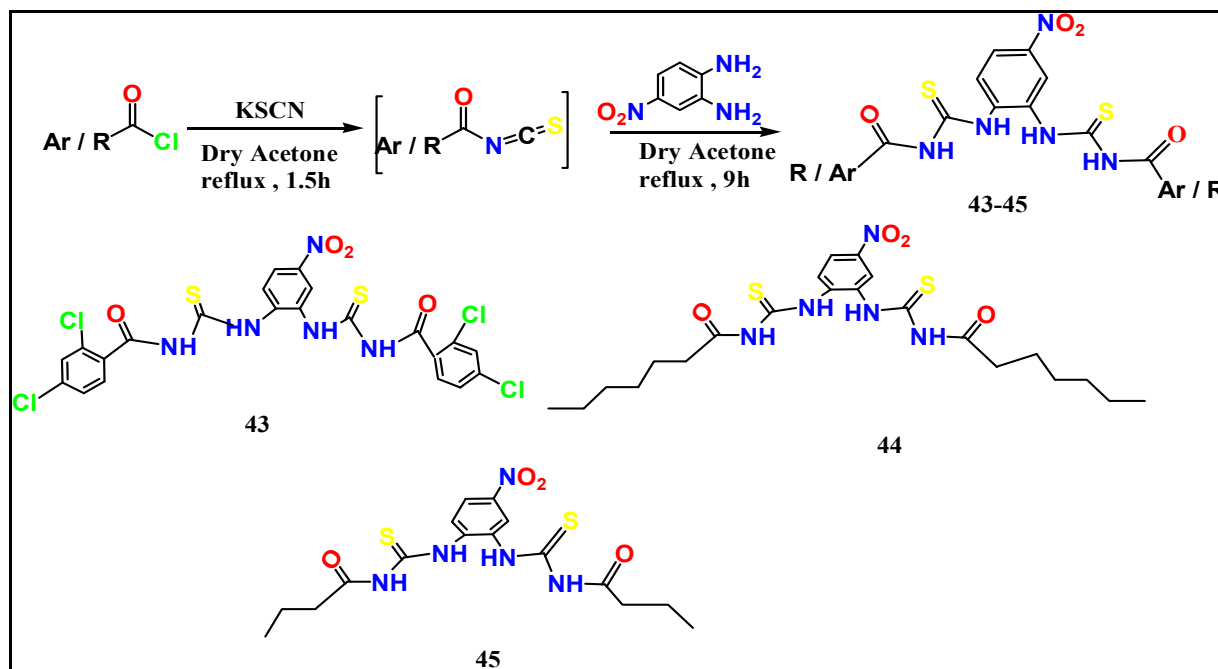

Figure 8. Compounds containing a bis-thiourea nucleus: (**a**) Phenyl-bis phenylthiourea; (**b**) Polyamine analog of alkylated bis-thiourea [60].

Nasima et al. [60], synthesized three bis-thiourea derivatives using the method outlined in Scheme 13. Before adding 4-nitrobenzene-1,2-diamine, they introduced KSCN in acetone to convert appropriately substituted acid chlorides to corresponding acyl isothiocyanates. Acyl thioureas were obtained by recrystallizing the resultant products from ethanol, with a yield that varied between 73% and 89%.

The molecular docking analysis revealed that the three drugs exhibited groove binding, incomplete contact and mixed mode DNA binding. Furthermore, all three of the compounds (**43–45**) showed 2D interactions with the urease enzyme. N-N/diarylthiourea derivatives, which are included in a number of pharmaceutically active compounds, represent another interesting class of prospective anticancer medications [61–63].

Scheme 13. Newly synthesized bis-thiourea derivatives: synthesis and structures [60].

It is crucial to adjust the balance between the produced compounds' lipophilicity and hydrophilicity in order to look into the inhibitory mechanisms of the compounds. To enhance permeability through lipophilic cellular membranes, a lengthy non-polar alkyl terminal chain containing six to sixteen carbon atoms must be included in the synthesis of novel diaryl thiourea derivatives. Moreover, adding a fluorine group as a hydrogen bond acceptor group can increase the proposed compounds' aqueous solubility [61]. By combining phenolisocyanate or 4-fluorophenyl isothiocyanate with alkoxy anilines (4-hexyloxyaniline, 4-octyloxyaniline or 4-hexadecyloxyaniline) in dichloromethane at an ambient temperature, Mohamed et al. produced N, Nl disubstituted thiourea derivatives **46–51**. Scheme 14 [64] shows the equimolar amounts used in this reaction that was conducted.

Scheme 14. Synthesis of urea and thiourea derivatives **46–51** [64].

The efficacy of the produced compounds in treating breast cancer was evaluated by testing them against MCF-7 cells. The findings indicated that compound **49** might have more promise as an anticancer drug due to its lower IC_{50} value (338.3 $\pm$ 1.52 µM). Unlike untreated control cells, treated MCF-7 cells with compound **49** displayed alterations in cell size and shape as well as a progressive decline in cell viability, as the compound concentration increased, as seen in Figure 9. This outcome was comparable to that of 4-nitrobenzoyl-3-allylthiourea, another arylthiourea derivative that, at an IC_{50} value of 225 µM, had good efficacy against breast cancer cells [65].
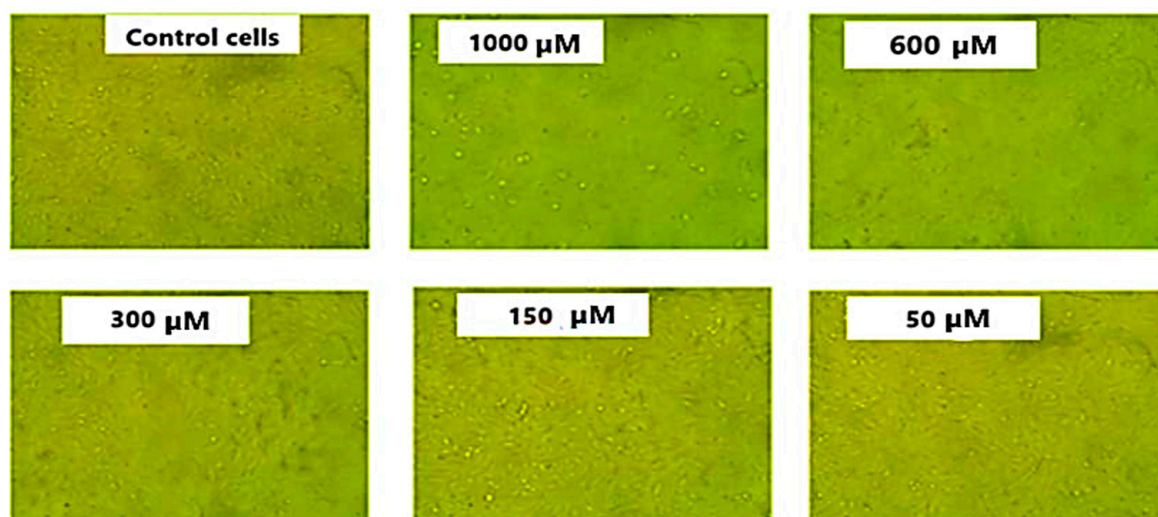

Figure 9. Comparing the morphological changes in MCF-7 cells treated for 24 h with different doses (50–1000 µM) of compound **49** to untreated control cells under a microscope [64].

Compound **49** was discovered to have a significant effect on LDH enzyme activity. The study indicated that treated MCF-7 cells had LDH levels that were 521.77 ± 30.8 U/L, significantly higher than those of untreated control cells (85.35 ± 4.2 U/L). According to these findings, compound **49** effectively prevents MCF-7 cell growth. In addition, the cell cycle of the treated cells was investigated. It was shown that a sizable portion of the cells were created in the S phase, suggesting that apoptosis was initiated and that the cell cycle was stopped at that point. This result demonstrates that compound **49** therapy is effective in stopping the growth of cancer cells and can disturb normal cell cycle progression [66,67].

