Propylthiouracil Derivatives: Synthesis and Evaluation of Antimicrobial Efficacy Against Pathogenic Strains

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Abstract

This manuscript details the synthesis and evaluation of novel bioactive derivatives of propylthiouracil (PTU), highlighting their pharmacological significance. We synthesized several PTU derivatives through various chemical transformations, notably derivatives **2** and **3** from 4-chloro-2-oxo-2H-chromene-3-carbaldehyde and chloroacetyl chloride, respectively. Derivative **4** was produced by reacting PTU derivative **1** with chloroacetic acid and 4-chlorobenzaldehyde, while hydrazinyl product **5** was obtained by treating PTU derivative **1** with hydrazine hydrate. Further reactions led to triazolopyrimidinone derivatives 6 and Schiff's base derivative **7**. Antimicrobial testing revealed that derivative **2** showed significant efficacy against Gram-positive bacteria, particularly *Staphylococcus aureus* and *Bacillus subtilis*, but none were effective against Gram-negative strains or *Candida albicans*. These results highlight the potential of PTU derivatives as antimicrobial agents while indicating the need for structural modifications to enhance effectiveness against resistant pathogens. This study contributes to the understanding of PTU's synthetic versatility and biological potential in medicinal chemistry. This study presents a novel approach to the synthesis of bioactive derivatives of propylthiouracil (PTU), expanding the existing knowledge of this compounds pharmacological potential. The innovative chemical transformations employed to create derivatives **2** to **7** highlight the versatility of PTU as a scaffold for developing new antimicrobial agents.

Keywords: Propylthiouracil (PTU), Pyrimidine, Antimicrobial, Thyroras Drug.

Introduction

Thyroras (Propylthiouracil or PTU) is a medication primarily used for managing thyroid conditions, particularly hypothyroidism. It contains active ingredients that help restore normal thyroid hormone levels, alleviating symptoms associated with thyroid hormone deficiency, such as fatigue, weight gain, and sensitivity to cold. As a member of the thiouracil family, Propylthiouracil is a heterocyclic compound known for its diverse pharmacological properties and synthetic adaptability [**1**, **2**, **3**, **4**, **5**].PTU, a unique molecular structure with nitrogen and sulfur atoms, is crucial in medicinal chemistry due to its ease of synthesis and functionalization [**6**, **7**, **8**, **9**, **10**]. PTU and its derivatives have antimicrobial activity against various pathogens, making them promising for treating infectious diseases, inflammatory conditions, and neurodegenerative disorders. Synthesis involves chemical modifications to the parent PTU molecule, with the choice based on desired structural modifications and target biological activities [**11**, **12**, **13**, **14**, **15**, **16**, **17**, **18**, **19**]. Propyl thioracyl, a pyrimidine derivative, possesses significant pharmacological actions due to the pyrimidine nucleus, which is linked to many biological and therapeutic effects in different medications. The incorporation of pyrimidine and its derivatives in the structure offers significant potential for the development of pharmaceuticals that can effectively mitigate human suffering [**20**, **21**, **22**, **23**, **24**, **25**]. This manuscript investigates the synthesis, reactivity, and antimicrobial activity of propylthiouracil heterocyclic derivatives. Its objective is to elucidate structure-activity relationships, assess therapeutic potential, and connect synthetic chemistry with pharmacology.

Experimental

The chemicals used in the experiments were obtained from commercial suppliers and were of analytically pure quality, eliminating the need for additional purification. Melting points (m.p.) were uncorrected and measured using a Fisher-John apparatus. The ^{1}H and ^{13}C NMR spectra were recorded on an INOVA 500 instrument, using

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DMSO-d_6 as the solvent, with chemical shifts expressed in parts per million (ppm). For FT-IR spectra, a Thermo Nicolet 6700 USA spectrophotometer was utilized, employing the KBr wafer method. The supplemental file (Section S1) has comprehensive details on the materials, toolsand techniques used for structural confirmation and application. (Section S2): procedure of antimicrobial activity [**26**,**27**,**28**,**29**,**30**].

