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Synthesis, Structural Determination, Docking Study and Bioactivity of Novel Thiophene Derivatives

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The present study reveals 4-methyl-3-(propylamino)thiophene-2-carboxylic acid (Articaine acid) as precursor derivative to synthesize novel thiophene compounds to evaluate their biological activity. The synthesized compounds were subjected to comprehensive characterization techniques including mass spectra, NMR and IR spectroscopy, confirming their structural integrity. Their antimicrobial activity was assessed *via* minimum inhibitory concentration (MIC) assay against selected bacterial strains. The results emphasize the potential therapeutic applications of these thiophene analogues as efficacious antimicrobial agents, thereby encouraging further investigation. Molecular docking was used to examine thiophene derivative binding affinities on the *S. aureus* tyrosyl-tRNA synthetase protein and it was found that phenylethylamine derivatives had the highest binding affinity, followed by cyclohexyl methyl and benzylamine derivatives.

Keywords: Thiophene derivatives, Structure-activity relationship, Antimicrobial agents, Drug discovery.

INTRODUCTION

Thiophene derivatives have garnered significant attention in the field of medicinal chemistry due to their diverse pharmacological properties and potential as bioactive agents [1-3]. In particular, their antimicrobial activity has become a focal point in light of the global threat of antimicrobial resistance [4-6]. The antimicrobial properties of thiophene can be attributed to the crucial role-played by the sulfur atom within the thiophene ring [7]. This sulfur atom possesses distinct characteristics that contribute to the antimicrobial efficacy of thiophene derivatives [8]. When compared to oxygen, nitrogen and sulphur, its electronegativity is lower, which means it interacts favourably with enzymes and receptors inside microorganisms [9,10]. Through its chelating qualities, which enable it to form coordination complexes with metal ions, the sulfur atom can interfere with metal-dependent enzymes that are necessary for microbial growth and metabolism [11,12].

Furthermore, the presence of sulfur atom enhances the hydrophobicity of thiophene derivatives, facilitating their partitioning into the hydrophobic regions of microbial cell membranes [13,14]. This process disrupts membrane integrity, ultimately leading to cell death. Moreover, the sulfur-containing compounds can engage in redox reactions, generating reactive oxygen species (ROS) and other free radicals that induce oxidative damage in microbial cells [15]. Additionally, the sulfur atom enables interaction with microbial proteins through non-covalent forces like hydrogen bonding, van der Waals interactions and hydrophobic interactions, thereby impeding essential microbial processes [16,17]. The antimicrobial activity of thiophene is further influenced by structural features, such as functional groups and substitution patterns on the thiophene ring [18-20].

This study focuses on the synthesis, characterization and evaluation of novel thiophene derivatives as potential antimicrobial agents, aiming to unravel their intricacies and enhance their therapeutic efficacy.

EXPERIMENTAL

All the chemicals and solvents were purchased from Sigma-Aldrich, USA. The starting material 4-methyl-3-(propylamino)-

thiophene-2-carboxylic acid (articaine acid) (**M2**) was obtained from Suyog Life Sciences Pvt. Ltd. The TLC plates (silica gel 60 F_{254}) were obtained from Merck, Germany. The melting points were measured using an uncorrected Cintex melting point apparatus. The IR spectra were recorded in KBr using a Shimadzu FTIR spectrophotometer. The NMR spectra were obtained in $CDCl_3$ or DMSO-d_6 on a Bruker DRX-400 MHz NMR instrument, with chemical shifts reported in ppm using TMS as the internal standard. The mass spectra of the compounds were acquired using an Agilent 1100 series mass spectrometer.