The thiazole, pyrazole and pyran moieties found in several thiourea derivatives have also been shown to have promising anticancer action [68]. Certain physicochemical and structural characteristics that impact thiourea's pharmacological properties are conferred by the integration of these heterocyclic moieties [69–71]. Their therapeutic potential is increased by their interaction with molecular targets, which modify cellular activities and signaling cascades [72]. Figure 10 [73] illustrates the series of thiourea derivatives that Ahmed et al. synthesized that contain heterocyclic moieties. 4-Aminoacetophenone (**i**) was refluxed with phenyl isothiocyanate in dry toluene to form the pyrazole-based derivative 1-(4-acetylphenyl)-3-phenylthiourea (**ii**). This was then refluxed with the reagent, dimethylformamide-dimethyl acetal (DMF-DMA), in dioxane to convert it into its corresponding enaminone (**iii**). Compound **iii** reacted with two distinct nitrogen binucleophiles (phenyl hydrazine and hydrazine hydrate) via refluxing in ethanol and triethylamine, yielding compounds **50a** and **50b**, which are phenyl thiourea pyrazoles. Compound (**iii**) was used to create compound **51**, thiazolopyrimidine-phenylthiourea, by reacting with 2-aminothiazole in boiling methanol and sodium methoxide to create thiazole derivatives. The equivalent benzothiazolo [3,2-a] pyridine-phenylthiourea compound **52** was produced by compound **iii** reacting with benzothiazole-2-yl acetonitrile while under refluxing acetic acid. In glacial acetic acid, compound **iii** reacted with acetylacetone to yield the corresponding 1-(4-(5-acetyl-6-methyl-4H-pyran-2-yl) phenyl)-3-phenylthiourea-based pyran compound **53**, whereas compound **iii** reacted with dimedone to yield tetrahydrochromenephenylthiourea, compound **54**. Scheme 15 shows the pathway of synthesis.
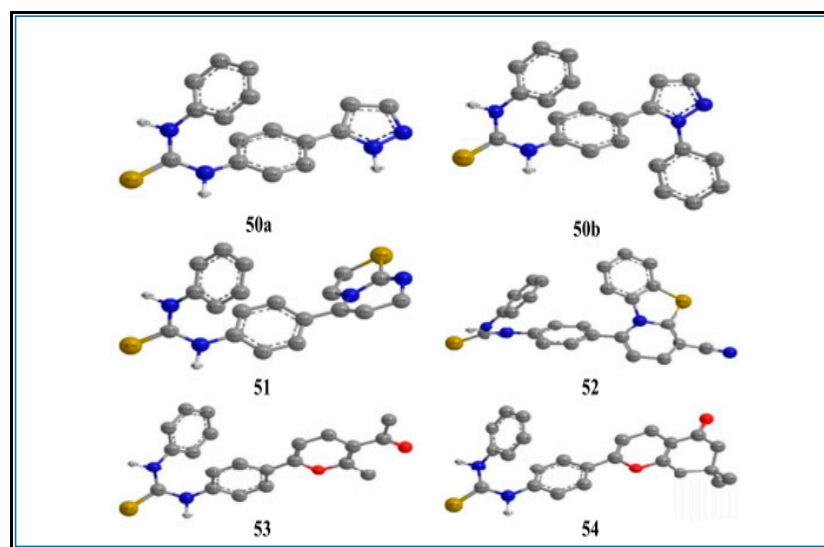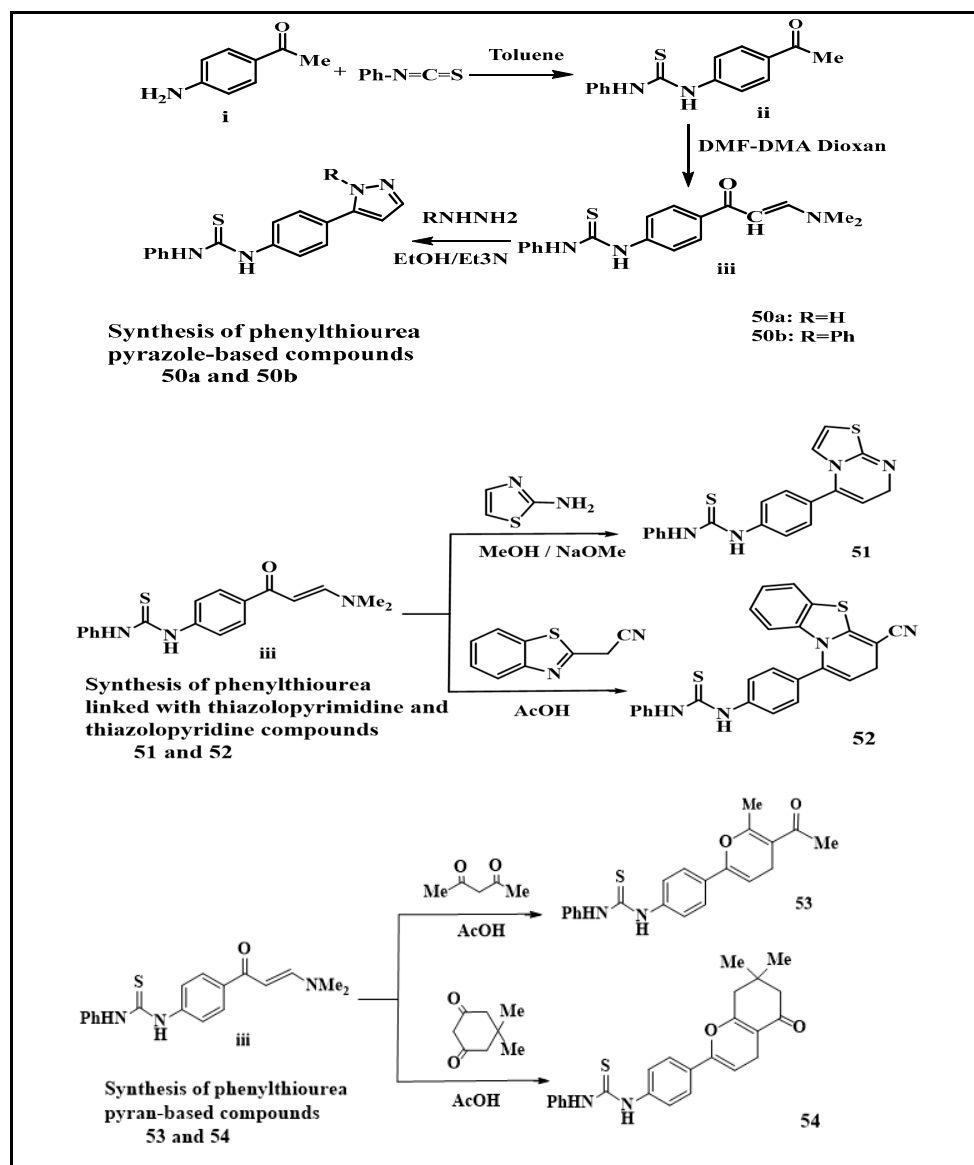

Figure 10. Optimized structures of compounds 50–54 [73].

