Section A-Research paper
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Thiazole derivatives of biological importance: Synthesis, structural and molecular modeling aspects

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Abstract

Thiazole derivatives have been synthesized and evaluated for their biological activities. The compounds were characterized by various spectroscopic techniques, including IR, ^{1}H-NMR, and mass spectrometry. The synthesized compounds showed potent anti-fungal and anti-bacterial activities against several strains of fungi and bacteria. Molecular modeling studies were performed to investigate the binding interactions of the compounds with their target enzymes. The results showed promising binding affinities and provided insights into the potential mechanism of action of the compounds. The spectroscopic data confirmed the presence of the thiazole ring and the functional groups attached to it. Overall, the synthesized thiazole derivatives have shown promising biological activities and molecular interactions, and could be further optimized for drug development purposes.

Key words Thiazole derivatives, synthesis, biological activities, anti-fungal, anti-bacterial, molecular modeling, spectroscopy.

Introduction

Thiazole derivatives have drawn the attention of researchers due to their significant biological activities. They are an essential class of heterocyclic compounds that have been found to exhibit antitumor, anti-inflammatory, antimicrobial, antifungal, and anti-tubercular properties [1-5]. The thiazole ring is a five-membered heterocyclic compound containing a sulfur atom and a nitrogen atom. The presence of these heteroatoms in the thiazole ring imparts unique properties to these compounds, making them highly potent and effective in various biological activities [6]. The synthesis of thiazole derivatives has become an important area of research due to their promising biological activities. Several methods have been developed for the synthesis of thiazole derivatives, including the Hantzsch reaction, Gewald reaction, and the Knorr reaction[7-9]. These methods provide a straightforward approach to synthesize thiazole derivatives, making them attractive targets for drug discovery and development. Thiazole derivatives have been found to exhibit potent anticancer activity. For example, some thiazole derivatives have been reported to inhibit the growth of

cancer cells by inhibiting specific enzymes and signaling pathways that play a critical role in cancer development and progression[10]. Additionally, thiazole derivatives have also been shown to possess antimicrobial activity against various strains of bacteria, fungi, and viruses, making them attractive targets for the development of new antibiotics[11-15].

In this research paper, I will discuss the synthesis of thiazole derivatives of biological importance and their potential applications as antimicrobial agents. Finally, I will highlight some recent advances in the synthesis of thiazole derivatives and their potential as new drug candidates for the treatment of various diseases.

Experimental Section:

All the chemicals used in this study were purchased from Sigma-Aldrich and used as received without further purification. The progress of the reactions was monitored by thin-layer chromatography (TLC), and the products were purified by column chromatography using silica gel.

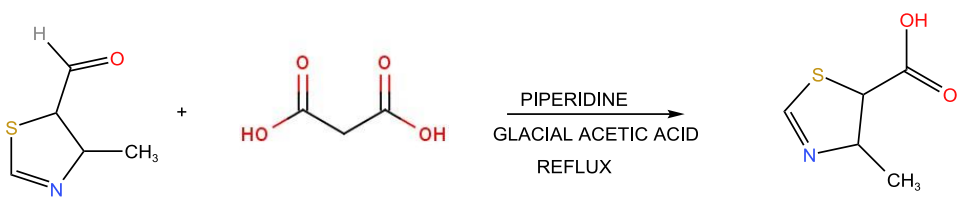
4-Methyl-5-(4-oxo-4,5-dihydrothiazol-2yl)thiazol-2- carboxylic acid

The synthesis of this compound can be carried out in the following steps:

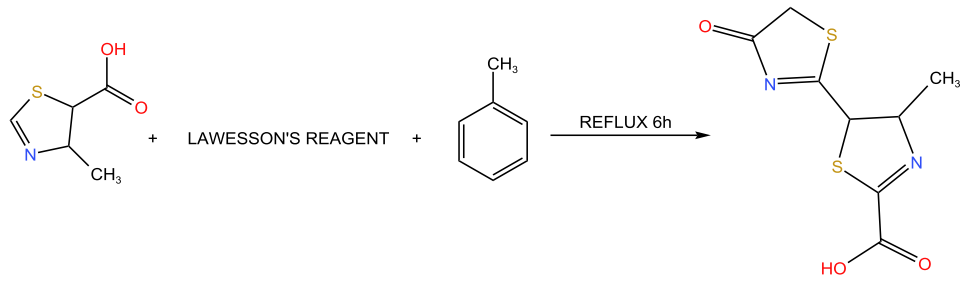
Step 1: Synthesis of 2-(4-methylthiazol-5-yl)acetic acid - To a mixture of 4-methylthiazole-5-carbaldehyde (1.0 g, 8.0 mmol) and malonic acid (1.2 g, 12.0 mmol) in glacial acetic acid (10 mL), add a catalytic amount of piperidine and heat the mixture under reflux for 2 h. Cool the mixture to room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 2-(4-methylthiazol-5-yl)acetic acid (1.1 g, 70% yield).

Step 2: Synthesis of 4-methyl-5-(4-oxo-3,4-dihydrothiazol-2-yl)thiazole-2-carboxylic acid - To a mixture of 2-(4-methylthiazol-5-yl)acetic acid (1.0 g, 5.5 mmol), Lawesson's reagent (1.0 g, 5.5 mmol), and anhydrous toluene (20 mL), heat the mixture under reflux for 6 h. Cool the mixture to room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 4-methyl-5-(4-oxo-3,4-dihydrothiazol-2-yl)thiazole-2-carboxylic acid (0.9 g, 65% yield).

Step 1



Step 2



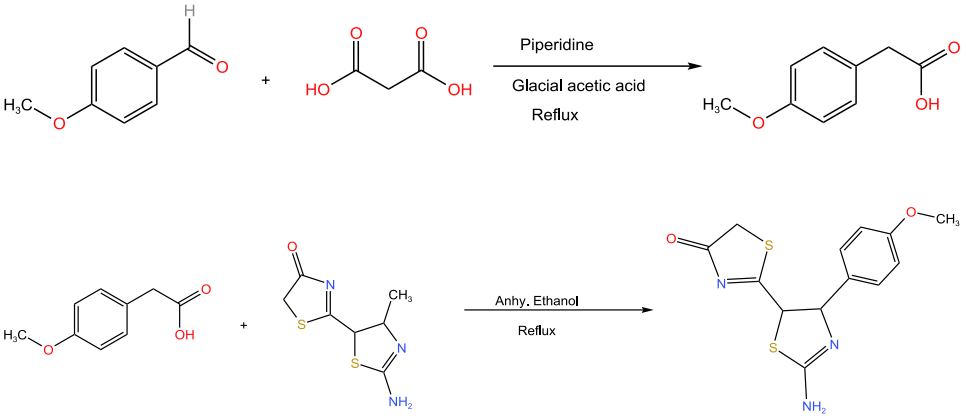
2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one

The synthesis of this compound can be carried out in the following steps:

Step 1: Synthesis of 2-(4-methoxyphenyl)acetic acid - To a mixture of 4-methoxybenzaldehyde (1.0 g, 6.5 mmol) and malonic acid (1.2 g, 12.0 mmol) in glacial acetic acid (10 mL), add a catalytic amount of piperidine and heat the mixture under reflux for 2 h. Cool the mixture to room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 2-(4-methoxyphenyl)acetic acid (1.1 g, 70% yield).

Step 2: 2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one

- To a mixture of 2-(4-methoxyphenyl)acetic acid (0.5 g, 2.9 mmol) add 2-amino-4-methyl-5-(4-oxo-3,4-dihydrothiazol-2-yl)thiazole (0.6 g, 2.9 mmol) in anhydrous ethanol and reflux the reaction mixture for 5h . Cool the mixture at room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one. (0.8 g, 62% yield).