Synthesis

Step-1: Synthesis of methyl 4-methyl-3-[1-(propylamino)-ethyl]thiophene-2-carboxylate (articaine base) (M1): Charge methyl 4-methyl-3-amino thiophene-2-carboxylate (50 g, 0.292 mol), K_2CO_3 (50 g, 0.362 mol) and 150 mL of toluene in three-necked RBF equipped with an overhead stirrer. After stirring for 15 min, slowly dropwise added 2-bromo propionyl bromide (64.6 g, 0.30 mol) till 1 h at 35-45 ºC. After the addition, maintain the reaction at 50-55 ºC for 3 h and reaction was monitored on TLC (toluene:methanol: 9:1). Cooled to 20-30 ºC after the reaction completion and filtered. Charged the filtrate with K_2CO_3 (25 g, 0.181 mol) and 100 mL of toluene in RBF at room temperature. After 15 min of stirring, added *n*-propylamine (50 g, 0.85 mol) and raise the temperature slowly to 50-60 ºC for 5-6 h. The reaction was again monitored on TLC (toluene:methanol: 9:1). Cooled the solution to 20-30 ºC after the completion of the reaction and filtered. Washed the filtrate with 100 mL of toluene and the organic solvent layer was dried on anhydrous Na_2SO_4 and filtered it through a cotton plug. Distilled toluene under vacuum at 70 ºC in order to obtain the desired product as oil which was recrystallized using methylcyclohexane to get off-white colour solid (yield: 84 g).

Step-2: Synthesis of 4-methyl-3-(propylamino)thiophene-2-carboxylic acid (articaine acid) (M2): Charge articaine base (80 g, 0.280 mol) and 100 mL water in three-necked RBF followed by the slow addition of 200 mL of 30% NaOH solution and then raise the temperature to 50-60 ºC for 6 h. The progress of the reaction was monitored with TLC (toluene: methanol: 9:1). After the reaction completion, adjust it with 50% HCl solution to pH 6-7, then extract it with 3 × 50 mL of methylene dichloride (MDC) and washed with 50 mL brine solution. Separated the MDC layer and distilled it under vacuum to obtain the product (yield: 72 g).

Step-3: Synthesis of 4-methyl-3-(2-propylaminopropionylamino)thiophene-2-carboxylic acid propylamide: Charge articaine acid (5.0 g, 0.019 mol) and 25 mL of MDC in three-necked RBF followed by the addition of 0.5 mL of DMF while stirring for 15 min and then added thionyl chloride (3 g, 0.025 mol) at 20-30 °C through addition funnel. Stirred the solution for 1 h, distilled the excess solvent under vacuum and degassed for 30 min. Now in this reaction mixture, slowly added *n*-propylamine (2 g, 0.033 mol) and heat it at 40-45 ºC for 6 h. The progress of the reaction was monitored on TLC (toluene:methanol: 9:1). Washed with water after reaction completion, followed by a brine solution. The MDC layer was distilled under vacuum to obtain 4-methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid propylamide (**1a**) (**Scheme-I**).