Scheme 15. Synthesis of phenylthiourea pyrazole-based compounds **50a**, **50b**, thiazolopyramidine and thiazolopyridine compounds **51**, **52** and phenylthiourea pyran-based compounds **53**, **54** [73].
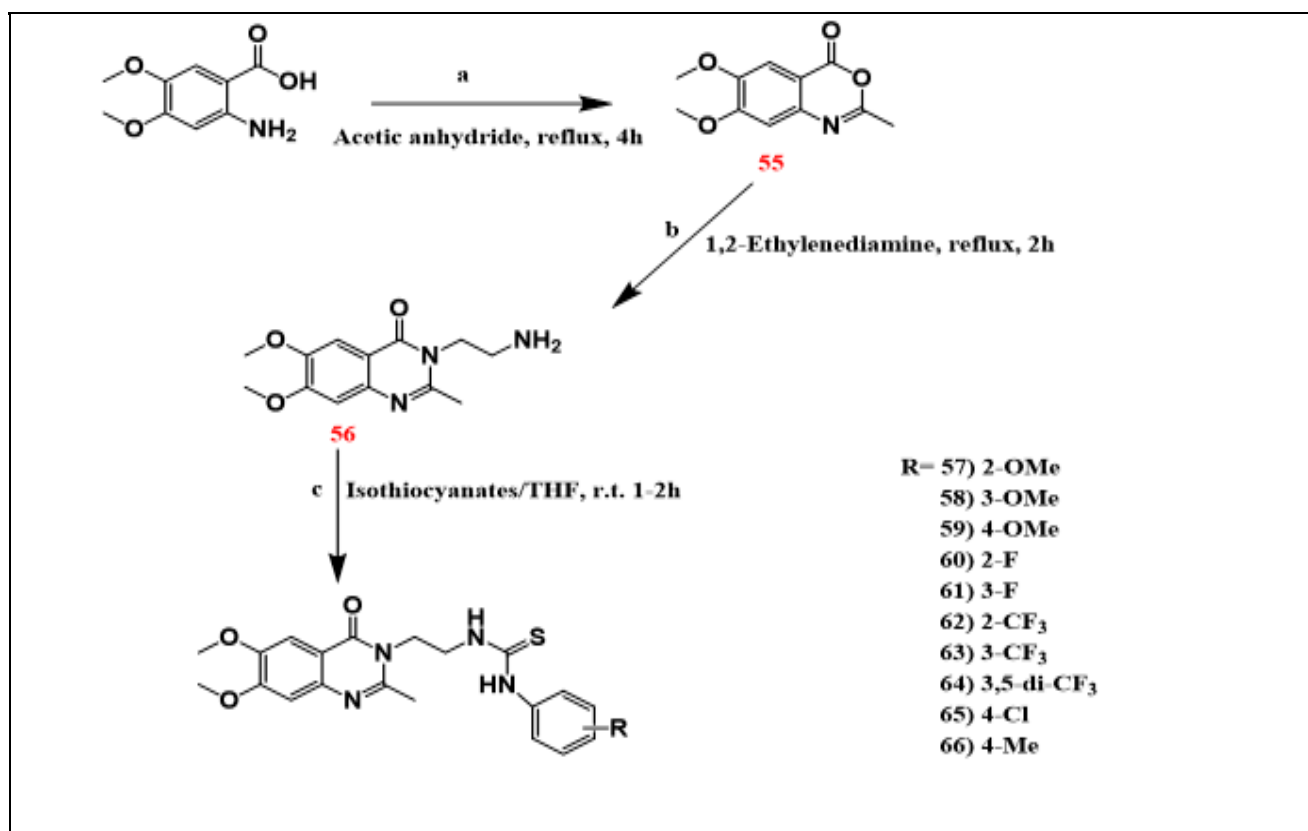
Using the MTT approach, all of the synthesized compounds, **50(a, b)**, **51**, **52**, **53** and **54**, were tested for in vitro cytotoxicity against several cancer lines, including HepG2, HCT-116, MCF-7, PC3 and WI38 [74]. The medicine used as a reference was doxorubicin. The chemicals' reactivity with the cell lines under investigation was as follows: PC3 > MCF-7 > HepG2 > HCT-116. Compounds **51**, **52** and **54** had significant cytotoxic efficacy in the HCT-116 cell line (IC$_{50}$ = 2.29, 9.71 and 7.36 µM, respectively), whereas compound **53** demonstrated appropriate efficacy (IC$_{50}$ = 12.41 µM), and compounds **50a** and **50b** demonstrated the least activity (IC$_{50}$ = 20.19 and 17.85 µM).

5. Anti-Inflammatory Activity

Inflammation is characterized as a local or systemic reaction to injury to tissue or any other stimuli, including those that are chemical, physical, biological or thermal [75]. Hyperinflammation is brought on by an increase in the levels of proinflammatory markers, cytokines and inflammatory chemokines [76]. Reactive oxygen species (ROS) and hyperinflammation work together to promote the growth of a number of illnesses, including diabetes, cancer, arthritis and cardiovascular disorders [77,78]. Through a num-

ber of cytokine-signaling pathways, two significant multifunctional pro-inflammatory cytokines—tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6)—are involved in the pathophysiology of autoimmune, inflammatory, cardiovascular, neurological and cancer illnesses [79]. Thus, TNF-α and IL-6 are crucial molecular targets for pharmaceuticals in the therapy of several illnesses [80].

As shown in Scheme 16 [81], Ashish et al. prepared a number of novel 2-methylquinazolin-4(3H)-one derivatives carrying thiourea. Compound **55** is the precursor of 6,7-dimethoxy-2-methyl-4H-benzo[d][1,3]oxazin-4-one. Compound **55** was reacted with 1,2-ethylenediamine at reflux for two hours to yield compound **56**, 3-(2-aminoethyl)-6,7-dimethoxy-2-methylquinazolin-4(3H)-one. Then, at an ambient temperature, compound **56** was reacted with the suitable arylisothiocyanates to create the required thiourea derivatives, **57–66**. Every synthesized compound was tested for its inhibitory effect on IL-6 and TNF-α at a concentration of 10 µg/mL. Compared to the conventional dexamethasone (1 µg/mL), compounds **60** and **62** showed stronger inhibitory efficacy against TNF-α (78% and 72%) and IL-6 (89% and 83%). Conversely, compounds **57** and **64** showed modest levels of IL-6 (67% and62%) and TNF-α (52% and 50%). Little to no inhibitory activity was demonstrated by the remaining compounds.

Scheme 16. Synthesis of new 3-(2-aminoethyl)-2-methylquinezolin-4(3H)-one thiourea derivatives [81].

Two types of COX that are triggered by inflammatory stimuli are COX-1 and COX-2. 5-LOX is an additional enzyme that contributes to lipid peroxidation and generates lipid peroxides. Inhibiting 5-LOX can aid in cognitive recovery, whereas increasing its activity is linked to neuroinflammation and may result in memory problems [82]. The polyunsaturated omega-6 fatty acid arachidonic acid can be processed by the enzymes cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) via a variety of routes [82].

Studies have demonstrated the good anti-inflammatory action of naproxen derivatives with substituted 1,2,4-triazole rings [83]. Furthermore, it has been discovered in multiple

investigations that naproxen's thiourea derivatives have anti-inflammatory qualities. In comparison to naproxen, thiourea derivatives of naproxen in combination with aminopyridines [84], 4-chloroaniline [85] and amino acids [86] have exhibited negligible ulcerogenic effects and a greater percentage of paw edema reduction.

New thiourea derivatives of naproxen, including aromatic amines and aromatic amino acid esters, were produced by Nikola et al. [87]. The synthesis process was followed as illustrated in Scheme 17. To create a modified naproxen scaffold, they started with S-naproxen. When aromatic amines were present, naproxenoyl chloride, which was created when naproxen and oxalyl chloride combined, could react with potassium thiocyanate to form compounds **67–71** or with esters of aromatic amino acids to form compounds **72** and **73**.

67–71

67 R=-C$_6$H$_4$-F-*P*

68 R=-C$_6$H$_4$-OCH$_3$-*P*

69 R=-C$_6$H$_4$-OCH$_2$CH$_3$-*P*

70 R=-C$_6$H$_4$-OCH$_3$--*m*

71 R=-C$_6$H$_4$-C(=O)CH$_3$-*P*

72 R$_1$=--CH$_2$-C$_6$H$_{45}$, R$_2$ = -CH$_2$CH$_3$

73 R$_1$=-CH$_2$-(N-methyl-1H-indole-3-yl), R$_2$= -CH$_2$

Scheme 17. Synthesis of tested compounds [87].

