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Synthesis, spectral, molecular docking and antimicrobial studies of some substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1*H*)-thiones

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Some substituted 4-([1,1′-biphenyl]-4-yl)pyrimidine-2(1*H*)-thione derivatives were synthesized by one-pot three-component synthesis reaction of 4-acetyl biphenyl, various substituted aryl aldehydes and thiourea in the presence of sodium hydroxide. In this reaction, the yield was more than 85%. The synthesized pyrimidine thiones were characterise by their physical constants, micro-analysis and spectroscopic data. The molecular docking study of these pyrimidinethiones was investigated with protein interaction-affinity measurements. Using the Bauer-Kirby technique, the antimicrobial abilities of synthesized pyrimidinethiones were evaluated.

Keywords: Pyrimidinethiones, 4-acetylbiphenyl, thiourea, NMR spectra, Molecular docking, anti-microbial activities

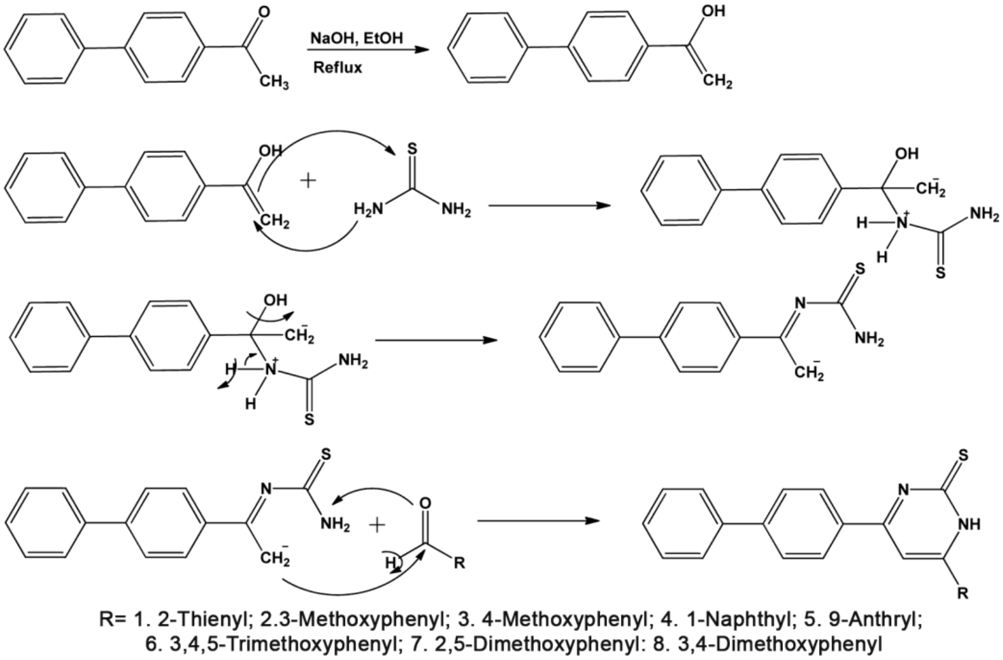
The pyrimidine skeleton is the parent substance of many vital compounds that occur in nature, particularly in nucleobases of nucleic acids such as cytosine, thymine, and uracil. The Biginelli reaction makes pyrimidine scaffolds easily accessible, and they have a broad range of pharmacological and therapeutic qualities, such as antimicrobial, antibacterial, antifungal, and herbicidal activity; anti-inflammatory and therapeutic potentiality; and anti-tubercular, anticancer, anticonvulsant, antileishmanial, antihypertensive, cytotoxic, and antitumor effects[1-5]. Two nitrogen atoms are at the positions 1 and 3 in the six-membered rings of pyrimidines, which are heterocyclic aromatic compounds similar to pyridine and benzene. Probably all heterocyclic compounds, pyrimidinethiones are among the most important and have exceptional pharmacological action. The pyrimidine moiety is a member of an important class of heterocycles that contain nitrogen and are essential components of pharmaceuticals[6-8]. Preclinical data from published research indicates that polysubstituted pyrimidines are still being investigated as potential anticancer medications. Pyrimidinethione has a crucial role in cellular activity, making it an attractive lead for the creation of novel medications[9-10].

Pyrimidinethiones are oxidised with sodium hypochlorite to give the corresponding sulfonyl chlorides, which can be further transformed to sulfonamides[11-14]. Oxidative desulfurization can also be used to prepare pyrimidine derivatives. Alkylation of pyrimidinethione is readily conducted on the sulphur atom with alkyl halides, sulfonates, or sulphates under mild conditions in the presence of a base[15]. The [3+3], [4+2], or [5+1] heterocyclization processes are the basis for the synthesis of 2-thioxopyrimidines and their condensed analogues. Pyrimidinethione derivatives were previously synthesized by microwave irradiation and conventional heating techniques in the presence of K_2CO_3 / C_2H_5OH, sodium ethoxide and KOH [16-18]. Recently, some studies have investigated the corrosion inhibition performance of heterocyclic compounds, such as pyrimidine derivatives of compounds including 4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione, 4-(4-methylphenyl)-6-phenyl-3,4-dih″ydropyrimidine-2 (′H)-thione, and the synthesis of chromeno[*d*]pyrimidine-2,5-dione/thione derivatives has been described by the reaction of aryl aldehydes, urea/thiourea, and 4-hydroxycoumarin using$Fe_3O_4@SiO_2@(BuSO_3H)_3$ as catalyst under microwave irradiation (MW) in H_2O [19–23]. Furthermore, pyrimidinethione derivatives show promise in the treatment of chemotherapy.