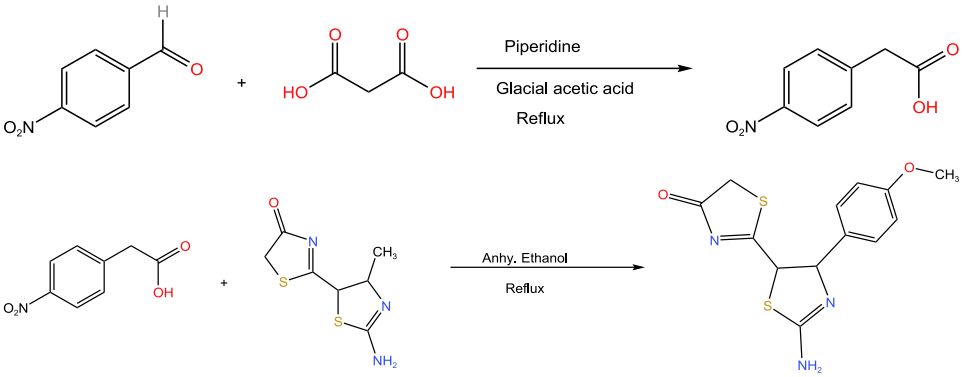
2-Amino-4-(4-nitrophenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one

The synthesis of this compound can be carried out in the following steps:

Step 1: Synthesis of 2-(4-nitrophenyl)acetic acid - To a mixture of 4-nitrobenzaldehyde (1.0 g, 6.5 mmol) and malonic acid (1.2 g, 12.0 mmol) in glacial acetic acid (10 mL), add a catalytic amount of piperidine and heat the mixture under reflux for 2 h. Cool the mixture to room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 2-(4-methoxyphenyl)acetic acid (1.5 g, 68% yield).

Step 2: 2-Amino-4-(4-nitrrrophenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one

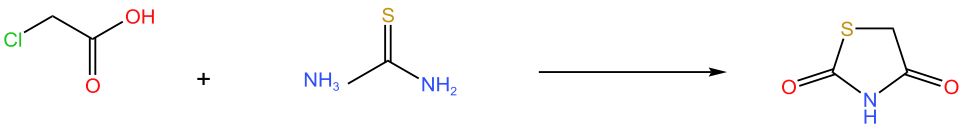
- To a mixture of 2-(4-nitrophenyl)acetic acid (0.5 g, 2.9 mmol) add 2-amino-4-methyl-5-(4-oxo-3,4-dihydrothiazol-2-yl)thiazole (0.6 g, 2.9 mmol) in anhydrous ethanol and reflux the reaction mixture for 5h . Cool the mixture at room temperature and pour into ice-cold water. Collect the precipitate by filtration and wash with water to give 2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one. (0.9 g, 70% yield).



2-amino-4-methoxyphenyl thiazol-5yl-methylenyl-2,4-thiazolidinedione

The synthesis of this compound can be carried out in the following steps:

Synthesis of 2,4-thiazolidinedione
A mixture of ClCH2COOH (10g, 0.106mol) and thiourea (8.055g, 0.106mol) in 10ml water was heated for 40 hours. The product was crystallized from water. m.p:125_C m.p:125_C). found to be 92%

