

Biological Application of Thiourea Derivatives

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Abstract: Thioureas have great medicinal applications as well as non-medicinal activities in industry, analytical chemistry and metallurgy. This review is a glimpse of methods of synthesis and applications of thioureas in the field of medicine and agriculture. Thioureas have a number of medicinal applications and a number of thioureas are in clinical use. Medicinal applications of thioureas are increasing with the passage of time. In the field of agriculture, thioureas are used as insect growth regulator, anti-fungal agents and herbicides. 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: Thioureas, Synthesis, Molecule Design, Biological Activities, Cancer Study

I. INTRODUCTION

Thiourea is an organosulfur compound with a chemical formula of $\text{SC}(\text{NH}_2)_2$, and its structure is represented in Figure 1. Its structure is similar to that of urea ($\text{H}_2\text{N}-\text{C}(=\text{O})-\text{NH}_2$), 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 $(\text{R}_1\text{R}_2\text{N})(\text{R}_3\text{R}_4\text{N})\text{C}=\text{S}$. 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 isothioureia.

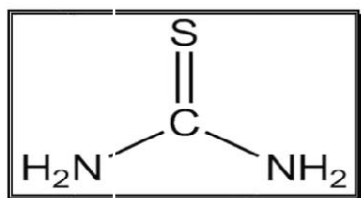


Figure 1. The chemical structure of

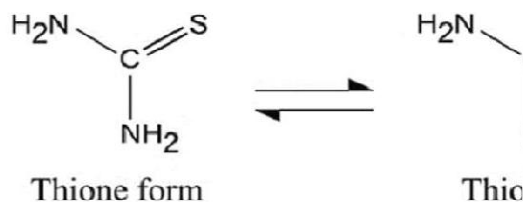


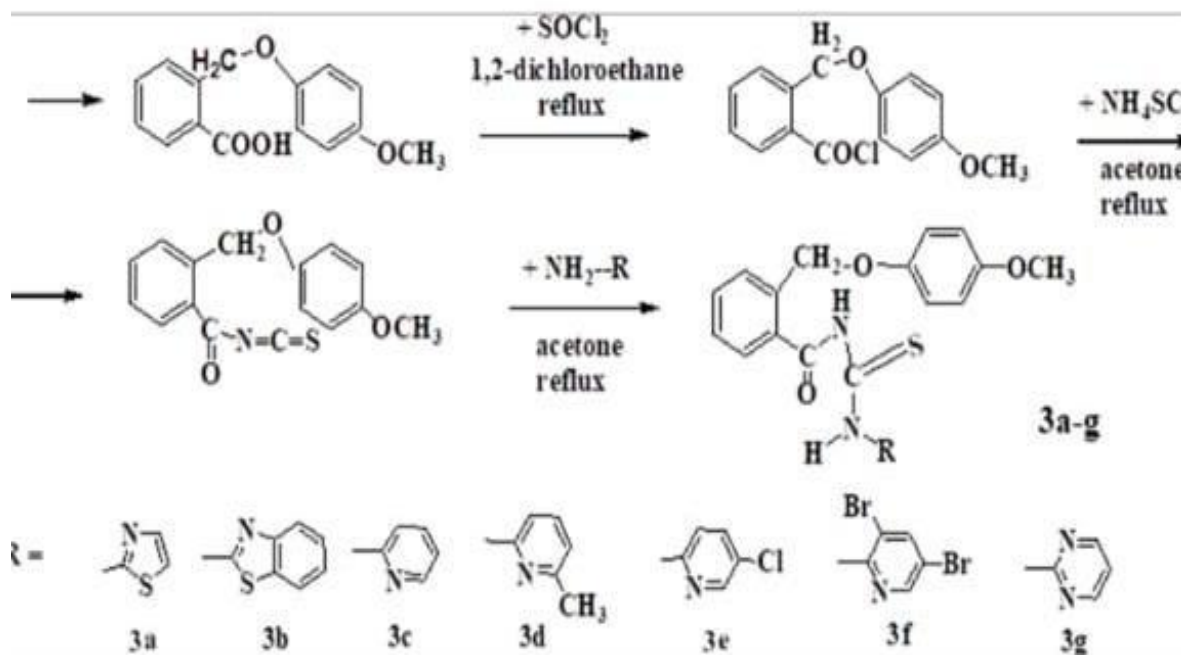
Figure 2. Equilibrium between the tautomeric



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.

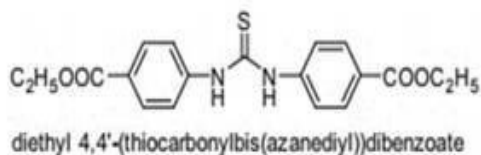
1. Antibacterial Activity

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.

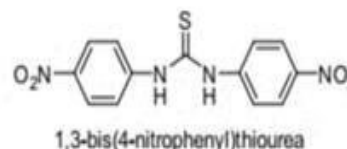


Scheme 2. The synthesis route of novel N-acyl thiourea derivatives 3a–3g [14].