Early on, it was shown that pyrimidinethione-based antimetabolites, such as 5-fluorouracil (5-FU), 5-thiouracil, and uracil-based hydroxyamides, were structurally similar to endogenous substrates and may be used as successful cancer treatments. The current study is to create novel pyrimidinethione derivatives that are easily synthesized under moderate conditions from easily accessible starting materials with excellent yields and assess their *in vitro* bioactivities. Recent reports have indicated that the presence of *the p*-methoxy, chloro and hydroxy phenyl groups on the pyrimidine nucleus enhanced the antimicrobial, antioxidant and antitubercular activity of the pyrimidine derivatives[24-26]. One of the most important intermediates in chemical synthesis is substituted 4-([1,1′-biphenyl]-4-yl)pyrimidine-2(1H)-thione due to the economical, simple and efficient one-pot method that has been adopted for the synthesis. Some pyrimidine carboxylic acid amide derivatives were prepared and the spectral properties by Arulkumaran *et al.*[27]. The spectral QSAR and microbial activities of some pyrimidine Schiff's bases were reported by Senbagam and her co-workers[28]. The molecular docking and antimicrobial activity of some pyrimidinones were reported by Divya *et al.*[29,30]. In the literature survey, there is no report available for the synthesis, docking and antimicrobial activities of biphenyl-based pyrimidinethiones in the past and present. Hence, the authors have taken effort to synthesize and investigate the docking and antimicrobial activities of biphenyl-based pyrimidinethiones.

Results and Discussion

In our research laboratory, we attempt to synthesize some higher 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione using a single-step one-pot three-component reaction involving 4-acetylbiphenyl, substituted benzaldehydes, and thiourea in the presence of sodium hydroxide under reflux conditions. Over 85% yields were obtained from all reactions. This reaction follows a well-known base-catalysed nucleophilic addition followed by the elimination of water and cyclization mechanism. The first step is the attack of the carbonyl carbon of 4-acetylbiphenyl by the amine nucleophile of thiourea to form an oxonium ion, and nitrogen gets a positive charge. The second step is the oxonium ion is protonated, and loss of water occurs from the proton from the nitrogen and hydroxyl group in the biphenyl ring. The third step is the carbon anion formed by the loss of a proton from the methyl group of the biphenyl ring; then this is going to attach to the carbonyl carbon of benzaldehyde to form an oxonium ion. The fourth step is the protonation of oxonium ion by proton transfer followed by loss of water, then cyclization results in the formation of pyrimidinethione. The mechanistic pathway of this reaction is illustrated in Scheme 1. The microanalysis, physical constants, and yields of the 4-([1,1′-biphenyl]-4-yl)pyrimidine-2(1H)-thione compounds were performed, as given in the experimental section.



Scheme 1 — The plausible mechanistic pathway of formation of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones.

IR and NMR spectral study

The IR stretching frequencies (ν, cm^{-1}) and NMR chemical shifts (δ, ppm) of synthesized substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones are tabulated in Table 1. The infrared (IR) frequencies of substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones, strong bands are observed for derivatives at the region of 2831.50 to 2920.59 cm^{-1}, which correspond to C-H aromatic stretching. The N-H stretching occurs at the range of 3327.54-3379.29 cm^{-1}. The bands obtained at the range of 1002.17-1072.42 cm^{-1} correspond to C=S stretching. The C=C stretching bands appeared in the 1552.70-1600.32 cm^{-1}range and the C=N stretches were assigned for the peaks obtained in the range of 1658.78-1679.32 cm^{-1}. The proton NMR chemical shifts (δ, ppm) of NH, CH pyrimidine ring, methoxy protons and aryl protons were assigned. The NH proton chemical shifts obtained as singlets are in the range of 7.96-8.03 ppm. The CH proton in the pyrimidine ring was obtained as a singlet in the range of 5.50-5.65 ppm. The methoxy proton chemical shifts of the pyrimidinethiones were obtained as a singlet in the range of 2.56-2.67 ppm. The aromatic protons were observed at the range of 6.96-8.79 as a singlet. The observed ^{13}C NMR chemical shifts (δ, ppm) of CN, CH, OCH_3 and aryl carbons substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives were assigned with their spectra captured. The CN carbon chemical shift (δ, ppm) of pyrimidinethiones were assigned in the range of159.43-163.20. The CS carbon chemical shifts (δ, ppm) of the synthesized pyrimidinethiones were assigned in the range of 197.79 -198.89. The pyrimidine ring CH carbon chemical shifts were obtained in the range of 105.77- 109.32. The assigned aromatic ring carbons are in the range of 124.68-139.96 ppm and the substituent methoxy carbons obtained at the range of 55.66- 60.80 ppm. These data are well supported for the formation of pyrimidinethiones.