The synthesized compounds were shown to be non-toxic and were evaluated for their anti-inflammatory properties using the acute inflammation model of carrageenan-induced paw edema, which is frequently employed in the testing of novel anti-inflammatory medications. It was discovered that a few of compounds **67–73** have the ability to suppress inflammation later on. Examining the effects of the produced molecule on COX-2 and 5-LOX, the findings revealed that none of the compounds inhibited COX-2 at concentrations below 100 μM by more than 50%, suggesting a poor inhibitory effect. As shown in Figure 11, compounds **67**, **68**, **69**, **70** and **71**, however, were capable of inhibiting 5-LOX, with compound **70** exhibiting the greatest efficiency. Its IC$_{50}$ value (0.3 μM) was similar to those of commercial anti-inflammatory drugs [87,88].
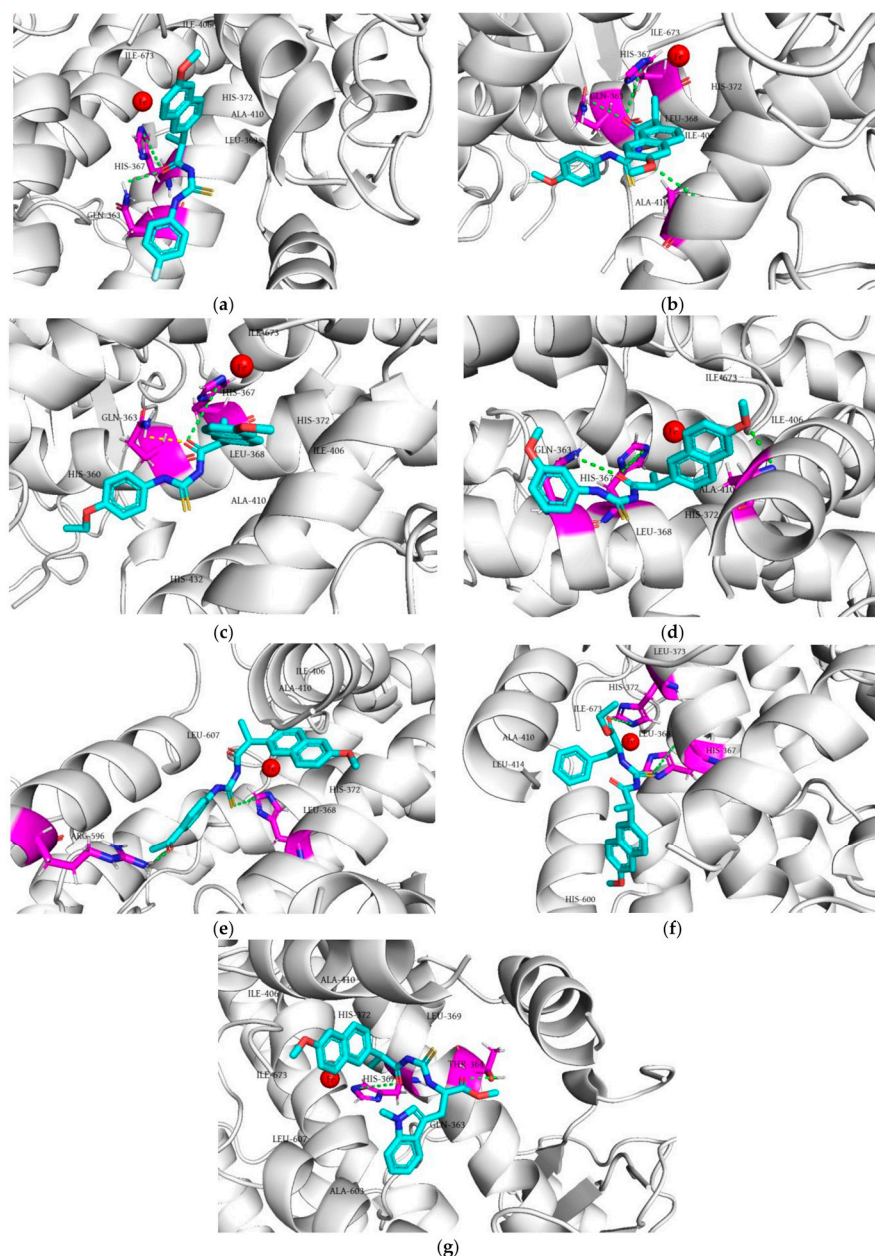
Figure 11. Molecular docking of compound **67** (**a**), **68** (**b**), **69** (**c**), **70** (**d**), **71** (**e**), **72** (**f**) and **73** (**g**) into the 5-LOX enzyme. The blue shapes represent the chemical structure of the tested compounds 67 to 73 and its binding with the 5-LOX enzyme by hydrogen bonds (green dashed lines) [87].

It has been discovered that urea–thiourea hybrids have a broad spectrum of anti-inflammatory effects. Numerous new urea–thiourea hybrids have been created and thoroughly examined. These hybrids are created by reacting several isothiocyanate derivatives with 2,3-diaminonaphthalene-1,4-dione. These hybrids were shown to have anti-inflammatory properties on mammalian macrophages in an in vivo test by inhibiting PI3K activation and reducing the generation of proinflammatory cytokines [89].

6. Antituberculosis Activity

Due to the evolution of medication resistance, tuberculosis (TB), a lung disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*), continues to pose a serious threat to the world. As seen in Figure 12, the World Health Organization (WHO) estimates that 7.5 million individuals worldwide passed away from tuberculosis (TB) in 2022 [90].
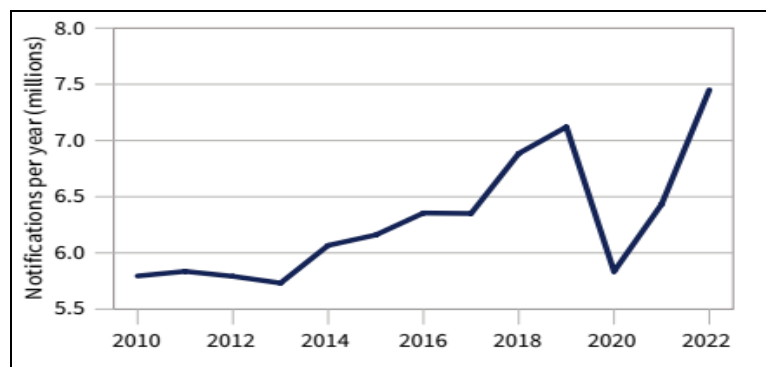
Figure 12. The global trend in case notifications of people newly diagnosed with TB, 2010–2022 (WHO 2022) [90].

A useful building block for the discovery of novel pharmaceuticals with a variety of therapeutic uses is the thiourea scaffold. An essential component of *M. tuberculosis's* mycolic acid production pathway is InhA, an enoyl-acyl carrier protein reductase. Because of this, InhA is essential for the growth of *M. tuberculosis* (TB) and presents a promising target for the development of novel antituberculosis drugs [91]. Şengül et al. [92] synthesized thiourea derivatives **74** and **75**, depicted in Figure 13, which possess essential structural components to function as InhA inhibitors and growth inhibitors of *M. tuberculosis*.
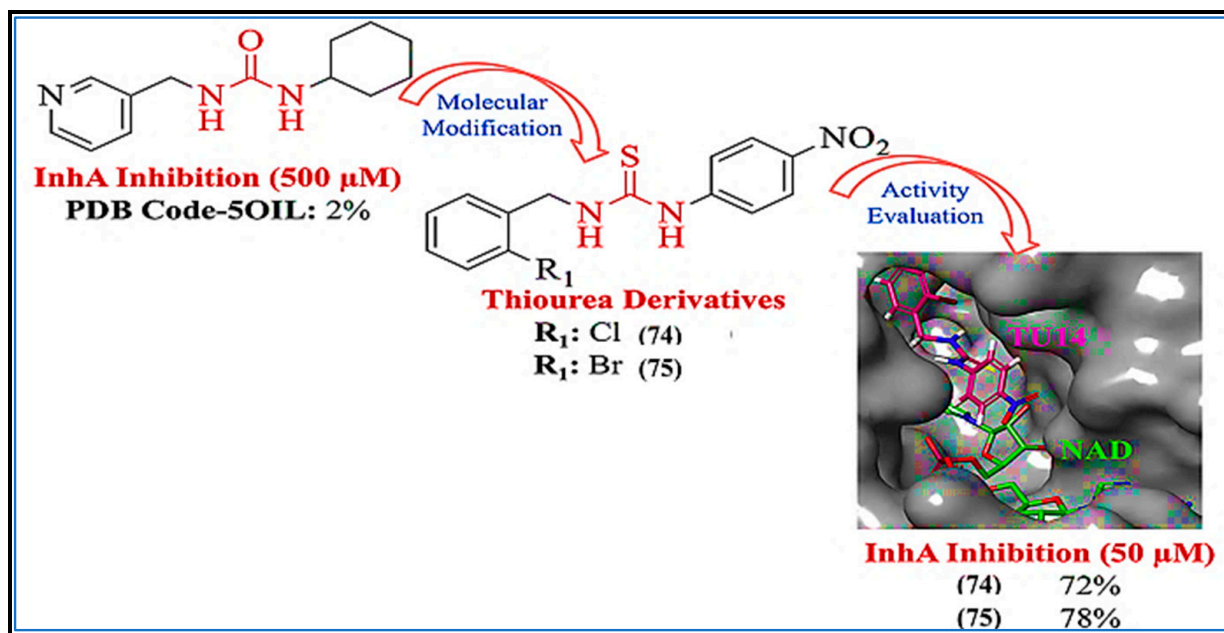

Figure 13. Structural moieties to be *M. tuberculosis* growth and InhA inhibitors [92].