Synthesis of the proposed compounds

2-oxo-4-((6-oxo-4-propyl-1,6-dihydropyrimidin-2-yl)thio)-2H-chromene-3-carbaldehyde(2)

(1g, 5.88 mmol) of propyl thiouracil was dissolved in 20 ml of ethanol, to which (0.96 g , 11.76 mmol) of sodium acetate was added. The reaction mixture was heated under reflux for 2 hours. Subsequently, (1.1g, 5.88 mmol) of 4-chloro-2-oxo-2H-chromene-3-carbaldehyde was introduced, and the reaction mixture was subjected to reflux for 6 hours. Following this, the mixture was allowed to cool, and the resulting solid precipitate was filtered, dried, and recrystallized from ethanol, resulting in the formation of white crystals.; m.p. 200-202 ºC; yield 81 %.**FT-IR** (KBr) cm^{-1}3134(NH group), 2955(C-H aromatic), 2870,2931 (C-H aliphatic), 1655,1724 (2 C=O). The **^{1}H NMR** (400 MHz, DMSO-d_6)showed the following chemical shifts:δ 0.93 (t,3H, CH_3), 1.63 (m,2H, CH_2), 2.48 (t,2H, CH_2), 6.34 (s,1H, CH pyrimidine), 7.40 (s,1H, CHO), 7.50-7.80 (m,4H, Ar-H), 7.84 (s,1H,NH).**^{13}C NMR** (101 MHz,DMSO-d_6) exhibited the following chemical shifts: δ13,89,20.92,38.37,69.64,110.36,115.99,116.53,117.62,124.92,125.79,134.21, 145.20,151.89,153.97,156.93,159.90,166.61.

1-(2-chloroacetyl)-6-propyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (3)

Chloroacetyl chloride (0.46 ml, 5.88 mmol) was added dropwise while stirring at room temperature to a solution of propyl thiouracil (1 g, 5.88 mmol) in 20 ml of pyridine. The reaction mixture was stirred overnight at room temperature, then poured into 100 ml of cold water and neutralized with a 10% sodium carbonate solution to obtain a slightly alkaline pH. The resulting solid precipitate was recrystallized from a mixture of petroleum ether and ethanol, yielding white crystals; m.p. 150-152 ºC; yield 73 %. **FT-IR** (KBr) cm-13088(NH group), 2930,2960 (C-H aliphatic), 1654,1698 (2 C=O).**^{1}H NMR** (400 MHz, DMSO-d6) showed the following chemical shifts: δ 0.88 (t,3H, CH3), 1.59 (m,2H, CH2), 2.37 (t,2H, CH_2), 3.91 (s,2H, CH_2),5.96 (s,1H, CH pyrimidine), 12.34 (S,1H,NH).**^{13}C NMR** (101 MHz, DMSO-d_6) exhibited the following chemical shifts: δ13.86,20.97,33.61,40.56,103.46,157.07,161.71,170.07,176.09.

2-(4-chlorobenzylidene)-7-propyl-5H-thiazolo[3,2-a]pyrimidine-3,5(2H)-dione (4)

A mixture of propyl thiouracil**1** (1 g, 5.88 mmol), chloroacetic acid (0.55 g, 5.88 mmol), and 4-chlorobenzaldehyde (0.82 g, 5.88 mmol) was prepared in a solvent mixture of glacial acetic acid (30 mL) and acetic anhydride (15 mL), along with anhydrous potassium carbonate (1.62 g, 11.76 mmol). This mixture was refluxed for 10 hours. After cooling, the solution was gradually added to cold water, and the resulting precipitate was washed multiple times with water, filtered, and recrystallized from ethanol, yielding yellow crystals.m.p 189-190 ºC; yield 83 %.**FT-IR** (KBr) cm^{-1}3032(C-H aromatic), 2930,2960 (C-H aliphatic), 1696,1762 (2 C=O).**^{1}H NMR** (400 MHz, DMSO-d_6) showed the following chemical shifts:δ0.93 (t,3H, CH_3), 1.62 (m,2H, CH_2), 2.45 (t,2H, CH_2), 6.14 (s,1H, CH pyrimidine), 7.50-8.00 (m,4H,Ar-H),8.03 (s,1H,CH=C). **^{13}C NMR** (101 MHz, DMSO-d_6) exhibited the following chemical shifts δ:13,84,20.56,33.97,98.50,103.46,128.68,129.14,133.85,136.64,152.76,157.04,161.33,165.03,176.78.