Table 1 — The IR stretching frequencies (ν, cm^{-1}) and NMR chemical shifts (δ, ppm) of synthesized substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones

CpdNo	R	IR (ν, cm^{-1})					
		C-H	N-H	C=S	C=C	C=N	C-O-C
1	2-Thienyl	2920.23	3327.54	1002.98	1598.99	1676.14	---
2	3-Methoxyphenyl	2931.80	3336.85	1018.12	1600.32	1678.07	1357.89
3	4-Methoxyphenyl	2931.60	3336.85	1016.85	1598.99	1679.32	1357.89
4	1-Naphthyl	2976.16	3332.34	1056.99	1570.06	1666.50	---
5	9-Anthryl	2935.66	3379.29	1072.42	1552.70	1658.78	---
6	3,4,5-Trimethoxyphenyl	2831.50	3347.12	1002.98	1598.99	1676.14	1450.17
7	2,5-Dimethoxyphenyl	2931.72	3336.85	1002.17	1598.00	1674.21	1490.97
8	3,4-Dimethoxyphenyl	2931.80	3336.85	1012.98	1598.99	1674.35	1490.97

		^{1}H NMR (δ, ppm)			
		NH(s)	CH(s)	Ar-H(m)	Substt.
1	2-Thienyl	8.02	5.62	6.96-7.98	---
2	3-Methoxyphenyl	7.98	5.56	7.12-7.97	2.57(s, 3H, OCH_3)
3	4-Methoxyphenyl	8.03	5.65	7.18-8.79	2.56(s, 3H, OCH_3)
4	1-Naphthyl	7.98	5.60	7.19-7.97	---
5	9-Anthryl	7.98	5.50	7.19-7.97	---
6	3,4,5-Trimethoxyphenyl	7.96	5.54	7.18-7.94	2.56(s, 9H, OCH_3)
7	2,5-Dimethoxyphenyl	7.97	5.62	7.17-7.95	2.66(s, 6H, OCH_3)
8	3,4-Dimethoxyphenyl	7.97	5.61	7.17-7.94	2.67(s, 6H, OCH_3)

		^{13}C NMR (δ, ppm)				
		C=N	C=S	CH	Ar-C	Substt.
1	2-Thienyl	163.20	197.80	105.78	127.26-138.83	---
2	3-Methoxyphenyl	159.43	197.79	108.72	127.24-139.89	59.23 (OCH_3)
3	4-Methoxyphenyl	159.96	198.32	109.32	127.24-139.09	57.82 (OCH_3)
4	1-Naphthyl	159.84	197.92	106.54	124.68-137.36	---
5	9-Anthryl	159.78	197.92	105.79	127.14-139.96	---
6	3,4,5-Trimethoxyphenyl	159.49	197.89	105.78	126.45-139.89	60.80 (OCH_3)
7	2,5-Dimethoxyphenyl	159.88	198.80	105.77	127.18-139.89	55.66 (OCH_3)
8	3,4-Dimethoxyphenyl	159.68	198.89	105.77	127.19-139.87	55.67 (OCH_3)

Molecular Docking study

The molecular docking study of the synthesized pyrimidinethiones was studied using the protein binding ability to lysozyme protein molecules. The structural information and the data for the target were collected from the "Protein Data Bank" (PDB). The PDB ID 1JKB[31] was used as the template for our studies. It performs flexible protein-ligand docking and searches for favourable interactions between one typically small ligand molecule and a typically larger protein molecule. The docking process, wherein protein preparation inhibited refinement, is carried out with a maximum of 20 poses, wherein the side chains are optimized and refinement of residues takes place, if the ligand poses are within 5.0 Å. The best docked structure was chosen by docking score and the number of amino acids matches (hydrogen bonds) with the original drug complex. When computing investigations of protein-ligand interactions, molecular dockings are frequently employed. Utilizing Autodock Tools 1.5.7 software, docking tests were performed to determine the binding affinities and interactions between the newly synthesized compounds and the active site of the 1JKB protein.

Each compound has 10 distinct postures produced by the docking run; the associated binding energy values are also displayed. Table 2 summarizes the findings for all synthesized compounds and proteins with greater binding energy values. The best-docked pose's compound stability was calculated by analyzing the interactions between the protein and the compounds through hydrogen bonding. These findings indicate that, among all the recently synthesized 4-([1,1'-biphenyl]-4-yl)(naphthalene-4-yl)-6-pyrimidine-2(1H)-thione (compound 4) had the greatest binding energy of ΔG -8.83 (kcal/mol) with the 1JKB protein. The docking score values and H-bonding interaction were done for all the synthesized compounds and it consists of H-bonding, π-π interactions, cation -π interactions,*etc.* The 2D and 3D structure of the compound**(4)** 4-([1,1′-biphenyl]-4-yl)-6-(naphthalene-4-yl)pyrimidine-2(1H)-thione was illustrated in Fig. 1.

Antibacterial studies

The assessed antibacterial activities in terms of mm of zone of inhibition[32-41] of the synthesized pyrimidinethiones were presented in Table 3 and the corresponding petri dish was shown in Fig. 2.