Five thiourea derivatives were synthesized by Emine et al. [93] and are represented in Figure 14 as follows: N-((2-chloropyridin-3-yl)carbamothioyl)thiophene-2-carboxamide (**76**), N-((6-methylpyridin-2-yl)carbamothioyl)thiophene-2-carboxamide (**77**), N-(allylcarbamothioyl) thiophene-2-carboxamide (**78**), 2-chloro-N-(methyl(1-phenylethyl) carbamothioyl) benzamide (**79**) and 2-chloro-N-(bis((R)-1-phenylethyl) carbamothioyl) benzamide (**80**). Five common bacterial strains—H37RV, INH resistant, RIF resistant, STM resistant and EMB resistant— were used to test these drugs' antituberculosis effectiveness. According to the results, derivative **79** had the highest activity.
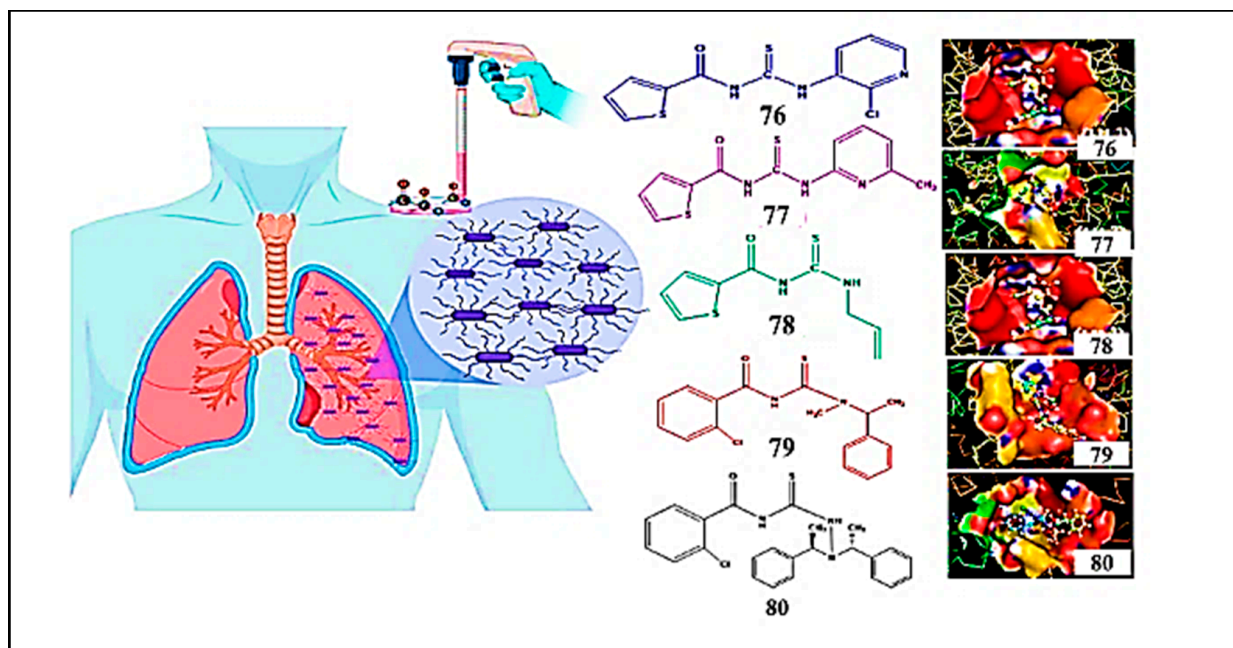
Figure 14. The structure of synthesized compounds **76–80** with antituberculosis activity [93].

Anna et al. [94], investigated the antitubercular capabilities of a series of halogenated copper (II) complexes. To assess the impact of substitution isomerism and electron-withdrawing functions, they employed various phenyl ring substituent arrangements. Among the thiourea derivative complexes were those containing 1-(2-bromophenyl)-halogenated copper (II) complexes: 1-(2-bromophenyl)-3-(4-chloro-3-nitrophenyl)thiourea (**81**), 1-(3-bromophenyl)-3-(4-chloro-3-nitrophenyl)thiourea (**82**), 1-(4-bromophenyl)-3-(4-chloro-3-nitrophenyl)thiourea (**83**), 1-(3-chloro-4-fluorophenyl)-3-(4-chloro-3-nitrophenyl) thiourea (**84**), 1-(4-chloro-3-nitrophenyl)-3-(3,4-dichlorophenyl)thiourea (**85**), 1,3-bis(4-chloro-3-nitrophenyl)thiourea (**86**), 1-(2-fluorophenyl)-3-(4-chloro-3-nitrophenyl) thiourea (**87**) and 1-(4-iodophenyl)-3-(4-chloro-3-nitrophenyl)thiourea (**88**), according to Figure 15. The antituberculosis activity of each complex was evaluated, and the findings indicated that combinations including streptomycin and halogenated copper (II) complexes **83** or **84** were more successful. These mixtures show potential utility in *M. tuberculosis* 800 strains that are INH mono-resistant and multidrug-resistant. The development of MDRTB strain 210 was suppressed by all complexed thiourea compounds, with MICs ranging from 2 to 8 μg/mL. When measured against the reference medicines, isoniazid (INH), rifampicin (RMP), streptomycin (SM) and ethambutol (EMB), the most effective 3,4-dichlorophenylthiourea coordinate acted 8–16 times stronger.
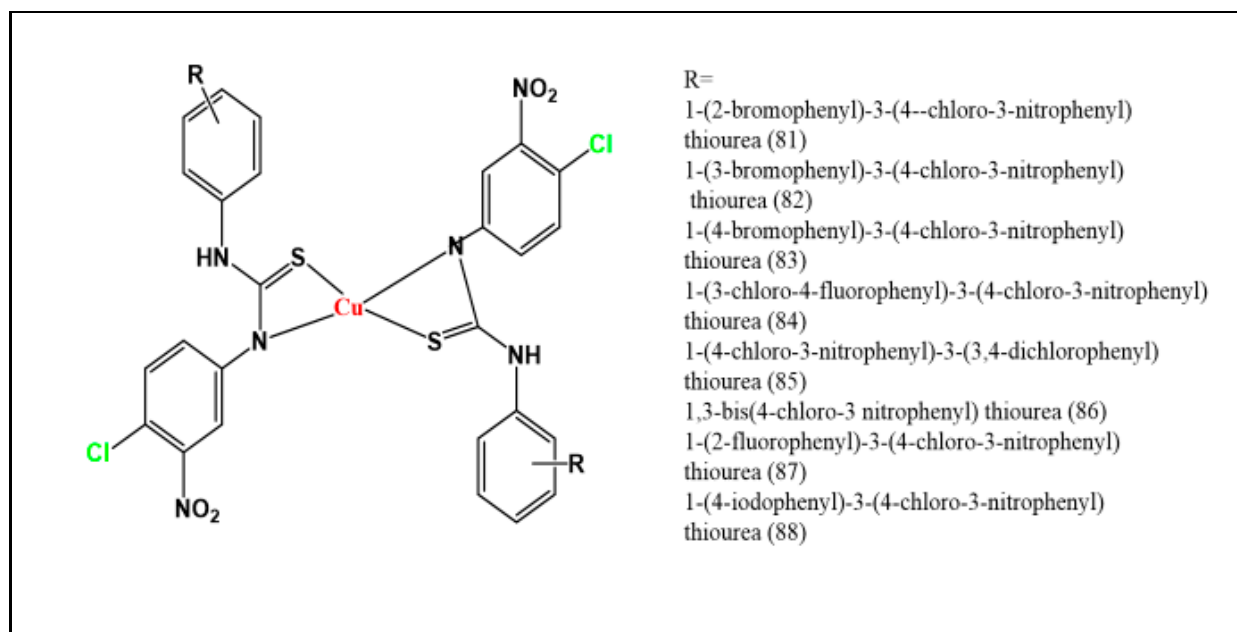
Figure 15. Structure of 3-(4chloro-3-nitrophenyl) thiourea-copper (II) complexes [94].