2-hydrazinyl-6-propylpyrimidin-4(3H)-one (5)

A mixture of propyl thiouracil (3 g, 17.64 mmol) in 20 ml of pure ethanol and hydrazine hydrate (0.88 ml, 17.64 mmol) was refluxed for 10 hours. After cooling, the resulting product was filtered, dried, and recrystallized from ethanol, resulting in white crystals. m.p 205-206 ºC; yield 75 %. **FT-IR** (KBr) cm^{-1}3091,3435 (2NH,NH_2groups), 2930,2958(C-H aliphatic), 1655 (C=O). **^{1}H NMR** (400 MHz, DMSO-d_6) displayed the following chemical shifts:δ1.01 (t,3H, CH_3), 1.68 (m,2H, CH_2), 2.41 (t,2H, CH_2), 5.76 (s,1H, CH pyrimidine), 7.26 (s,3H, NH,NH_2), 10.26 (s,1H, NH).

7-propyl-3-thioxo-2,3-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (6)

A mixture of compound **4** (1 g, 5.95 mmol) and carbon disulfide (2 mL) was heated in a water bath with 20 mL of pyridine for 8 hours. After allowing the reaction mixture to cool to room temperature, the solid product was filtered, dried, and recrystallized from ethanol, yielding yellow crystals. m.p 260-262 ºC; yield 86 %. **FT-IR** (KBr) cm^{-1} 3089(NH group), 2932,2962 (C-H aliphatic), 1665 (C=O).**^{1}H NMR** (400 MHz, DMSO-d_6) displayed the following chemical shifts:δ0.90 (t,3H, CH_3), 1.54 (m,2H, CH_2), 2.51 (t,2H, CH_2), 5.68 (s,1H, CH pyrimidine), 12.22 (s,1H, NH), 12.34 (S,1H, NH). **^{13}C NMR** (101 MHz, DMSO-d_6) demonstrated the following chemical shifts δ: 0.50,12.83,19.89,105.80,156.25,157.61,160.25,164.91.

2-(2-(4-chlorobenzylidene)hydrazinyl)-6-propylpyrimidin-4(3H)-one (7)

A mixture of compound 4 (1 g, 5.95 mmol) and 4-chlorobenzaldehyde (0.83 g, 5.95 mmol) in 20 ml of absolute ethanol, along with a few drops of piperidine, was refluxed for 8 hours. After cooling, the solid formed was filtered, dried under suction, and recrystallized from ethanol, yielding yellow crystals. m.p 170-172 ºC; yield 76 %. **FT-IR** (KBr) cm^{-1}showed bands at 3099,3350 (2NH group), 3040 (C-H aromatic), 2930,2957 (C-H aliphatic), 1655 (C=O). **^{1}H NMR** (400 MHz, DMSO-d_6) displayed the following chemical shifts: δ 0.90 (t,3H, CH_3), 1.54 (m,2H, CH_2), 2.31 (t,2H, CH_2), 5.51 (s,1H, CH pyrimidine), 5.66 (s,1H, CH =N), 7.00-8.00 (m,4H, Ar-H), 11.43 (s,2H,2NH). **^{13}C NMR** (101 MHz, DMSO-d_6) demonstrated the following chemical shifts: δ 0.50,13.18,20.19,105.80,127.87,128.17,132.56,132.84, 134.87,135.54,151.89,157.91,160.62,164.91.

Antimicrobial activity

The synthesized derivatives were evaluated for their antimicrobial activity against several reference standard strains, which included two Gram-positive bacteria: *Staphylococcus aureus* ATCC 6538 (*S. aureus*) and *Bacillus subtilis* ATCC 6633 (*B. subtilis*), along with two Gram-negative bacteria: *Escherichia coli* ATCC 8739 (*E. coli*) and *Pseudomonas aeruginosa* ATCC 9027 (*P. aeruginosa*). The yeast strain *Candida albicans* ATCC 10231 (*C. albicans*) was also included in the tests. The antimicrobial effectiveness of the derivatives was compared to control agents: Cefotaxime was used as the positive stander for antibacterial activity, Fluconazole as the positive stander for antifungal activity, and Dimethyl sulfoxide (DMSO) as the negative control. Culture turbidity was standardized to 0.5 McFarland (1.5×108 cfu/mL) for the assays [**28**, **29**, **30**, **31**].