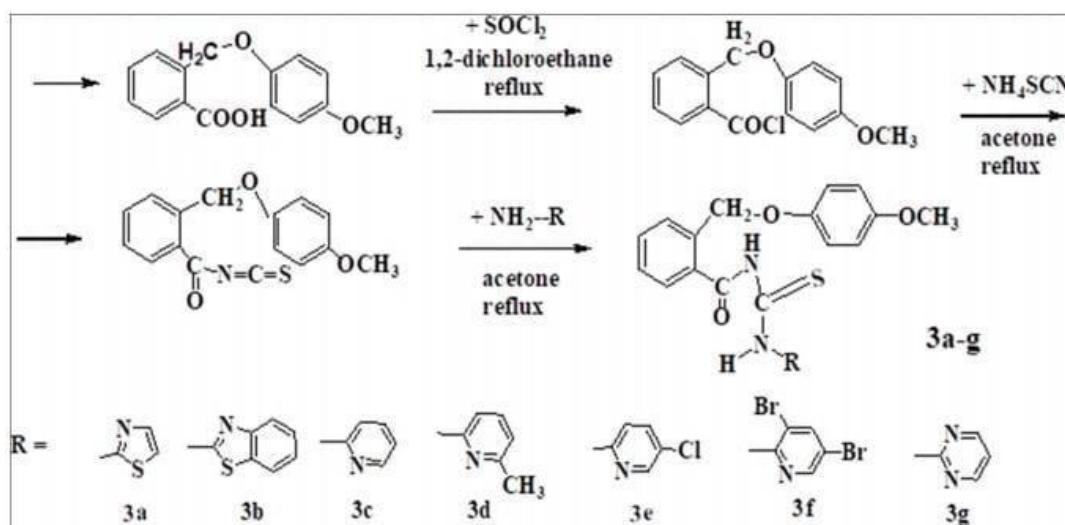


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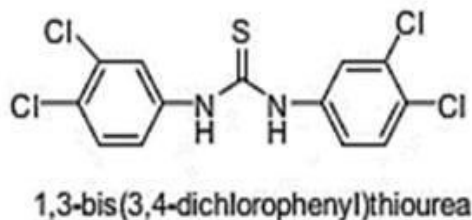
A novel set of seven N-acyl thiourea derivatives, namely 3a–3g, were developed by Roxana et al. [14]. Their synthesis method employed the condensation of acid chloride and ammonium thiocyanate in an anhydrous acetone solution. The resulting isocyanate was then allowed to react with a heterocyclic amine,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

2. Anti oxidant Activity :

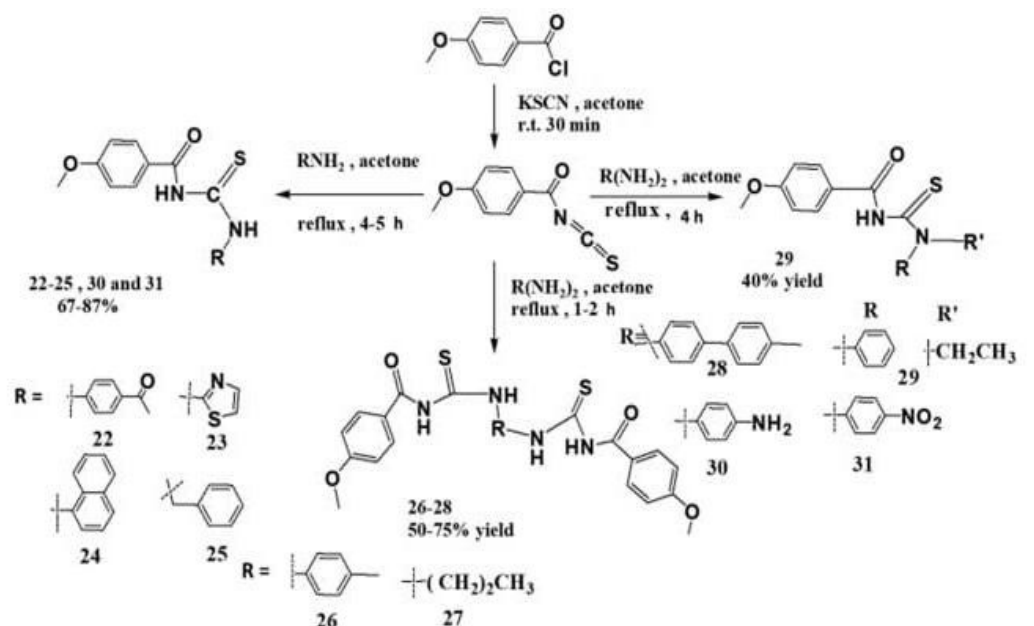
Thiourea derivatives such as 1-(2-aminoethyl) thiourea, N, N'-(iminodiethane-2,1-diyl) bis(thiourea) and 1-[1methyl-2-(phenylamino)ethyl] thiourea were prepared by Sudzhaev et al. [22]. Additionally, 1,3-bis(3,4-dichlorophenyl) thiourea 21, a new thiourea derivative, was synthesized by Sumaira et al. [23] and demonstrated strong antioxidant activity. This derivative had a high reducing potential when tested against ABTS free radicals, with an IC50 of 52 µg/mL and a DPPH assay value of 45 µg/mL.