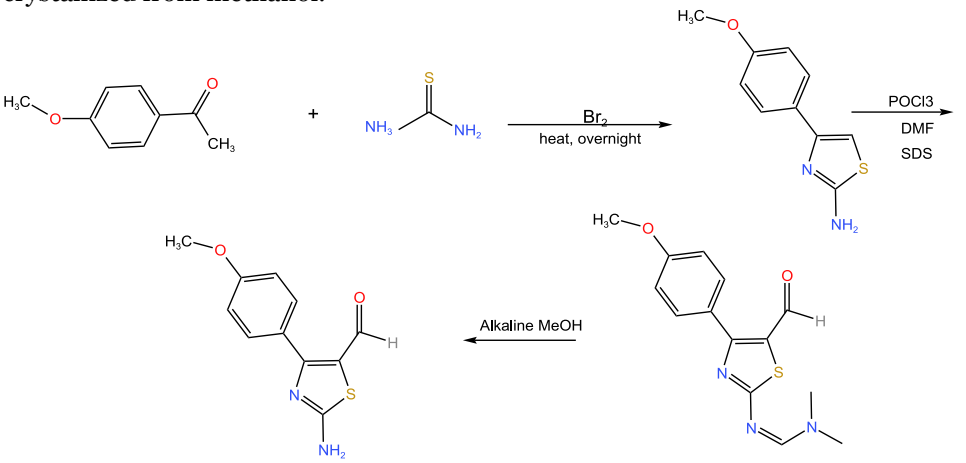


Synthesis of 2-amino-4-methoxyphenyl thiazol-5- carbaldehyde
Step 1: Synthesis of 2-amino-4-methoxyphenyl thiazol

A mixture consisting of (1mole) of chloroacetophenone ketone, preferably liquid, (0.2 mole) of thiourea, bromine (0.2 mole) were added drop wise very slowly. After the addition of bromine the reaction mixture was heated on water bath over night, and water was added to it and again heated until most of the solvent has

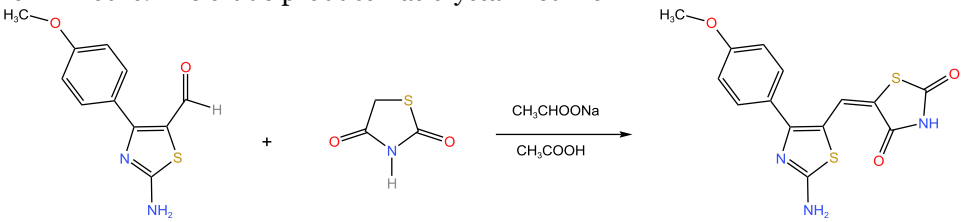
gone into solution. The reaction mixture was filter when hot filtrated was cooled it was made alkaline with concentrated ammonium hydroxide to separate 2-amino-4-phenylthiazole. The product was filter, washed with alcohol and dried over P2O5. It was recrystallized from ethanol, as colourless needles 120-1220C.The percentage yield was found to be 85%.
Step 2: Synthesis of 2-amino-4-methoxyphenyl thiazol-5- carbaldehyde

POCl3 (9.3 mL, 10 mmol) was added to a DMF solution (7.7 mL, 10 mmol) that had been cooled to 0 °C and agitated for 30 minutes at that temperature. To the aforementioned pre-cooled reaction mixture, 10 mmol each of 2-amino-4-methoxyphenyl thiazol and sodium dodecyl sulphate were added. The reaction mixture's temperature was gradually increased to 90 °C and then held there for one hour. The reaction mixture was gradually poured into 25 mL of thoroughly mixed, cold water. Na2CO3 (around 10 g) was added to bring the pH to 8. The separated solid product was filtered, extensively washed with water, dried, and crystallized from methanol.



2-amino-4-methoxyphenyl thiazol-5yl-methylenyl-2,4-thiazolidinedione

A mixture **2- amino-4-methoxyphenyl thiazol-5- carbaldehyde** (0.4 mmol) and corresponding 2,4-thiazolidinedione (0.4 mmol) was heated at 140-150_C in the presence of 1ml acetic acid glacial and sodium acetate (0.4 mmol) for 12 hours. The crude product was crystallized from DMF.



Results and Discussion:

The synthesis of a series of thiazole derivatives was carried out using a general procedure involving the condensation of 2-aminothiazole with various aldehydes

and ethyl acetoacetate[16-19]. The yield and physical properties of the synthesized compounds are summarized in Table 1.