Agar Well Diffusion Technique

The antimicrobial efficiency of the derivatives and controls against the strains was assessed using the agar well diffusion technique. The derivatives were dissolved in sterile DMSO, and serial dilutions were created at concentrations of 25, 50, and 100 mg/mL to establish the minimum inhibitory concentration (MIC) [**29**, **30**].

Antimicrobial activity bioassay

To assess the antimicrobial activities of the derivatives, two types of media were utilized: Mueller-Hinton agar for bacterial strains and Sabouraud Dextrose Agar for the yeast strain. The prepared inocula were evenly spread across the surface of the media. Wells were created by using a sterile cork borer, and 150 µL of each concentration was added to the respective wells. Bacterial isolates were incubated at 37°C for 24 hours, while yeast were incubated at 28°C for 48 hours. This was accomplished by measuring the diameter of the inhibition zone surrounding each well to assess antimicrobial activity. The lowest concentration that prevented microbial growth was recorded as the MIC, with all tests performed in triplicate [**26**, **27**].

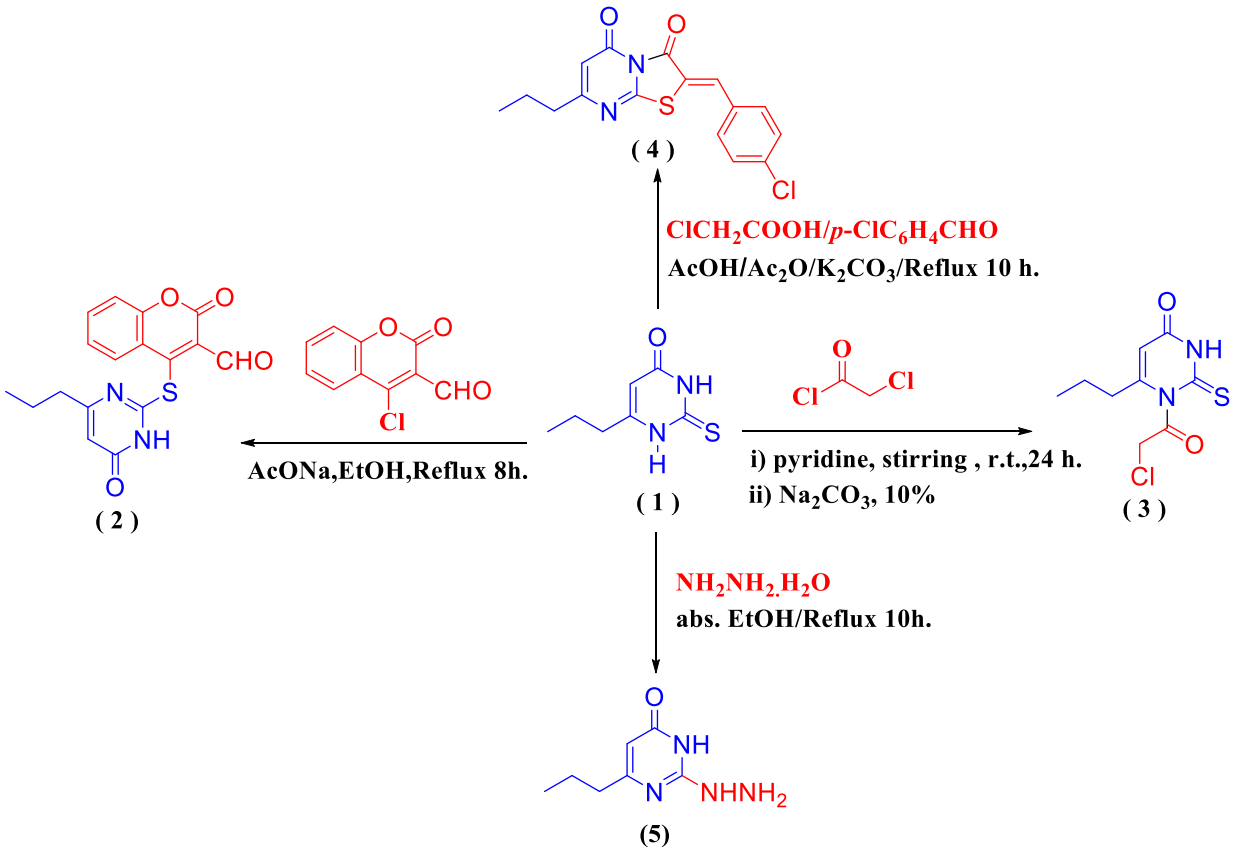
Results and Discussions

Chemistry of the synthesized compounds

We proposed a synthetic strategy for obtaining new propylthiouracil heterocycles as depicted in Scheme **1**, **2**. Initially, Propyl thiouracil is employed as a precursor preliminary material for the synthesis of new derivatives, for example. 3-((6-oxo-4-propyl-1,6-dihydropyrimidin-2-yl)thio)quinoline-4-carbonitrile (**2**) was synthesized by the reaction of propyl thiouracil **1**with 4-chloro-2-oxo-2H-chromene-3-carbaldehyde in refluxing ethanol, utilizing sodium acetate as a catalyst. The elucidation of compound **2** structure was verified by the FT-IR spectra by the presence of bands at 1724 cm^{-1}, indicative of the (C=O) group.

^{1}H NMR analyses validate the predicted chemical structure of compound **2**, evidenced by the presence of a unique singlet signal for the CHO proton at δ 7.40 ppm. Also,multiplet signals at δ 7.50-7.80 ppm for aromatic protons and a singlet signal at δ 7.84 ppm for the NH group were observed in the ^{1}H NMR spectrum of compound **2**. CHO and C=O groups exhibited characteristic