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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 IC₅₀ values of 5.8, 42.3 and 45 µg/mL, respectively, when compared to normal ascorbic acid, which had an IC₅₀ value of –33.22 µg/mL. The other drugs' IC₅₀ values varied between 89 and 245 µg/mL.

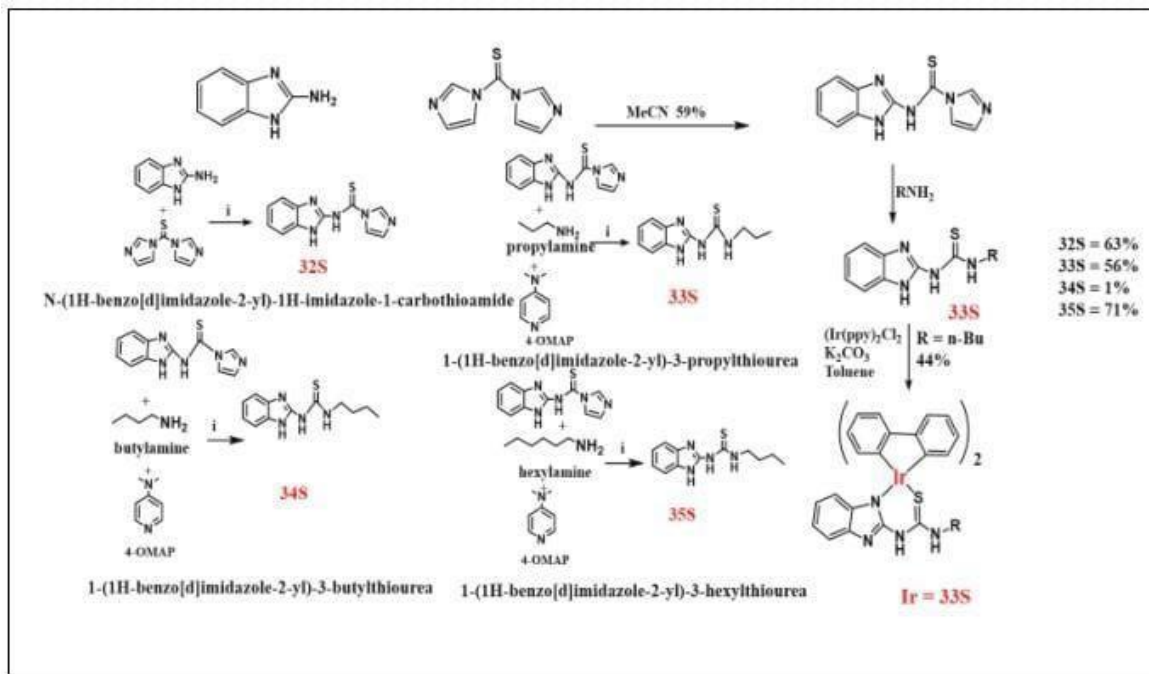


3. Anticancer Activity :

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 LC₅₀ 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 IC₅₀ 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 IC₅₀ values as low as 1.50 µM [36]. Lung, liver and breast malignancies demonstrated positive LC₅₀ 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 2aminobenzimidazole reaction in acetonitrile, 1,1 thiocarbonyldiimidazole was monosubstituted efficiently. When compounds 32S – 35S were purified, they had a 63–81% yield. This was due to a series of amines replacing the second imidazolyl 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 $[\text{Ir}(\text{ppy})_2\text{Cl}]_2$ 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].

4. Anti Malarial Activity :

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 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.