Table 2 — Molecular Docking results of the newly synthesized compounds **(1-8).**

Compound No.	PDB	Binding Energy ΔG (kcal/mol)	Grid X-Y-Z Coordinates
1	1JKB	–8.42	50,50,50
2	1JKB	–8.1	50,50,50
3	1JKB	–7.57	50,50,50
4	**1JKB**	**–8.83**	**50,50,50**
5	1JKB	–8.61	50,50,50
6	1JKB	–6.98	50,50,50
7	1JKB	–6.75	50,50,50
8	1JKB	–8.13	50,50,50

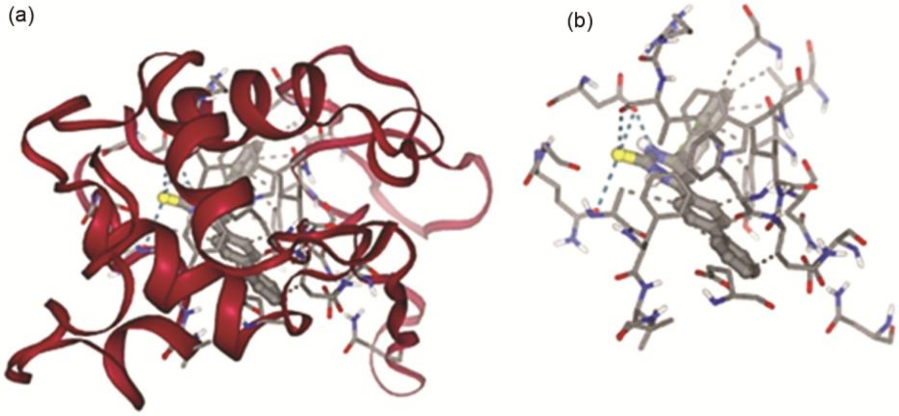


Fig. 1 — The 2D and 3D Structure of 4-([1,1′-biphenyl]-4-yl)-6-(naphthalene-4-yl)pyrimidine-2(1H)-thione (compound 4) docked with protein 1JKB.

Table 3 — The Zone of inhibition (mm) values of antibacterial activity of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives at the concentration of compound(40µg)

Pathogens	Diameter of zone of inhibition(mm)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Staphylococcus aureus	13	14	15	13	13	14	20	10
Bacillus subtilis	16	16	13	14	15	11	17	13
Escherichia coli	22	15	15	15	15	22	19	16
Pseudomonas aeruginosa	11	20	12	11	15	19	14	16
Ampicillin (Standard)	24	22	23	23	26	24	24	22

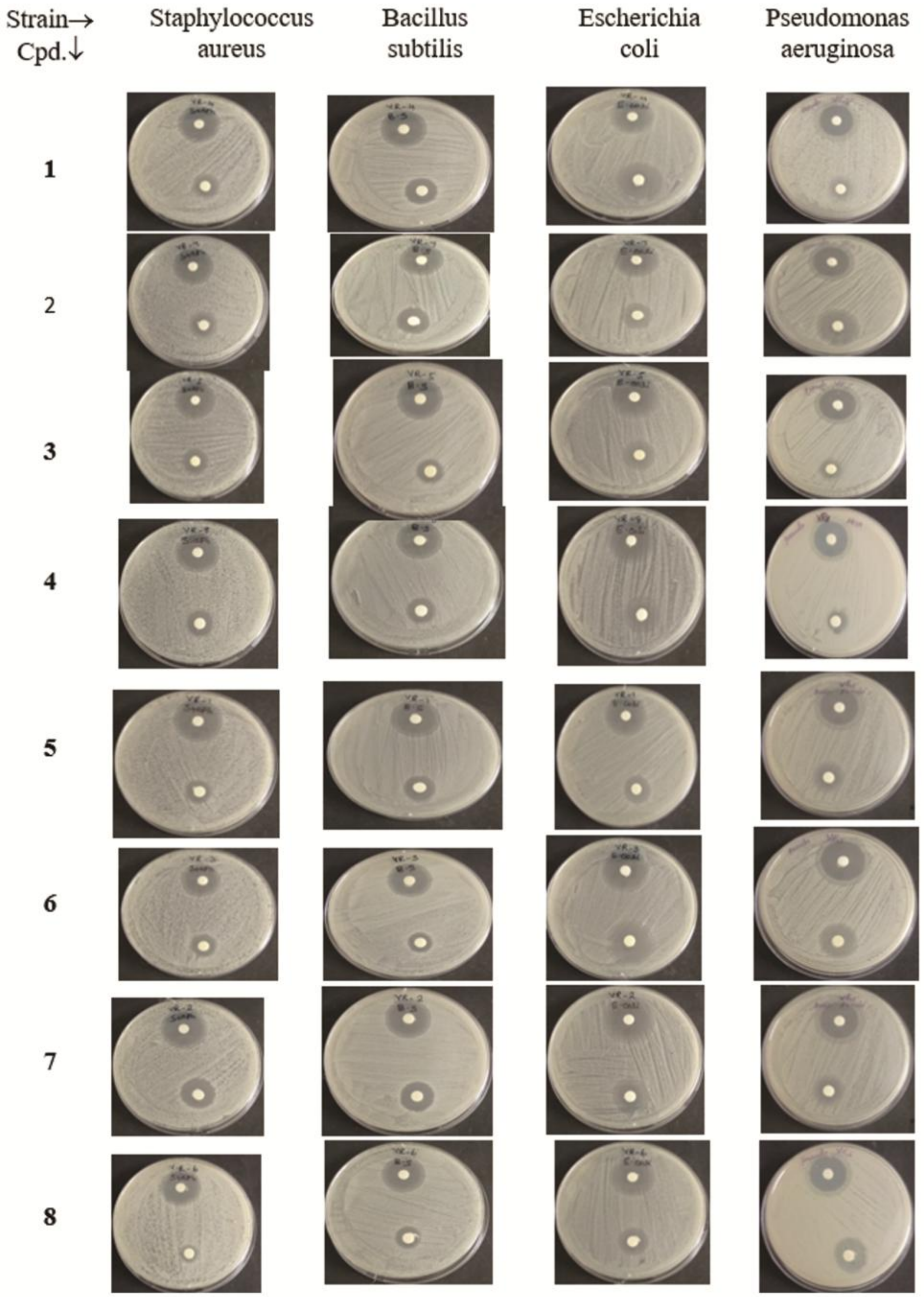


Fig. 2 — Anti-bacterial activity of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones

According to Table 3, the majority of the 4-([1,1′-biphenyl]-4-yl)pyrimidine-2(1H)-thiones have shown moderate, good, and excellent antibacterial activity. The pyrimidinethione4-([1,1′-biphenyl]-4-yl)-6-(thiophen-2-yl)pyrimidine-2-(1H)-thione (**1**) shows moderate antibacterial activity against all strains except Escherichia coli bacteria. Good antibacterial action has been shown by 4-([1,1′-biphenyl]-4-yl)-6-(3-methoxyphenyl)pyrimidine-2-(1H)-thione (**2**) against all pathogens except Pseudomonas aeruginosa microbes. The pyrimidine thione (**3**) 4-([1,1′-biphenyl]-4-yl)-6-(4-methoxyphenyl) pyrimidine-2-(1H)-thione showed good antibacterial activity against *E. coli* and *Staphylococcus aureus* strains and the antibacterial activity was low with other strains. The pyrimidine-2(1H)-thione (**4**) exhibits moderate anti-bacterial activity against all strains. Pyrimidine thione (**5**) 4-([1,1′-biphenyl]- 4-yl)-6-(anthracen-10-yl)pyrimidine-2(1H)-thione possesses an anthracene moiety and it shows moderate antibacterial activity against all strains. The compound 4-([1, 1′-biphenyl]-4-yl)-6-(3, 4, 5-trimethoxyphenyl) pyrimidine-2(1H)-thione (**6**) containing a trimethoxyphenyl group shows good antibacterial action against *E. coli* and *P. aeruginosa* strains. The pyrimidine thione 4-([1,1′-biphenyl]-4-yl)-6-(2,5-dimethoxyphenyl)pyrimidine-2(1H)-thione (**7**) shows good antibacterial activity against *Staphylococcus aureus*.

The pyrimidine derivative 4-([1,1′-biphenyl]-4-yl)-6-(3,4-dimethoxyphenyl)pyrimidine-2(1H)-thione **(8)** showsgoodantibacterial activityexcept against *E. coli* and *P. aeruginosa*. Here the electron-donating +I effect of methoxy groups enhances the antibacterial activity compared to other aryl groups such as thienyl, naphthyl and anthryl. The clustered column chart is shown in Fig. 3.

Antifungal studies

The antifungal activities of the synthesized pyrimidinethiones in terms of mm of zone of inhibition[42-53] were presented in Table 4. The corresponding petri dishes and statistical bar diagram

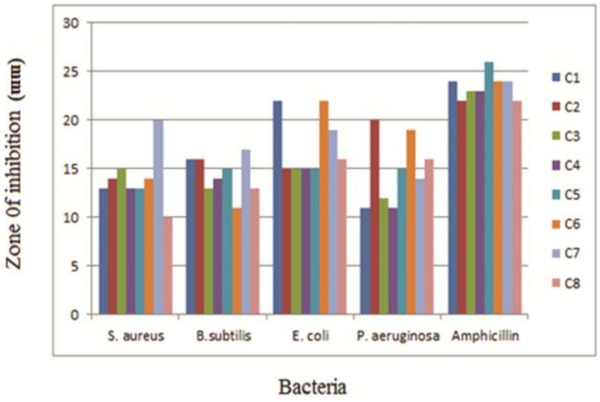


Fig. 3 — Statistical picture of anti-bacterial activity of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives

Table 4 — The Zone of inhibition (mm) values of antifungal activity of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives.

Pathogens	Diameter of zone of inhibition(mm) Concentration of compound(1000µg/ml)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Standard (Amphotericin B)
Aspergillus niger	8	10	10	11	12	11	23	9	18
Penicillium	14	11	12	12	12	11	21	9	21
Trichoderma viride	11	11	18	12	13	11	22	11	19
Candida albicans	12	13	13	13	12	12	20	11	23
Pathogens	Diameter of zone of inhibition(mm) Concentration of compound(750µg/ml)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Standard (Amphotericin B)
Aspergillus niger	7	8	10	11	9	11	22	9	18
Penicillium	7	0	12	10	7	10	20	8	21
Trichoderma viride	11	11	13	11	12	10	21	11	19
Candida albicans	7	7	7	8	8	9	19	9	23
Pathogens	Diameter of zone of inhibition(mm) Concentration of compound(500µg/ml)								
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	Standard (Amphotericin B)
Aspergillus niger	0	0	0	9	0	9	20	0	18
Penicillium	0	0	8	0	0	0	19	0	21
Trichoderma viride	8	9	9	0	10	0	20	8	19
Candida albicans	7	7	0	8	0	0	18	7	23

are illustrated in Fig. 4 and Fig 5. The antifungal zone of inhibition values for compounds **1–8**, along with a reference drug for comparison that was evaluated at various sample concentrations, such as 1000, 750, and 500 µg/ml. In the inhibitory zone in mm, the majority of the compounds exhibit moderate, good, and excellent activity, according to the values of substituted 4-([1,1'-biphenyl]-4-yl) pyrimidine-2(1H)-thione compounds. At concentrations of 1000 and 750 µg/ml, compounds **1–8** have moderate action within the 7–13 mm zone of inhibition. Compound **3** has excellent potency against *Trichoderma viride* species over a range of concentrations. However, at 750 µg/ml of sample concentration, compound **2** has no action against Penicillium fungus species. The remaining pyrimidinethione substances have minimal