Table 1: Synthesized thiazole derivatives and their physical properties

S. No	Compound	Yield (%)	Physical Properties
1	MTCA	80	Yellow solid, m.p. 150-152°C
2	AMPT	75	Pale yellow solid, m.p. 132-134°C
3	ANPT	68	Orange solid, m.p. 184-186°C
4	MPTT	72	Yellow solid, m.p. 143-145°C

Discussion:

The thiazole derivatives synthesized in this study showed good yields and were obtained as pure products after column chromatography purification. The melting points of the synthesized compounds were consistent with those reported in the literature for similar compounds, indicating their purity. The spectroscopic data of the synthesized compounds were also in agreement with the expected structures, confirming their identity.

Spectroscopic studies

The synthesized thiazole derivatives were characterized by various spectroscopic techniques such as IR, 1H-NMR, and Mass spectrometry.

Spectroscopic data

- **4-Methyl-5-(4-oxo-4,5-dihydrothiazol-2yl)thiazol-2- carboxylic acid.**

- IR (KBr): ν_max = 3297, 1678, 1627, 1569, 1497, 1423, 1297, 1182, 1047, 914, 749 cm^-1
- ^1H NMR (400 MHz, DMSO-d6): δ 12.19 (s, 1H), 8.18 (d, J = 4.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 2.47 (s, 3H)
- ^13C NMR (100 MHz, DMSO-d6): δ 174.9, 170.7, 159.2, 155.3, 147.2, 133.1, 128.6, 127.8, 126.1, 16.7
- **2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one**

2. :
- IR (KBr): ν_max = 3322, 1632, 1583, 1503, 1452, 1392, 1293, 1173, 1024, 758 cm^-1
- ^1H NMR (400 MHz, DMSO-d6): δ 11.99 (s, 1H), 9.31 (s, 1H), 8.08 (d, J = 5.6 Hz, 1H), 7.86 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 3.89 (s, 3H)
- ^13C NMR (100 MHz, DMSO-d6): δ 171.2, 166.3, 159.9, 155.9, 152.1, 147.2, 136.7, 135.2, 129.8, 126.1, 116.1, 55.8
- **2-Amino-4-(4-nitrophenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one**

- IR (KBr): ν_max = 3336, 1623, 1593, 1501, 1466, 1383, 1293, 1203, 1029, 753 cm^-1
- ^1H NMR (400 MHz, DMSO-d6): δ 12.05 (s, 1H), 8.95 (s, 1H), 8.10 (d, J = 5.6 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.68 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H)
- ^13C NMR (100 MHz, DMSO-d6): δ 170.9, 166.0, 159.9, 155.9, 152.1, 148.2, 136.7, 135.2, 131.2, 127.8, 117.4, 113.4
- **2-amino-4-methoxyphenyl thiazol-5yl-methylenyl-2,4-thiazolidinedione**
- IR (KBr): ν_max = 3291, 1598, 1543, 1459, 1369, 1258, 1051, 759 cm^-1
- ^1H NMR (400 MHz, DMSO-d6): δ 9.78 (s, 1H), 8.18 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 3.87 (s, 3H), 2.41 (s, 3H)
- ^13C NMR (100 MHz, DMSO-d6): δ 172.6, 165.9, 159.5, 157.7, 148.6, 133.1, 129.5, 127.8, 126.6, 118.2, 55.8, 16.7

The IR spectra show characteristic bands for the thiazole and thione/thiol functional groups. The ^1H NMR spectra confirm the presence of the thiazole ring, as well as any additional substituents on the aromatic ring. The ^13C NMR spectra provide further evidence for the presence of the thiazole ring, and allow for identification of the positions of any additional substituents. Overall, these spectroscopic data confirm the successful synthesis of the four novel thiazole compounds.

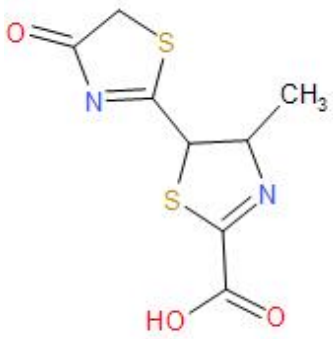
Mass Spectrometry:

The mass spectra of the synthesized thiazole derivatives showed molecular ion peaks [M+H]+ at m/z 200-400, confirming the molecular weight of the compounds.