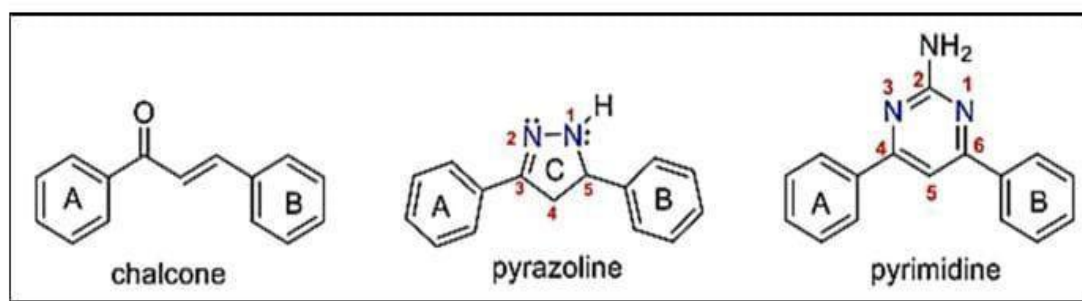
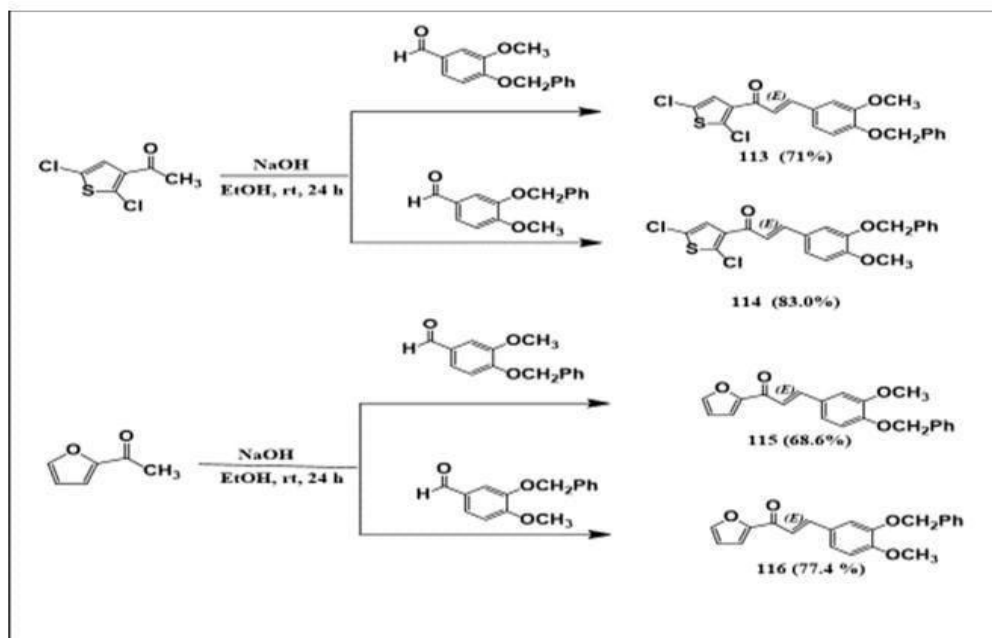


Figure 23. Structures of chalcone, pyrazoline and pyrimidine [109].



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.



Scheme 18. Synthesis of chalcones 113–116 [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' IC₅₀ 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. Chemistry 2024, 6, FOR PEER REVIEW 28 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

5. 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.

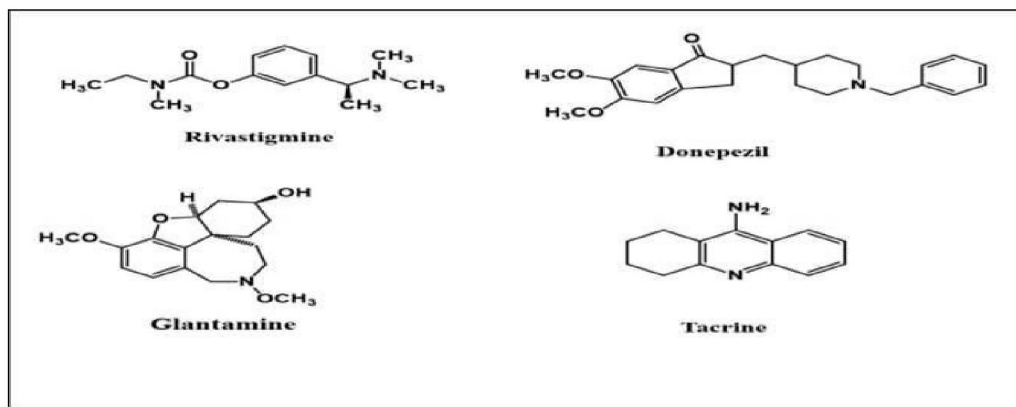


Figure 19. Anti-Alzheimer drugs [103].

6. 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 vanillylamine hydrochloride and isothiocyanates at room temperature and under green solvent (water) conditions with good /excellent yield.