signals at δ 166.61 and 153.97 ppm, respectively, in the ^{13}C NMR spectrum of compound **2**.Reaction of compound **1** with chloroacetyl chloride at ambient temperature in the presence of few amount of pyridine to get 1-(2-chloroacetyl)-6-propyl-2-thioxo-2,3-dihydropyrimidin-4(1H)-one **(3)**. Compound **3** was identified through spectral and elemental analysis. FT-IR analysis showed that compound **3** exhibited absorption bands characteristic of the (C=O) group at 1698 cm^{-1}.In contrast, the ^{1}H NMR spectrum exhibited a singlet signal at δ 3.91 ppm, which was associated with the CH_2 group.and a singlet signal at δ 12.34 ppm that corresponds to the NH group. The ^{13}C NMR spectrum revealed the emergence of new signals at δ 40.56 and 170.07 ppm, which correspond to new C=O groups and CH_2, respectively.

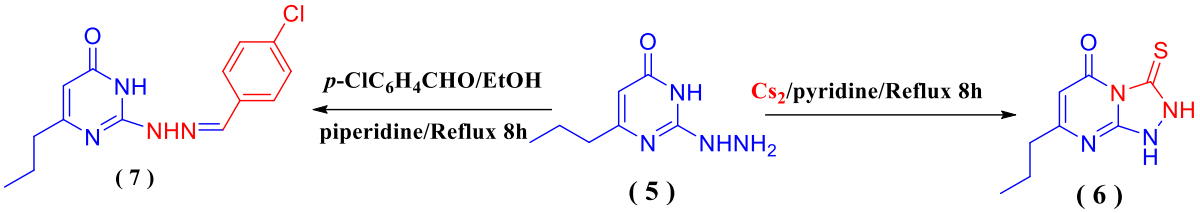
On the other hand, Multicomponent reactions (MCRs) using thioxopyrimidine **1** and chloroacetic acid, in combination with 4-chlorobenzaldehyde in a mixed solvent, yielded thiazolopyrimidindione derivatives **4**. Such compounds were previously synthesized by progressive reaction processes [**32**, **33**, **34**]. The FT-IR, ^{1}H NMR, and ^{13}C NMR spectra were used to confirm the formation of compound 4. The FT-IR spectrum of compound 4 displayed absorption bands at 1762 cm^{-1}, which are indicative of the (C=O) group. The ^{1}H NMR spectrum revealed the presence of multiplet signals at δ 7.50 - 8.00 ppm for aromatic protons and a singlet signal at δ 8.03 ppm that was attributed to the CH=C proton. The ^{13}C NMR spectrum exposed signals at δ 103.46 ppm for C=C and δ 152.67 ppm for CH=C, as well as a new signal for the carbonyl group at δ 176.78 ppm. 2-hydrazinyl-6-propylpyrimidin-4(3H)-one **(5)** was synthesized with remarkable yield and purity by the reaction of propyl thiouracil **1** with hydrazine hydrate in absolute ethanol under reflux conditions. The confirmation of compounds **5** was obtained from the FT-IR spectrum, which exhibited bands at 3091 and 3435 cm^{-1} corresponding to the 2NH and NH_2 groupsrespectively. Characteristic signals of δ 7.26 and 10.26 ppm for the NH_2 and NH groups, respectively, were observed in the 1H NMR spectrum of compound **5**. **(Scheme 1)**