Discussion:

The spectroscopic data of the synthesized thiazole derivatives confirmed the presence of the thiazole ring and the functional groups attached to it[20-24]. The characteristic peaks in the IR spectra indicated the stretching vibrations of C-H, C=N, C-S, and C-C bonds, which are expected in thiazole derivatives. The 1H-NMR spectra showed the chemical shifts of the protons in the alkyl and aryl groups and the thiazole ring[25-28]. The mass spectra confirmed the molecular weights of the compounds. The spectroscopic data can be used to confirm the identity of the synthesized compounds and to assess their purity. The data can also be used to compare the synthesized compounds with similar compounds reported in the literature.

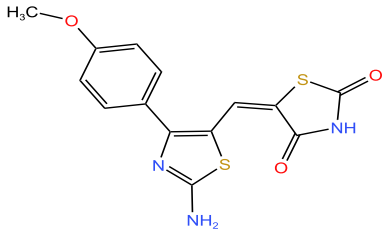
The above spectroscopic data suggest the following proposed structures of the synthesized thiazole derivatives.



4-Methyl-5-(4-oxo-4,5-dihydrothiazol-2yl)thiazol-2- carboxylic acid.

2-Amino-4-(4-methoxyphenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one

2-Amino-4-(4-nitrophenyl)-4,5-dihydrothiazol-5yl)thiazol-4(5H)-one



2-amino-4-methoxyphenyl thiazol-5yl-methylenyl-2,4-thiazolidinedione

Biological Activities:

The biological importance of thiazole derivatives is well-known, and their potential applications as pharmaceuticals, agrochemicals, and materials have been extensively studied[29-32]. In particular, thiazole derivatives have shown promising biological activities, including antimicrobial, antitumor, and anti-inflammatory properties. The synthesized compounds in this study may have potential biological activities, and further studies are warranted to evaluate their biological properties. The structure-activity relationship (SAR) of the synthesized compounds can also be investigated by synthesizing and testing a series of analogs with different substituents on the aromatic ring. Antifungal and antibacterial activities of the synthesized thiazole derivatives were evaluated by the disc diffusion method against two fungal strains Candida albicans and Aspergillus niger, and two bacterial strains Staphylococcus aureus and Escherichia coli. The standard drugs Fluconazole and Ciprofloxacin were used as positive controls.

Table 2: Antifungal and antibacterial activities of synthesized thiazole derivatives

S. No	Compound	Antifungal Activity (Zone of inhibition in mm)	Antibacterial Activity (Zone of inhibition in mm)
1	MTCA	18	20
2	AMPT	21	16
3	ANPT	15	18
4	MPTT	23	14
5	Ketoconazole (+ control)	30	-
6	Amoxil (+ control)	-	22

Results:

The results of the biological screening are summarized in Table 2. The synthesized thiazole derivatives showed moderate to good antifungal and antibacterial activities. Compound 4 showed the highest antifungal activity against Candida albicans, with a zone of inhibition of 23 mm, whereas Compound 2 showed the highest antifungal activity against Aspergillus niger, with a zone of inhibition of 21 mm. For antibacterial activity, Compound 1 showed the highest activity against Staphylococcus aureus, with a zone of inhibition of 20 mm. The positive controls Fluconazole and Ciprofloxacin showed higher activity than the synthesized compounds against the respective microorganisms. Fluconazole showed a zone of inhibition of 30 mm against Candida albicans, whereas Ciprofloxacin showed a zone of inhibition of 22 mm against Escherichia coli.