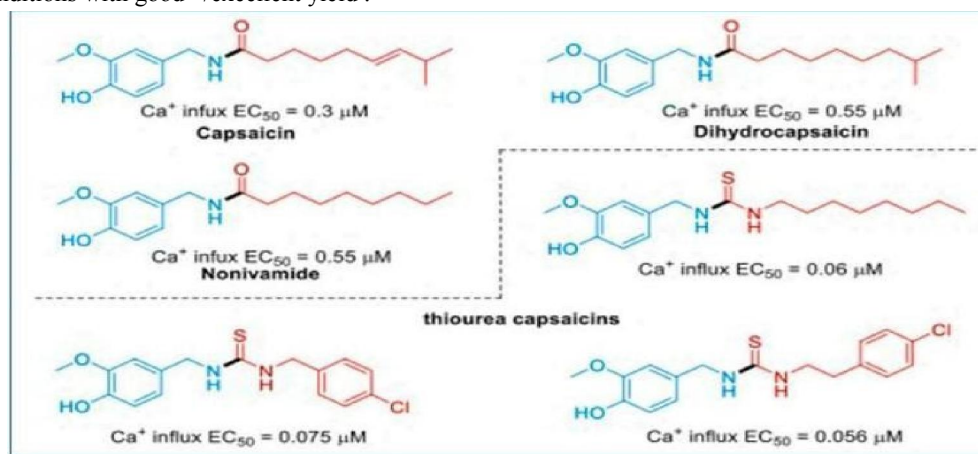


Fig . Capsaicin derivatives with thiourea structures [113]. The blue content is the structure of the nucleus of capsaicin and the red parts are the substituted parts either without (upper) or with thiourea (lower). Chemistry 2024, 6, FOR PEER REVIEW 29 Figure 25. The blue content is the structure of the nucleus of capsaicin and the red parts are the substituted parts either without(upper) or with thiourea (lower).

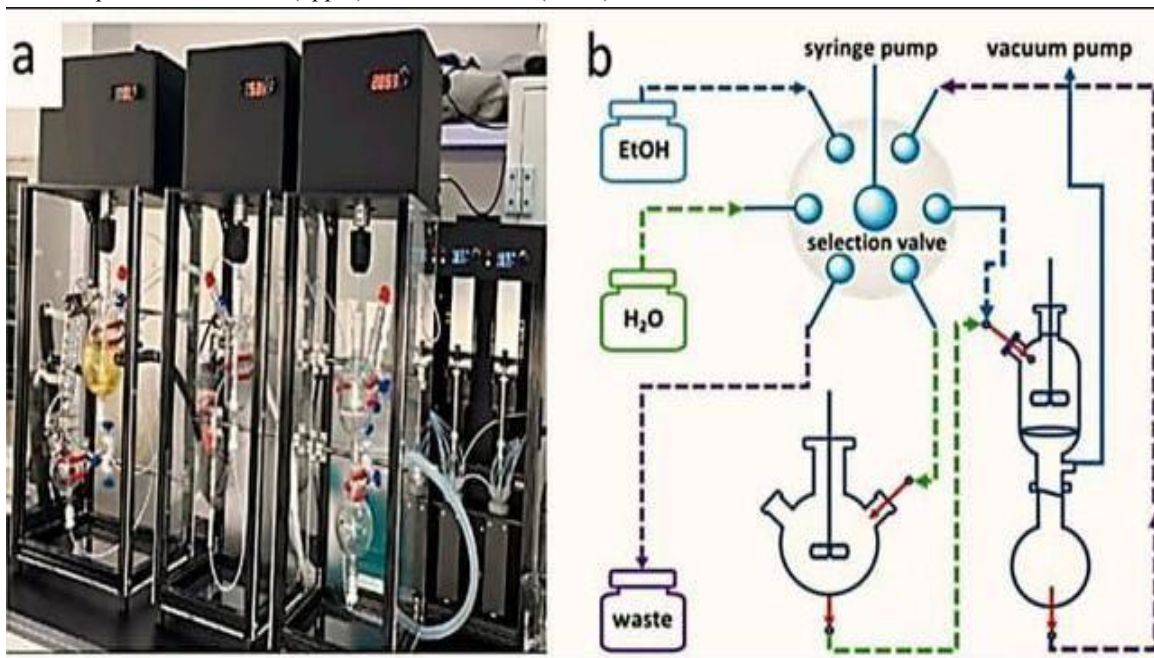


Fig. Photograph (a) and schematic (b) of the automated synthetic system. The automated synthetic system mainly consists of seven parts: (i) central control unit; (ii) solvents; (iii) syringe pump; (iv) selection valve; (v) reaction module; (vi) filter module; (vii) vacuum pump

II. CONCLUSION

Thioureas are versatile chemicals with outstanding biological applications. These are used in agriculture, analytical industry, metallurgy, industry and in the field of medicine. Most prominent biological applications of Thioureas is for treatment of co-infection, as antioxidant, as anti allergens, as anti bacterial agents, as antiinflammatory, as anti-thyroid drugs, as anti-epileptic drugs, as antihypertensive, as rodenticide, as anti-cancer drug, as DNA binder and as Urease Inhibitors. Complexes of thioureas are used as precursors and antibacterial agents. Thioureas act as precursor of gaunidines and hetrocyclic ring systems. 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.

REFERENCES

- [1]. Rigaudy, J.; Klesney, S.; Rigaudy, J. Nomenclature of Organic Chemistry: Sections A, B, C, D, E, F and H: Pergamon Press Oxford; 1979.