The synthesis and assessment of urea and thiourea derivatives of 5-phenyl-3-isoxazolecarboxylic acid methyl esters, which exhibit promise as anti-TB drugs, were reported by Santosh et al. [95]. Developing medications that work requires a deep comprehension of the Structure–Activity Relationship (SAR), as shown in Figure 16. This led to the synthesis of a number of thiourea derivatives based on isoxazole carboxylic acid methyl ester, as shown in Figure 17.
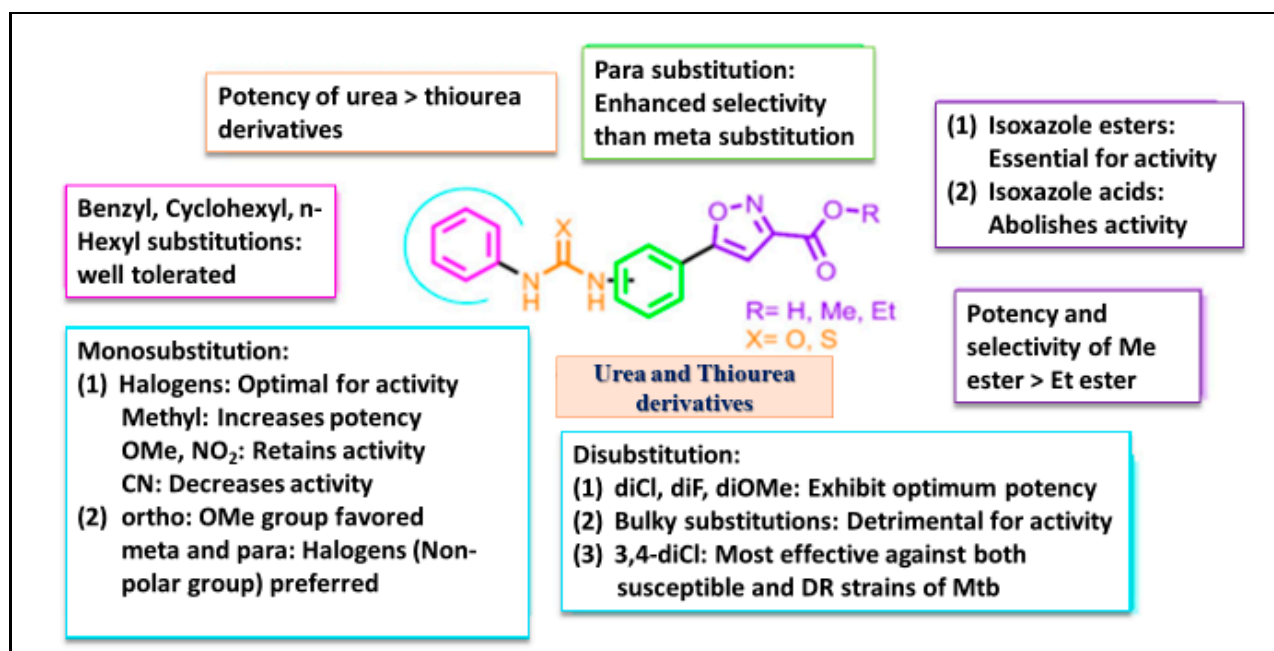

Figure 16. Overview of SAR of evaluated compounds. Highlighted colors of rectangular boxes indicate the identical color of part of the structure [95].
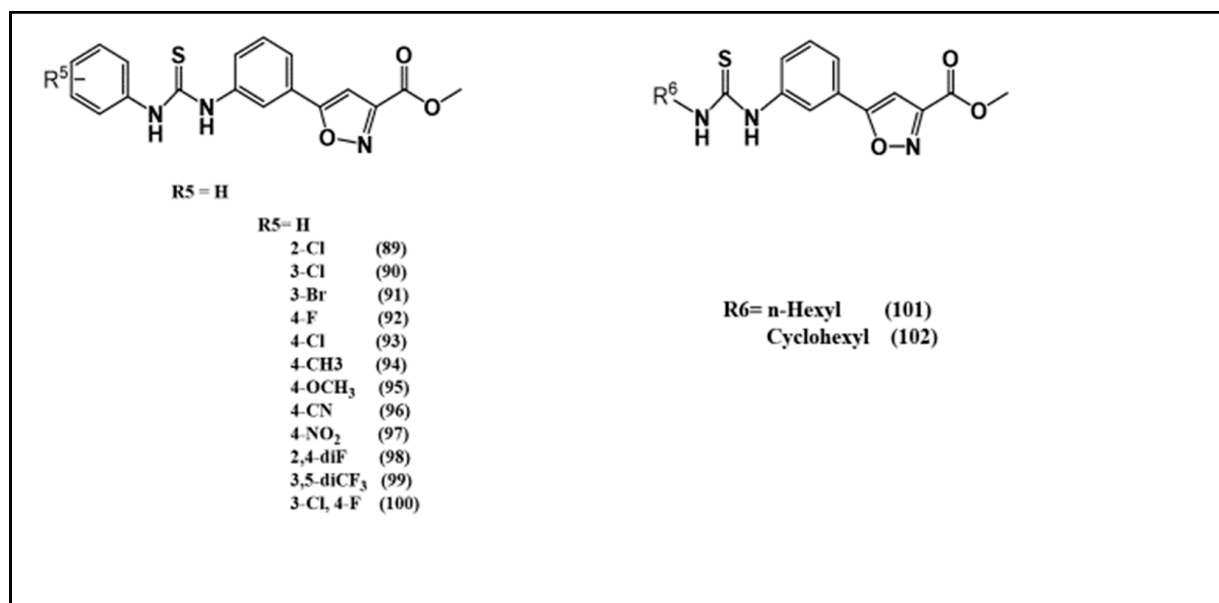
Figure 17. Synthetic route to 5-phenyl-3-isoxazole carboxylic acid methyl ester-linked thiourea derivatives [95].

When synthetic compounds **89–102** were examined for their ability to combat tuberculosis (TB), they all displayed nearly identical levels of efficacy. The most potent monosubstituted thiourea derivatives were those containing a chlorine atom, with p-chloro being the most active (MIC 1 µg/mL). On the other hand, the m-chloro and m-bromo compounds only showed a moderate level of efficacy. The 2,4-difluoro derivatives among the disubstituted analogs exhibited good efficacy (MIC 2 µg/mL).

7. Anti-Alzheimer

Dementia may result from Alzheimer's disease, a degenerative and crippling neurological condition that impairs cognitive function. Studies indicate that hereditary variables, including apolipoprotein E, can contribute to the onset of the illness. The two main processes that harm neural cells are oxidative damage and inflammation [96–98]. Research has demonstrated the potential application of sulfur-containing compounds, including thiols, disulfides and sulfides, in the treatment of Alzheimer's disease (Figure 18). In addition, various classes of compounds containing sulfur have demonstrated promise in the treatment of the disease, such as sulfoxides and thiocarboxylic acids with a +4 oxidation state, thioesters, thioketones, thioureas and heterocyclic compounds containing sulfur with a −2 oxidation state, and sulfones and sulfonamides with a +6 oxidation state [99,100].

Targeting the enzymes Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE), which are essential for the breakdown of different compounds, is the goal of treating Alzheimer's disease (AD). BChE also aids in the breakdown of ACh in a healthy brain, exacerbating the course of AD. In order to cure AD, it may be beneficial to inhibit both AChE and BChE [101]. As illustrated in Figure 19, AChE inhibitors such as donepezil, rivastigmine and galantamine are currently the most often prescribed medications for AD in clinics. Patients with mild to moderate AD may obtain symptom relief from these inhibitors, which interfere with the enzyme's active site [102].

Figure 18. Causes, mechanisms and treatment of Alzheimer's disease [99,100].

Figure 19. Anti-Alzheimer drugs [103].

As shown in Figure 20, Mehtab et al. [103] produced a range of thiourea and thiazolidinone compounds, **103–106**, and investigated their inhibitory activity against AChE and BChE.