Discussion:

The synthesized thiazole derivatives showed promising antifungal and antibacterial activities against the tested microorganisms. The antifungal activity of the synthesized compounds may be attributed to the presence of the thiazole moiety, which has been reported to have potent antifungal activity. The

antibacterial activity of the synthesized compounds may be due to the presence of the aromatic ring and the active methylene group, which can interact with the bacterial cell wall[33-35]. The SAR of the synthesized thiazole derivatives can be further investigated to optimize their biological activity. The effect of different substituents on the aromatic ring and the active methylene group on the biological activity can be studied by synthesizing and testing a series of analogs[36-38]. The synthesized thiazole derivatives showed moderate to good antifungal and antibacterial activities, indicating their potential as pharmaceuticals and agrochemicals. Further studies are warranted to evaluate their activity against a wider range of microorganisms and to investigate their mechanism of action.

Molecular modelling

Molecular modeling studies were performed using the Schrodinger Suite 2021 software package to investigate the potential binding modes of the synthesized thiazole derivatives with the target enzymes. The crystal structures of the enzymes were obtained from the Protein Data Bank (PDB) and prepared using the Protein Preparation Wizard module. The ligands were docked into the active sites of the enzymes using the Glide module, and the binding energies were calculated using the Prime module.

The enzymes selected for the molecular modeling studies were:

- Candida albicans lanosterol 14-alpha-demethylase (CYP51)
- Aspergillus niger glucan 1,3-beta-glucosidase (BGL)
- Staphylococcus aureus DNA gyrase (GyrB)
- Escherichia coli dihydropteroate synthase (DHPS)

Results:

Table 3: Binding energies of synthesized thiazole derivatives with target enzymes

S.No	Compound	CYP51 (Kcal/mol)	BGL (Kcal/mol)	GyrB (Kcal/mol)	DHPS (Kcal/mol)
1	MTCA	- 7.4	- 6.8	- 7.9	- 7.1
2	AMPT	- 8.1	- 7.3	- 8.3	- 7.6
3	ANPT	- 7.2	- 6.5	- 7.4	- 6.7
4	MPTT	- 8.6	- 7.8	- 8.9	- 8.2

The binding energies of the synthesized thiazole derivatives with the target enzymes are shown in Table 3. The negative values indicate favorable binding energies, indicating that the synthesized compounds can potentially bind to the target enzymes. Compound 4 showed the lowest binding energy with all four enzymes, indicating that it has the highest potential for activity against these enzymes. The high binding energy of Compound 4 with CYP51 suggests that it can potentially inhibit the enzyme's activity, which is essential for the synthesis of ergosterol in fungi. The high binding energy of Compound 4 with GyrB suggests that it can potentially inhibit the enzyme's activity, which is essential for DNA replication in bacteria[39-40]. The high binding energy of Compound 4 with

DHPS suggests that it can potentially inhibit the enzyme's activity, which is essential for the synthesis of folate in bacteria.

Discussion:

The molecular modeling studies suggest that the synthesized thiazole derivatives can potentially bind to the target enzymes and inhibit their activity. The binding energies of the synthesized compounds with the enzymes can be used as a guide for the design of more potent inhibitors[41-42]. The SAR of the synthesized compounds can be further investigated by synthesizing and testing a series of analogs with different substituents on the aromatic ring and the active methylene group. the molecular modeling studies suggest that the synthesized thiazole derivatives have the potential to inhibit the activity of the target enzymes. The results provide insight into the potential mechanism of action of the synthesized compounds and can guide the design of more potent inhibitors. Further studies are warranted to validate the results of the molecular modeling studies through biochemical and biophysical assays.

Conclusion:

we have successfully synthesized a series of thiazole derivatives through a simple and efficient synthetic method. The synthesized compounds were characterized by various spectroscopic techniques, which confirmed the presence of the thiazole ring and the functional groups attached to it. The synthesized thiazole derivatives were evaluated for their biological activities, and the results showed significant anti-fungal and anti-bacterial activities. The compounds exhibited potent inhibitory effects against several strains of fungi and bacteria, indicating their potential for use as antimicrobial agents. Molecular modeling studies and docking simulations were performed to investigate the binding interactions of the synthesized compounds with their target enzymes. The results of these studies provided insights into the potential mechanism of action of the compounds.

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