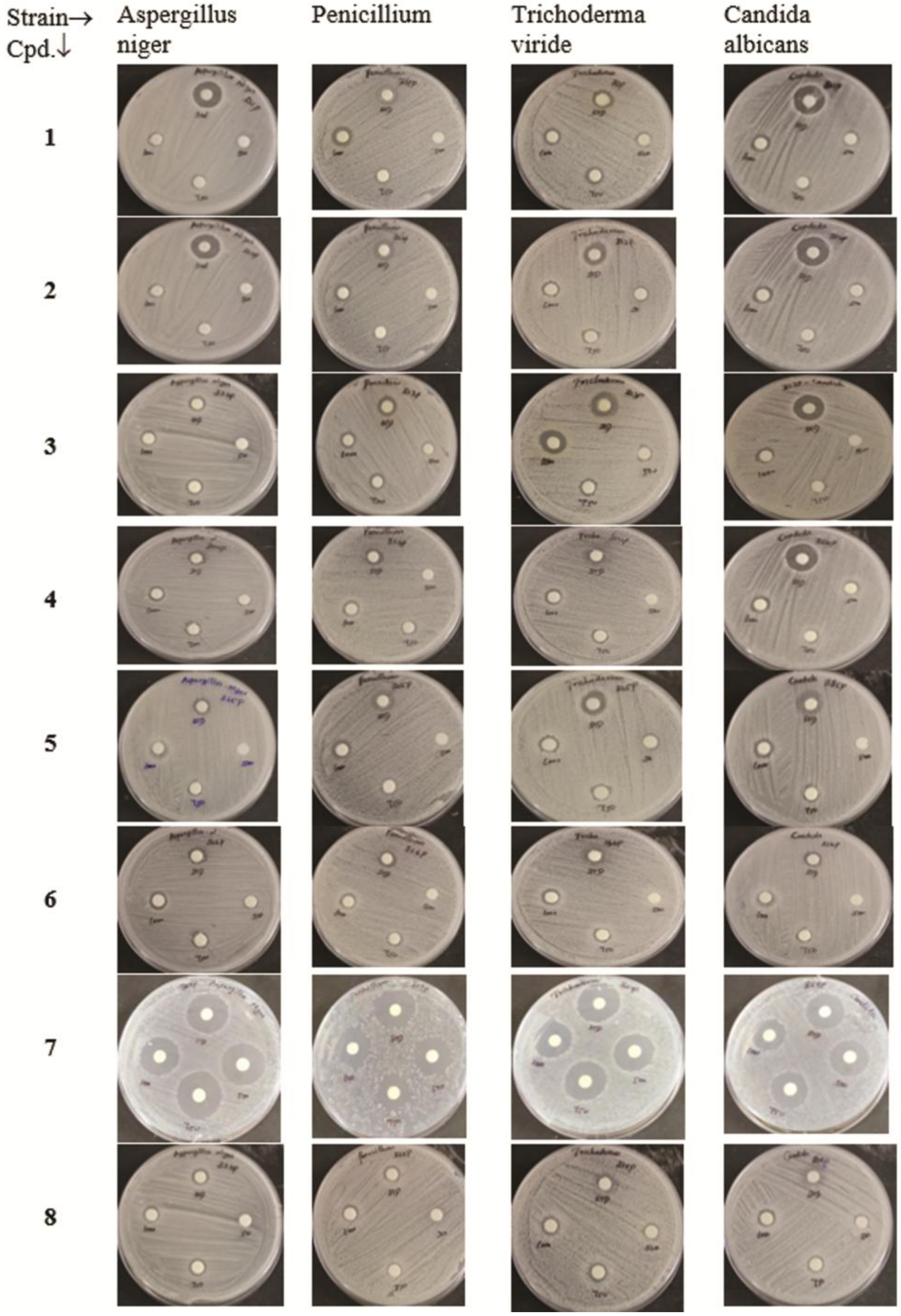


Fig. 4 — Antifungal activity of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives

activity against *Penicillium* and *Aspergillus niger* fungus species when evaluated, typically at 500 µg/ml sample concentration. At 500 µg/ml of sample concentration, the majority of substituted compounds have demonstrated moderate activity against the fungal species *Trichoderma viride* and *Candida albicans*. The 4-([1,1′-biphenyl]-4-yl) -6-(2,5-dimethoxyphenyl)pyrimidine-2(1H)-thione (**7**) exhibits excellent activity against all fungal organisms because of the +I effect of the OCH_3 group at distinct positions in the pyrimidine structure.