- [2]. Schroeder, D. C.; Chemical Reviews. 1955, 55, 181-228.
- [3]. Miyabe, H.; Takemoto, Y.; Bulletin of the Chemical Society of Japan. 2008, 81, 785-95.
- [4]. Koketsu, M.; Kobayashi, C.; Ishihara, H.; Heteroatom Chemistry. 2003, 14, 374-8.
- [5]. Huang, Y.-B.; Yi, W.-B.; Cai, C. Thiourea based fluorous organocatalyst. Fluorous Chemistry: Springer; 2012. p. 191-212.
- [6]. Maddani, M. R.; Prabhu, K. R.; The Journal of Organic Chemistry. 2010, 75, 2327-32.
- [7]. Ramadas, K.; Srinivasan, N.; Janarthanan, N.; Tetrahedro letters. 1993, 34, 6447-50.
- [8]. Tunaz, H.; Uygun, N.; Turkish Journal of Agriculture and Forestry. 2004, 28, 377-87.
- [9]. Brown, B.; Harris, R.; Pesticide Science. 1973, 4, 215-25.
- [10]. Yonova, P.; Guleva, E.; Bulgarian Journal of Plant Physiology. 1997, 23, 72-9.
- [11]. Rodriguez-Fernandez, E.; Manzano, J. L.; Benito, J. J.; Hermosa, R.; Monte, E.; Criado, J. J.; Journal of inorganic biochemistry. 2005, 99, 1558-72.
- [12]. Wu, J.; Shi, Q.; Chen, Z.; He, M.; Jin, L.; Hu, D.; Molecules. 2012, 17, 5139-50.
- [13]. Yonova, P.; Stoilkova, G.; Journal of Plant Growth Regulation.
- [14]. Favre, H.A.; Powell, W.H. Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names; IUPAC Blue book; RSC Publishing: London, UK, 2014; ISBN 978-0-85404-182-4. [CrossRef].
- [15]. Alcolea, V.; Plano, D.; Karelia, D.N.; Palop, J.A.; Amin, S.; Sanmartin, C.; Sharma, A.K. Novel seleno- and thiourea derivatives with potent in vitro activities against several cancer cell lines. Eur. J. Med. Chem. 2016, 113, 134–144. [CrossRef] [PubMed].
- [16]. Mertschenk, B.; Knott, A.; Bauer, W. Thiourea and thiourea derivatives. In Ullmann's Encyclopedia of Industrial Chemistry; Wiley: Hoboken, NJ, USA, 2000; Volume 15, pp. 1–15.
- [17]. Kerru, N.; Settypalli, T.; Nallapaneni, H.C.V. Novel thienopyrimidine derivatives Containing 1,2,4-triazoles and 1,3,4-oxadiazoles as potent antimicrobial activity. Med. Chem. 2014, 4, 623–629. [CrossRef].
- [18]. Rivera, A.; Maldonado, M.; Rios-Motta, J. A facile and efficient procedure for the synthesis of new benzimidazole-2-thione derivatives. Molecules 2012, 17, 8578–8586. [CrossRef].
- [19]. Kulakov, I.; Nurkenov, O.; Akhmetova, S.; Seidakhmetova, R.; Zhambekov, Z. Synthesis and antibacterial and antifungal activities of thiourea derivatives of the alkaloid anabasine. Pharm. Chem. J. 2011, 45, 15–18. [CrossRef]
- [20]. Mishra, A.; Batra, S. Thiourea and guanidine derivatives as antimalarial and antimicrobial agents. Curr. Top. Med. Chem. 2013, 13, 2011–2025. [CrossRef]
- [21]. Hasanen, J.; El-Deen, I.; El-Desoky, R.; Abdalla, A. Synthesis of some nitrogen heterocycles and in vitro evaluation of their antimicrobial and antitumor activity. Res. Chem. Interm. 2014, 40, 537–553. [CrossRef]
- [22]. Pattan, S.; Kedar, M.; Pattan, J.; Dengale, S.; Sanap, M.; Gharate, U.; Shinde, P.; Kadam, S. Synthesis and evaluation of some novel 2,4thiazolidinedione derivatives for antibacterial, antitubercular, and antidiabetic activities. Indian J. Chem. 2012, 51, 1421–1425. [CrossRef]
- [23]. Shivakumara, K.N.; Sridhar, B.T. Review on role of urea and thiourea derivatives of some heterocyclic Scaffold in drug design and medicinal chemistry. Int. J. Chem. Res. Dev. 2021, 3, 20–25.
- [24]. Riccardo, R.; Giada, M.; Andrea, C.; Antimo, G.; Emidio, C. Recent advances in urea- and thiourea-containing compounds: Focus on innovative approaches in medicinal chemistry and organic synthesis. RSC Med. Chem. 2021, 12, 1046–1064.
- [25]. Ezzat, K.; Sikandar, K.; Zarif, G.; Mian, M. Medicinal Importance, Coordination Chemistry with Selected Metals (Cu, Ag, Au) and Chemosensing of Thiourea Derivatives. A Review. Crit. Rev. Anal. Chem. 2021, 51, 812–834.
- [26]. Sumaira, N.; Muhammad, Z.; Muhammad, N.U.; Saad, A.; Muhammad, U.K.S.; Wasim, U. Synthesis, characterization, and pharmacological evaluation of thiourea derivatives. Open Chem. 2020, 18, 764–777.
- [27]. Roxana, R.; Lucia, P.; Miron, T.; Căproiu, F.; Dumitras, C.; Diana, C.N.; Irina, Z.; Petre, I.; Mariana, C.C.; Cornel, C.; et al. New N-acyl Thiourea Derivatives: Synthesis, Standardized Quantification Method and In Vitro Evaluation of Potential Biological Activities. Antibiotics 2023, 12, 807. [CrossRef]