Scheme 1. Synthesis of propyl thiouracil derivatives **2-5**.

The hydrazinyl pyrimidinone derivative **5** is a crucial, versatile precursor for synthesizing many heterocyclic compounds. Compound **5** was permitted to react with carbon sulfide in the presence of pyridine in a water bath

for 8 hours, yielding the corresponding 7-propyl-3-thioxo-2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1H) **(6)**. The validation of compound **6** was accomplished using FT-IR spectroscopy, evidenced by the absence of the NH_2 bands. Additionally, the ^{1}H NMR spectrum of compound **6** exhibited two different signals for the NH groups at δ 12.22 and 12.34 ppm, respectively. The ^{13}C NMR spectrum exhibited signals at δ 164.91 ppm corresponding to C=S group. Condensation reaction of 2-hydrazinyl-6-propylpyrimidin-4(3H)-one **(5)** with benzaldehyde in absolute ethanol under reflux condition, in the presence of a few drops of piperidine, yielded the corresponding Schiff's base **7**. The structure of compound **7** was determined through the use of spectral and elemental analysis. The absorption band associated with the NH_2 group was absent from the FT-IR spectrum of compound **7**. The ^{1}H NMR spectrum revealed multiplet signals at δ 7.00-8.00 ppm for aromatic protons and a singlet signal at δ 5.66 ppm for the CH=N group.The CH=N group was identified by a signal at δ 160.62 ppm in the ^{13}C NMR spectrum.**(Scheme 2)**The previously acquired findings of spectrum analysis supported the purity and chemical structures of our claimed products (**Scheme 1,2**), which were then submitted to biological activity applications.



Scheme 2. Reactions of compound **5** with carbon disulfide and 4-chlorobenzaldehyde

Antimicrobial activity

Activity against Gram-Positive Strains

The results show that derivative **2** has promising antibacterial activity against the Gram-positive strains *Staphylococcus aureus* (24 ± 0.1 mm) and *Bacillus subtilis* (19.5 ± 0.3 mm) at a MIC of 50 mg/mL. Due to its capacity to interact with or break the peptidoglycan-rich cell wall, derivative **2** may have a mode of action that targets structures particular to Gram-positive bacteria, as suggested by its selective activity. The observed effectiveness of derivative **2** may be explained by the thick, exposed peptidoglycan layer in Gram-positive bacteria, which makes chemical penetration easier and permits more efficient interaction with bacterial cell components.

In comparison, the control antibiotic Cefotaxime, a broad-spectrum antibiotic, had higher zones of inhibition (32 ± 0.6 mm for *S. aureus* and 30 ± 0.3 mm for *B. subtilis* and 15±0.4 mm for *P. aeruginosa* and 21±0.5 mm for *E. coli*) While demonstrating the promise of derivative **2**, this contrast also points to areas that could be optimized to equal or improve its antibacterial activity. The absence of activity in other derivatives against Gram-positive strains may be due to due to structural differences their ability to interact effectively with bacterial cell walls or penetrating the bacterial cytoplasm. Future compound enhancements may be guided by the exact functional groups or molecular characteristics in derivative **2** that give this action, which may be revealed by additional structural study and changes.

Figure 1. Anti-bacterial activity of compound **2** against S. aureus in comparison with Propylthiouracil compound **1** and Cefotaxime.