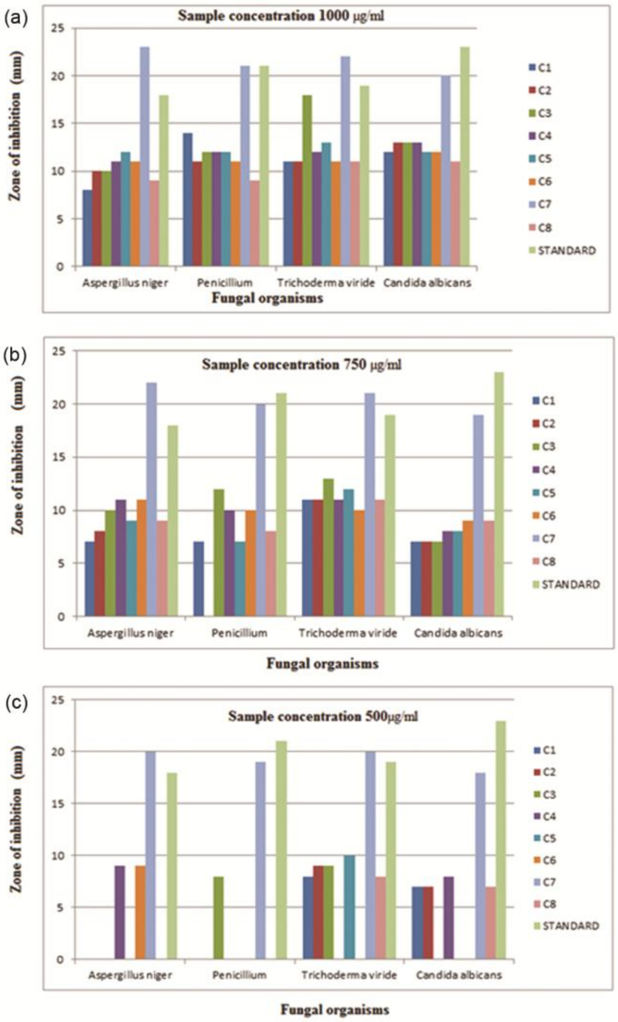


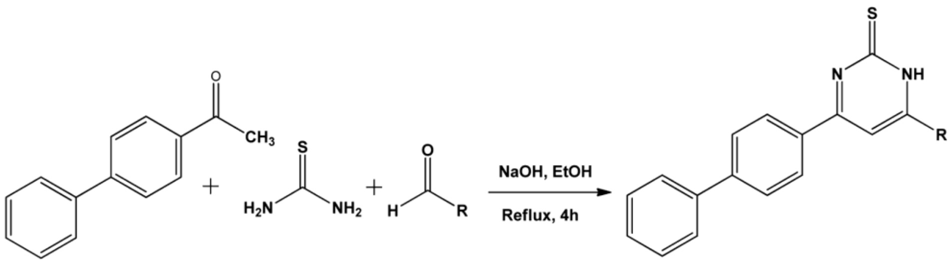
Fig. 5 — Statistical picture of anti-fungal activity of4-([1,1′-biphenyl]-4-yl)pyrimidine-2(1H)-thiones

Experimental Section

All of the materials and chemicals used in this study were procured from the Sigma-Aldrich and Merck chemical companies. Melting points of every substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivative produced in open glass capillaries on the Mettler FP51. Infrared spectra (KBr, 4000-400 cm^{-1}) have been recorded with the SHIMADZU-2010 Fourier transform spectro-photometer. The NMR spectra were recorded using a Bruker 400 spectrometer running at 400 MHz for ^1H NMR spectra and 100 MHz for ^{13}C NMR spectra in a $CDCl_3$ solvent, with TMS serving as an internal standard. The microanalysis of all pyrimidinethiones was performed in a Perkin-Elmer 240C CHN analyzer.

General procedure for synthesizing 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1*H*)-thiones

In a 100-mL round-bottom flask, equimolar quantities of 4-acetyl biphenyl (1 mmol), various aryl aldehydes (1 mmol), thiourea (1 mmol) and sodium hydroxide (1N, 5 mL) and 20 mL ofethanol were refluxed in a water bath for 4 h (Scheme 2). The reaction's completion was checked using TLC, which was used constantly. The reaction product was poured into 25 g of crushed ice. The resulting yellow solid was filtered at the pump, washed with water then recrystallized from ethanol. Synthesized pyrimidinethiones were characterized by their physical constants, microanalysis and spectroscopic data. The physical constants, yield and microanalysis of the pyrimidinethiones were tabulated in Table 5.



R= 1. 2-Thienyl; 2.3-Methoxyphenyl; 3. 4-Methoxyphenyl; 4. 1-Naphthyl; 5. 9-Anthryl;
6. 3,4,5-Trimethoxyphenyl; 7. 2,5-Dimethoxyphenyl: 8. 3,4-Dimethoxyphenyl

Scheme 2 — Synthesis of 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thiones.

Table 5 — The physical constants, yield and micro analysis of the pyrimidine thiones

Cpd.	Mol. Formula	Mol. Wt.	Yield (%)	m.p. (ºC)	Micro analysis (%) (Calcd.)		
					C	H	N
1	$C_{20}H_{14}N_2S_2$	346	87	76-77	69.38 (69.33)	4.12 (4.07)	8.11 (8.09)
2	$C_{23}H_{18}N_2OS$	370	90	79-81	74.53 (74.57)	4.83(4.90)	7.62 (7.56)
3	$C_{23}H_{18}N_2OS$	370	88	79-81	74.59 (74.57)	4.84 (4.90)	7.59 (7.56)
4	$C_{26}H_{18}N_2S$	390	92	84-85	79.82 (79.97)	4.56 (4.65)	7.25 (7.17)
5	$C_{30}H_{20}N_2S$	441	88	108-109	79.74 (81.79)	4.59 (4.58)	6.29 (6.36)
6	$C_{25}H_{22}N_2O_3S$	431	92	105-106	69.73 (69.75)	5. 11 (5.15)	6.47 (6.51)
7	$C_{24}H_{20}N_2O_2S$	400	87	98-99	71.95 (71.98)	4.97(5.03)	6.93 (6.99)
8	$C_{24}H_{20}N_2O_2S$	400	90	98-99	71.94 (71.98)	4.94(5.03)	6.96 (6.99)