- [28]. Saghi, S.; Ghorbani, N.M.; Masoud, M.Z.; Masood, G. Synthesis and Investigation of the Antibacterial Activity of New Tristhiourea Derivatives. *Pharm. Chem. J.* 2021, 55, 36–40.
- [29]. Mumtaz, J.; Arshad, A.; Saeed, M.A.H.; Nawaz, J. Iqbal. Synthesis, characterization and urease inhibition studies of transition metal complexes of thioureas bearing ibuprofen moiety. *J. Chil. Chem. Soc.* 2018, 63, 3934–3940.
- [30]. Zou, T.; Lum, C.T.; Lok, C.-N.; Zhang, J.-J.; Che, C.-M. Chemical biology of anticancer gold (III) and gold(I) complexes. *Chem. Soc. Rev.* 2015, 44, 8786–8801. [CrossRef] [PubMed].
- [31]. Mora, M.; Gimeno, M.C.; Visbal, R. Recent advances in gold-NHC complexes with biological properties. *Chem. Soc. Rev.* 2019, 48, 447–462. [CrossRef]
- [32]. Ott, I.; Quian, X.; Xu, Y.; Vlecken, D.H.W.; Marques, I.J.; Kubutat, D.; Will, J.; Sheldrick, W.S.; Jesse, P.; Prokop, A.; et al. A Gold(I) Phosphine Complex Containing a Naphthalimide Ligand Functions as a TrxR
- [33]. Inhibiting Antiproliferative Agent and Angiogenesis Inhibitor. *J. Med. Chem.* 2009, 52, 763–770. [CrossRef]
- [34]. Gutierrez, A.; Gracia-Fleta, L.; Marzo, I.; Catiuela, C.; Laguna, A.; Gimeno, M.C. Gold(I) thiolates containing amino acid moieties.
- [35]. Cytotoxicity and structure–activity relationship studies. *Dalton Trans.* 2014, 43, 17054–17066. [CrossRef] [PubMed]
- [36]. Ronconi, L.; Giovagnini, L.; Marzano, C.; Bettio, F.; Graziani, R.; Pilloni, G.; Fregona, D. Gold dithiocarbamate derivatives as potential antineoplastic agents: Design, spectroscopic properties, and in vitro antitumor activity. *Inorg. Chem.* 2005, 44, 1867–1881. [CrossRef] [PubMed]
- [37]. Quero, J.; Cabello, S.; Fuertes, T.; Mármol, I.; Laplaza, R.; Polo, V.; Gimeno, M.C.; Rodriguez-Yoldi, M.J.; Cerrada, E. Proteasome versus Thioredoxin Reductase Competition as Possible Biological Targets in
- [38]. Antitumor Mixed Thiolate-Dithiocarbamate Gold(III) Complexes. *Inorg. Chem.* 2018, 57, 10832–10845. [CrossRef] [PubMed]
- [39]. Berners-Price, S.J.; Sadler, P.J. Gold(I) complexes with bidentate tertiary phosphine ligands: Formation of annular vs. tetrahedral chelated complexes. *Inorg. Chem.* 1986, 25, 3822–3827. [CrossRef]
- [40]. Ortego, L.; Laguna, A.; Gonzalo-Asensio, J.; Villacampa, M.D.; Gimeno, M.C. (Aminophosphane)gold(I) and silver(I) complexes as antibacterial agents. *J. Inorg. Biochem.* 2015, 146, 19–27. [CrossRef]
- [41]. Baker, M.V.; Barnard, P.J.; Berners-Price, S.J.; Brayshaw, S.K.; Hickey, J.L.; Skelton, B.W.; White, A.H. Cationic, linear Au (I) N-heterocyclic carbene complexes: Synthesis, structure and anti-mitochondrial activity. *Dalton Trans.* 2006, 3708–3715. [CrossRef] [PubMed]
- [42]. Gallati, C.M.; Goetzfried, S.K.; Ausserer, M.; Sagasser, J.; Plangger, M.; Wurst, K.; Hermann, M.; Baecker, D.; Kircher, B.; Gust, R. Synthesis, characterization, and biological activity of bromido [3-ethyl-4-aryl-5-(2-methoxypyridin-5-yl)-1-propyl-1,3-dihydro-2H-imidazol-2-ylidene] gold(I) complexes. *Dalton Trans.* 2020, 49, 5471–5481. [CrossRef] [PubMed]
- [43]. Gallati, C.M.; Goetzfried, S.K.; Ortmeier, A.; Sagasser, J.; Wurst, K.; Hermann, M.; Baecker, D.; Kircher, B.; Gust, R. Synthesis, characterization and biological activity of bis [3-ethyl-4-aryl-5-(2-methoxypyridin-5-yl)-1-propyl-1,3-dihydro-2H-imidazol-2-ylidene] gold(I) complexes. *Dalton Trans.* 2021, 50, 4270–4279. [CrossRef]
- [44]. Khodjoyan, S.; Remadna, E.; Dossmann, H.; Lesage, D.; Gontard, G.; Forté, J.; Hoffmeister, H.; Basu, U.; Ott, I.; Spence, P.; et al. [(CC)Au(NN)]⁺ complexes as a new family of anticancer candidates: Synthesis, characterization and exploration of the antiproliferative properties. *Chem. Eur. J.* 2021, 27, 15773–15785. [CrossRef]
- [45]. Guillermo, C.; Lourdes, O.; Anabel, I.; Isabel, M.; Raquel, P.H. Concepción Gimeno. Synthesis of New Thiourea-Metal Complexes with Promising Anticancer Properties. *Molecules* 2021, 26, 6891.
- [46]. Banti, C.N.; Giannoulis, A.D.; Kourkoumelis, N.; Owczarzak, A.M.; Poyraz, M.; Kubicki, M.; Charalabopoulos, K.; Hadjikakou, S.K. Mixed ligand–silver(I) complexes with anti-inflammatory agents which can bind to lipoxygenase and calf-thymus DNA, modulating their function and inducing apoptosis. *Metallomics* 2012, 4, 545–560. [CrossRef] [PubMed]