The compounds showed varying degrees of inhibitory efficacy against AChE and BChE, according to the study. In particular, **103 < 105 < 104** was the sequence of inhibitory activities against AChE, whereas **105 < 104 < 103 < 106** was the sequence against BChE. The compound's IC_{50} values against AChE and BChE were 33.27–93.85 nM and 105.9–412.5 nM, respectively. All results showed that the compounds worked better against AChE than they did against BChE [103]. There have also been reports of other thiourea compounds acting

as enzyme inhibitors, including isobutylphenylthiourea and tert-butylphenylthiourea [104]. Six crystalline thiourea derivatives were evaluated against BChE and AChE in a different investigation [105]. Figure 21 displays the compounds that were produced.
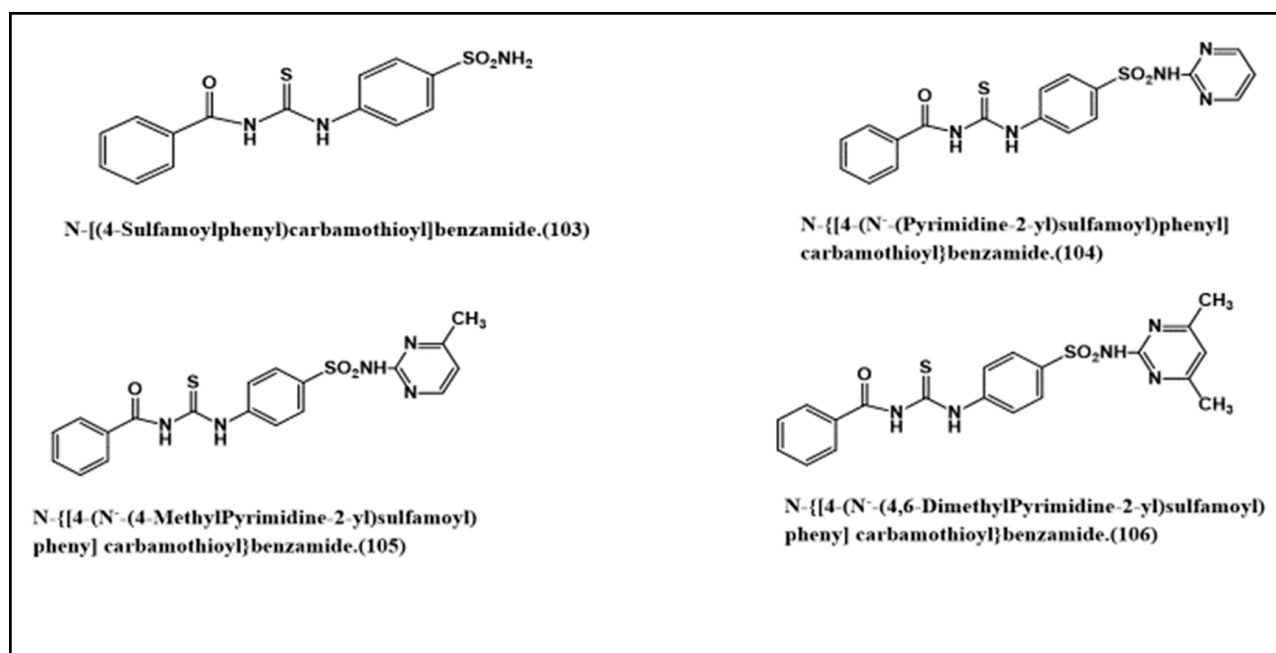

Figure 20. Synthesized thiazolidinone derivatives with both AChE and BChE activity [103].

Figure 21. Structure of asymmetrical thiourea derivatives, 1-cyclohexyl-3-(*iso*-butyl)thiourea **107**, 1-cyclohexyl-3-(*tert*-butyl)thiourea **108**, 1-cyclohexyl-3-(3-chlorophenyl)thiourea **109**, 1-phenyl-3-(1,1-dibutyl)thiourea **110**, 1-phenyl-3-(2-chlorophenyl)thiourea **111** and 1-phenyl-3-(4-chlorophenyl) thiourea **112** [105].

Compounds **110** and **109** showed outstanding inhibitory properties. Compounds **109** and **110** exhibited different IC_{50} values for AChE and BChE. Specifically, compound **109's** IC_{50} value was 50 μg/mL, and compound **110's** IC_{50} value was 63 μg/mL. Galantamine, the standard, had an IC_{50} value of 15 μg/mL against both enzymes.

Compound **109** established contact with Asn-83, Asn-85 and His-77, and compound **110** was effective in creating associations with Try-128 and Try-82, according to the results of the molecular docking of compounds **109** and **110**, as shown in Figure 22. Complicated interactions are what give compound **109** its increased potency.

Figure 22. Three-dimensional binding interaction modes of compounds **109** and **110** as inhibitors of AChE and BChE. (**a**,**b**)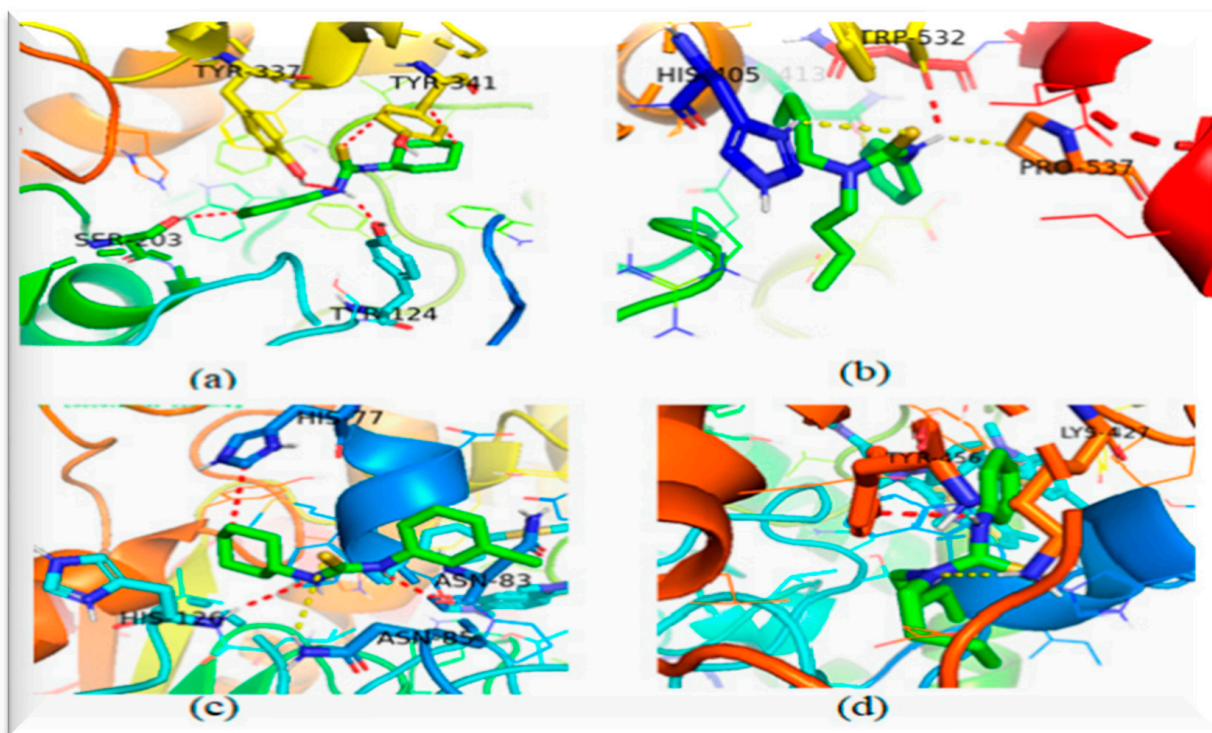 Interaction posing of compound **109** and **110** with AChE, respectively; (**c**,**d**) Interaction of compound **109** and **110** with BChE, respectively [105].

In comparison with the normal donepezil (IC$_{50}$, 2.16 and 4.5 µM, respectively), thiazole–thiourea hybrid compounds have recently demonstrated exceptional activity against both AChE and BChE enzymes, with IC$_{50}$ values ranging from 0.3 to 15 µM against AChE and 0.4 to 22 µM against BChE [106].