Lack of Activity against Gram-Negative Strains

Regarding Gram negative bacteria, none of all derivatives, including derivative **2**, showed inhibitory activity against the Gram-negative microorganisms such as *Pseudomonas aeruginosa* and *Escherichia coli*. This lack of efficacy could be attributed to the unique structural composition of Gram-negative bacteria, which have an outer membrane made of lipopolysaccharides, may be the cause of this lack of effectiveness. The distinct structural of Gram-negative bacteria, which have an outer membrane made of lipopolysaccharides, may be the cause of this lack of effectiveness. This extra barrier lowers permeability, which frequently prevents antimicrobial drugs from reaching Gram-negative organisms' cytoplasmic targets and peptidoglycan layer. The findings imply that these derivatives could not have the physicochemical or structural characteristics needed to pass through the outer membrane, which frequently calls for particular modifications like conjugation with targeted moieties that improve membrane permeability or increased hydrophobicity. Therefore, even while derivative **2** exhibits promise for Gram-positive bacteria, its lack of effectiveness against Gram-negative bacteria highlights the need for further chemical modification. It may be possible to increase Gram-negative permeability and broaden its antibacterial spectrum by adding hydrophobic side chains or changing the charge distribution.

Lack of Antifungal Activity Against Candida albicans

Similarly, derivative **2** and the other tested derivatives did not show any inhibitory activity against the yeast strain *Candida albicans*. Unlike bacterial cells, the cell walls of fungal cells, especially yeasts, contain β-glucans and chitin, while their plasma membranes contain ergosterol. This fact may explain such a lack of effectiveness because the tested derivatives cannot properly interact with these specific cellular components or cannot penetrate fungal cell membranes. All the above may hint that further structure modifications of the derivatives with respect to functional groups interacting specifically with ergosterol or other fungal-specific structures may give better results as far as antifungal activity is concerned. Also, a higher affinity of the derivatives towards β-glucans or enzymes responsible for cell wall synthesis in fungi might improve efficiency against yeasts.

Table 1. The MIC values of the tested derivative against the tested microbial standard strains.

Standard strains		Gram positive strains		Gram negative strains		Yeast
		Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*
Derivatives	MIC	ATCC 6538	ATCC 6633	ATCC 9027	ATCC 25416	ATCC 10231
1	50 mg/mL	0	0	0	0	0
2		24±0.1	19.5±0.3	0	0	0
3		0	0	0	0	0
4		0	0	0	0	0
5		0	0	0	0	0
6		0	0	0	0	0
7		0	0	0	0	0
Cefotaxime		32±0.6	30±0.3	15±0.4	21±0.5	----
Fluconazole		----	----	----	----	18±0.4
DMSO		0	0	0	0	0

Conclusion

In this study, we successfully synthesized novel bioactive derivatives of propylthiouracil (PTU) and assessed their antimicrobial properties. Through various chemical transformations, we generated several derivatives with diverse reactivity and structural characteristics. The antimicrobial tests revealed that derivative 2 showed promising efficacy against Gram-positive bacteria, particularly Staphylococcus aureus and Bacillus subtilis, indicating a targeted mechanism of action related to its ability to penetrate bacterial cell walls. However, the lack of activity against Gram-negative bacteria and the yeast strain Candida albicans highlights critical areas for future research. Future investigations should prioritize the optimization of PTU derivatives to enhance their effectiveness against Gram-negative bacteria and fungi. Specific research directions could include exploring modifications to the chemical structure of PTU derivatives to improve membrane permeability and efficacy against Gram-negative bacteria, potentially by incorporating hydrophilic moieties or utilizing pro-drug strategies, Investigating the synergistic effects of PTU derivatives with existing antibiotics or antifungals to

enhance their antimicrobial spectrum and combat resistance mechanisms and Conducting in-depth studies to elucidate the mechanisms by which these derivatives interact with microbial targets, particularly in Gram-negative bacteria and fungi, which may inform further structural optimization. This research not only contributes to the understanding of PTU's synthetic versatility but also opens avenues for developing new antimicrobial agents to address the growing concerns of antibiotic resistance. Overall, our findings lay the groundwork for future explorations into the therapeutic applications of PTU derivatives in the management of infectious diseases.

Conflict of Interest

None.

Declaration of Funding

No funding was received for this study

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