- [47]. Pandey, S.K.; Pratap, S.; Rai, S.K.; Marverti, G.; Kaur, M.; Jasinsk, J.P. Synthesis, characterization, Hirshfeld surface, cytotoxicity, DNA damage and cell cycle arrest studies of N, N-diphenyl-N'-(biphenyl-4-carbonyl/4-chlorobenzoyl) thiocarbamides. *J. Mol. Struct.* 2019, 1186, 333–344. [CrossRef]
- [48]. Abdel-Hadi, K.A.; Abdel-Razik, A.; Shoukry, M.M.; Shoheib, S.M. *Egypt. J. Chem.* 1996, 39, 179.
- [49]. Saeed, A.; Qamar, R.; Fattah, T.A.; Flörke, U.; Erben, M.F. Recent developments in chemistry, coordination, structure and biological aspects of 1-(acyl/aroil)-3-(substituted) thioureas. *Res. Chem. Intermed.* 2017, 43, 3053–3093. [CrossRef]
- [50]. Yaqeen, M.A.; Rafid, H.A. Synthesis, Anti-breast Cancer Activity, and Molecular Docking Studies of Thiourea Benzamide Derivatives and Their Complexes with Copper Ion. *Trop. J. Nat. Prod. Res.* 2023, 7, 3158–3167.
- [51]. Shing, J.C.; Choi, J.; Chapman, R.; Schroeder, M.; Sarkaria, J.; Fauq, A.; Bram, R.J. A novel synthetic 1, 3-phenyl bis-thiourea compound targets microtubule polymerization to cause cancer cell death. *Cancer Biol. Ther.* 2014, 15, 895–905. [CrossRef]
- [52]. Nowotarski, S.L.; Pachaiyappan, B.; Holshouser, S.; Kutz, C.; Li, Y.; Huang, Y.; Woster, P. Structure–activity study for (bis) ureidopropyl and (bis) thioureidopropyl diamine LSD1 inhibitors with 3-5-3 and 3-6-3 carbon backbone architectures. *Bioorg. Med. Chem.* 2015, 23, 1601–1612. [CrossRef] [PubMed]
- [53]. Nasima, A.; Uzma, P.; Pervaiz, A.C.; Aamer, S.; Waseem, S.S.; Fouzia, P.; Aneela, J.; Hammad, I.; Muhammad, I.M.; Atteeque, A.; et al. Investigation of Newly Synthesized Bis-Acyl-Thiourea Derivatives of 4-Nitrobenzene-1,2-Diamine for Their DNA Binding, Urease Inhibition, and Anti-Brain-Tumor Activities. *Molecules* 2023, 28, 2707. [CrossRef] [PubMed]
- [54]. Sun, Y.; Shan, Y.; Li, C.; Si, R.; Pan, X.; Wang, B.; Zhang, J. Discovery of novel anti-angiogenesis agents. Part 8: Diaryl thiourea bearing 1Hindazole-3-amine as multi-target RTKs inhibitors. *Eur. J. Med. Chem.* 2017, 141, 373–385. [CrossRef]
- [55]. Zhang, L.; Shan, Y.; Li, C.; Sun, Y.; Su, P.; Wang, J.; Li, L.; Pan, X.; Zhang, J. Discovery of novel anti-angiogenesis agents. Part 6: Multitargeted RTK inhibitors. *Eur. J. Med. Chem.* 2017, 127, 275–285. [CrossRef]