8. Antimalarial Activity

The parasite Plasmodium, a member of the phylum Apicomplexa, is the cause of malaria. About 50% of people worldwide are at risk of malaria, according to the World Health Organization (WHO) [107]. Malaria poses a threat to about half of the world's population. Drug-resistant forms of the malaria parasite have emerged as a result of the indiscriminate use of antimalarial medications like artemisinin and chloroquine. To tackle antimalarial drug resistance, Cheo et al. [108] and Mohamed et al. [109] synthesized promising compounds with chalcone pyrazoline and pyrimidine scaffolds, as seen in Figure 23.

Figure 23. Structures of chalcone, pyrazoline and pyrimidine [109].

Four chalcones, **113**–**116**, were created in the manner shown in Scheme 18. Twelve novel pyrazoline compounds, **113**–**116A**(**i**–**iii**), were produced by the cyclo-condensation reactions between the chalcones and hydrazine hydrate derivatives, as illustrated in Scheme 19.

Scheme 18. Synthesis of chalcones **113–116** [109].

Scheme 19. Synthesis of pyrazoline derivatives **113–116A**(**i–iii**) [109].

Scheme 20 illustrates the formation of eight novel pyrimidine derivatives, **113–116B**(**i–iii**), from the reaction of chalcones with guanidine or thiourea.

Scheme 20. Synthesis of pyrimidine derivatives **113–116B**(**i–iii**) [109].

All of the produced compounds were evaluated to see how well they worked against the chloroquine-resistant RKL9 strain of malaria, as well as the chloroquine-sensitive 3D7 strain. Next, the compounds' IC_{50} values were contrasted with those of chloroquine. Chalcones **113–116** were shown to be less efficient than the heterocyclic compound produced from them in combating P. falciparum malaria. Furthermore, it was shown that molecules with a methoxy group in the para position were more potent than those with a methoxy group in the meta position. An investigation into molecular docking was carried out on the ATPase 'PfATP4' enzyme, which is thought to be essential for resistance mechanisms. The strongest binding energies to the "PfATP4" receptor were exhibited by compounds **113**, **113Aiii** and **113Bi**, out of all the produced derivatives, according to the results. Figure 24 shows the compound model with the effective functional groups.

Figure 24. SAR of thiourea derivatives as antimalarial agents [109].

9. The Recent Strategies in the Synthesis of Thiourea Derivatives

As a result of the environmental problems associated with the diversity of the traditional chemical synthesis of organic compounds, the trend of using green chemistry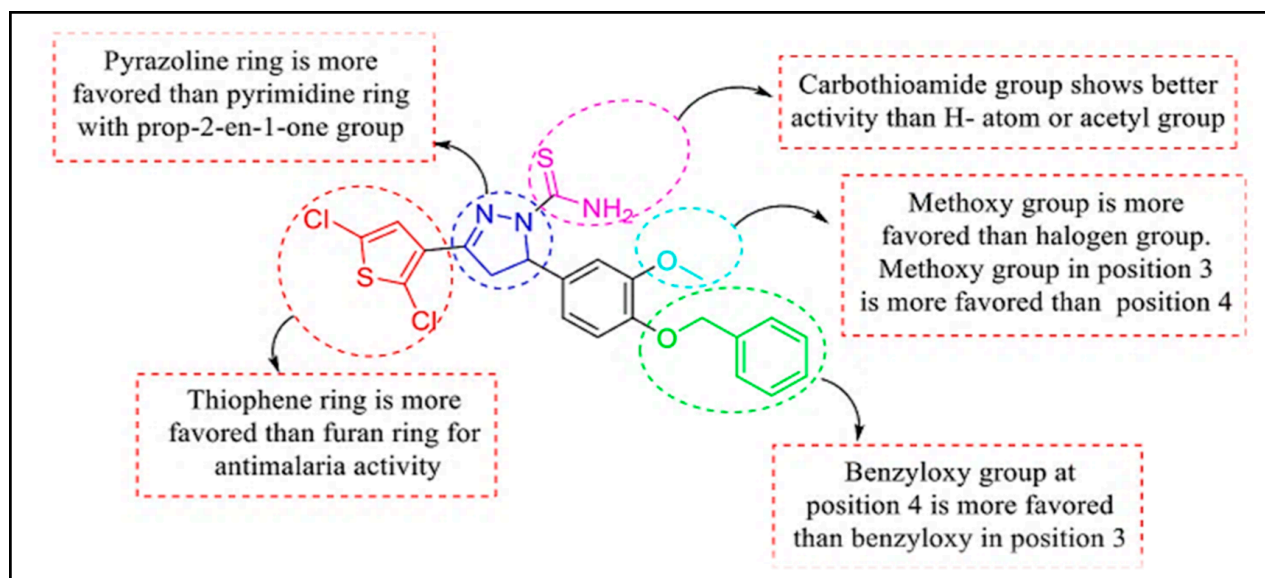 was the alternative to avoid these problems. The automated synthetic systems were a useful tool to accelerate the research of organic synthesis and reduce the harm of chemicals to the human body [110,111].

Capsaicin derivatives with thiourea structures (CDTS) are known for their higher analgesic potency in rodent models and higher agonism in vitro. As shown in Figure 25, capsaicin derivatives with thiourea structures showed higher analgesic potency in rodent models and higher agonism in vitro [112]. Lina et al. [113] reported a green, facile and practical synthetic method for capsaicin derivatives with thiourea structures, which was developed by using an automated synthetic system, as shown in Figure 26. The synthesis of CDTS was performed via a condensation reaction of vanilylamine hydrochloride and isothiocyanates at room temperature and under green solvent (water) conditions with goo/excellent yields [113].

Figure 25. Capsaicin derivatives with thiourea structures [113]. The blue content is the structure of the nucleus of capsaicin and the red parts are the substituted parts either without (**upper**) or with thiourea (**lower**).

Figure 26. Photograph (**a**) and schematic (**b**) of the automated synthetic system. The automated synthetic system mainly consists of seven parts: (i) central control unit; (ii) solvents; (iii) syringe pump; (iv) selection valve; (v) reaction module; (vi) filter module; (vii) vacuum pump [113].

10. Conclusions

Thiourea is a significant compound that is used as a basic building block to synthesize a wide range of derivatives with different biological activities. Strong antibacterial and anticancer effects have been demonstrated by these derivatives, which also comprise tris thioureas, complexes and symmetrical and asymmetrical bis thioureas. In addition, urea-thiourea hybrids have shown notable anti-inflammatory properties, and other thiourea-containing pyrazole, thiazole and pyran moieties have shown a variety of biological activities. Herien, I highlight several therapeutic applications and the development of synthetic strategies. I track the progress in this field by discussing traditional methods, green chemistry and, recently, the automated synthetic system. This system can be considered the starting point for improving not only the quality but also the quantity of the targeted product, while maintaining a healthy environment. According to the abovementioned information, I hope that this review will motivate researchers to conduct more research in this exciting field.

Data Availability Statement: Not applicable.
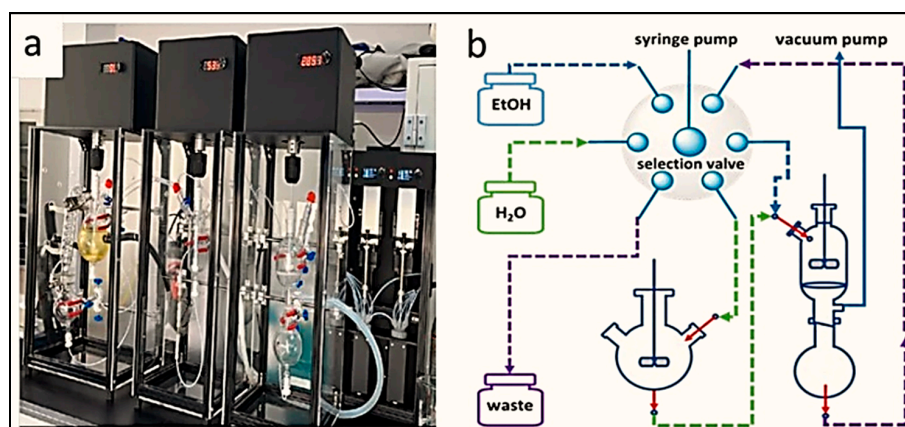
Conflicts of Interest: The author declares no conflicts of interest.

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