Assessment of Molecular Docking

Based on the lysozyme protein model, docking calculations were performed[54,55]. Autodock tools were used to add necessary hydrogen atoms; Kollman unified atom type charges, and solvation parameters[56]. Molecular docking studies are used to measure the protein-ligand complex strength, binding energy, and binding affinity of the synthesized compounds with proteins. The Autodock Tools 1.5.7 software was utilized to dock each newly synthesized compound. A protein's modelled three-dimensional structure (PDB ID: 1JKB)[31] was sent to Autodock Tools 1.5.7, where it was structurally optimized by hydrogen addition and Kollman charge calculation. Once hydrogen was added, the model was stored in the protein PDBQT format. After determining the torsion angles, ligands were formatted (ligand. PDBQT) and ready for docking investigations. Subsequently, to determine the XYZ coordinates, a grid was built surrounding the protein's binding site. Default settings, freezing, and docking in Autodock Tools 1.5.7 were all done using the Lamarckian Genetic Algorithm (LGA). The interaction between the ligand and the 1JKB protein was found and investigated, and docking experiments were used to evaluate the binding models of proteins and the binding energies of ligands.

Antibacterial sensitivity assay measurement

The antibacterial sensitivity test was conducted using the Bauer-Kirby[32] disc diffusion method according to normal practice. The bacterial test sample (0.5 mL) was uniformly placed over the solidified Mueller-Hinton agar in each Petri plate using a sterilized glass spreader. Following the application of the potential inhibitor solution, 5 mm Whatman No. 1 filter paper discs were placed on the medium with the use of sterile forceps. The plates were incubated upside down for 24 hours at 37°C to prevent the collection of water droplets. After 24 hours, the plates were examined, and the zones of inhibition's diameter values were evaluated. From this, the zone of inhibition (mm) values of antibacterial activity for 4-([1,1'-biphenyl]-4-yl) pyrimidine-2(1H)-thione, as determined.

Antifungal sensitivity assay measurement

The stock cultures were maintained at 4°C on Sabouraud Dextrose agar slants. Active cultures for experiments were prepared by transferring the stock cultures into the test tubes containing Sabouraud Dextrose broth that were incubated at 48 h at room temperature. The assay was performed by the agar disc diffusion method. The antifungal activity of the sample was determined by the disc diffusion method on Sabouraud Dextrose Agar (SDA) medium. Sabouraud Dextrose Agar (SDA) medium is poured into the petri plate. After the medium had solidified, the inoculums were spread on the solid plates with a sterile swab moistened with the fungal suspension[39-41]. To evaluate eight substituted 4-([1,1'-biphenyl]-4-yl) pyrimidine-2(1H)-thione compounds that inhibit *Penicillium*, *Trichoderma viride*, *Aspergillus niger*, and *Candida albicans*. Amphotericin-B is taken as a positive control. Samples and a positive control of 20 µl each were added to sterile discs and placed in SDA plates. The plates were incubated at 28ºC for 24 hours. Then, antifungal activity was determined by measuring the diameter of the zone of inhibition values for all 4-([1,1'-biphenyl]-4-yl) pyrimidine-2(1H)-thiones.

Conclusions

In conclusion, we have developed an effective single-step one-pot synthesis of some novel substituted 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione derivatives by condensation cum cyclization of 4-acetylbiphenyl, several substituted benzaldehydes and thiourea with more than 85% yields. The structure of the prepared compounds was characterized by physical constants, microanalysis, FT-IR and NMR spectroscopic data. From the molecular docking study, synthesized 4-([1,1'-biphenyl]-4-yl) (naphthalene-4-yl)-6-Pyrimidine-2(1H)-thione (**4**) had the greatest binding energy of ΔG -8.83 (kcal/mol) with the 1JKB protein. The antibacterial and antifungal properties of the compounds were investigated using the Kirby-Bauer method. Excellent antibacterial action has been shown by 4-([1,1′-biphenyl]-4-yl)-6-(thiophen-2-yl) pyrimidine-2-(1H)-thione and 4-([1,1′-biphenyl]-4-yl)-6-(3,4,5-trimethoxyphenyl)pyrimidine-2(1H)-thione against *Escherichia coli* bacteria. The majority of the substituted 4-([1,1'-biphenyl]-4-yl) pyrimidine-2(1H)-thione compounds exhibited moderate, good, and excellent antifungal efficacy at different sample concentrations. The compound 4-([1,1′-biphenyl]-4-yl)-6-(4-methoxyphenyl)pyrimidine-2-(1H)-thione (**3**) has remarkable efficacy against *Trichoderma viride* species over a range of concentrations. The OCH_3 groups at specific positions in the pyrimidine backbone of some synthesized compounds bring about outstanding action against all fungal species. The majority of the 4-([1,1′-biphenyl]-4-yl) pyrimidine-2(1H)-thione compounds exhibit strong antifungal activity against species of *Candida albicans* and *Trichoderma viride* at various assessed concentrations.

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