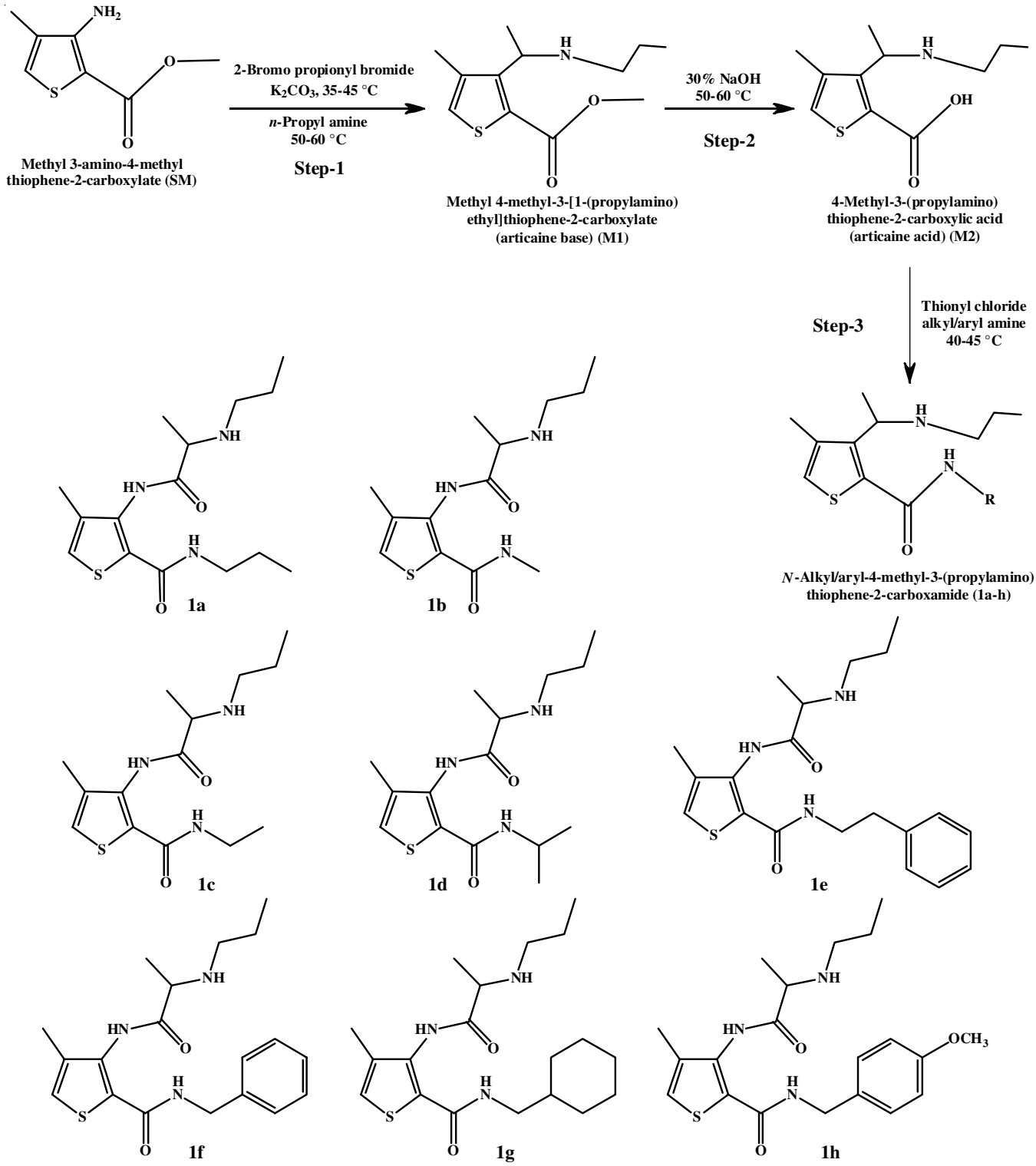
4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid propylamide (1a): Yield: 73%; m.p.: 121-123 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (N-H *str.*), 2956.56 (aliph. C-H *str.*), 1222.79 (C-S *str.*); 1557.41 (Ar-C=C *str.*); 1627.81 (C=O *str.* of amide); 1671.20 (C=O *str.* of amide); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.97 (t, 6H), 1.26-1.27 (d, 3H), 2.15 (s, 3H), 1.40-1.63 (m, 6H), 2.63-2.70 (t, 2H), 3.29-3.33 (d, 1H) 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 11.65, 14.87, 20.01, 22.77, 23.28, 41.54, 50.80, 58.77, 122.60, 127.11, 135.83, 136.04, 162.47, 165.42. Anal. calcd. (found) % for $C_{15}H_{25}N_3O_2S$ (*m.w.* 311.44): C, 57.85 (57.63); H, 8.09 (7.98); N, 13.49 (13.41); O, 10.27 (10.23); S, 10.30 (10.21); ESI-MS: 312.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid methylamide (1b): Yield: 65%; m.p.: 94-96 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (aliph. C-H *str.*), 2956.56 (N-H *str.*), 1671.20 (C=O *str.* of amide), 1627.81 (C=O *str.* of amide), 1557.41 (Ar-C=C *str.*) 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.97 (t, 3H), 1.26-1.27 (d, 3H), 1.45 (m, 2H), 2.15 (s, 3H), 2.63-2.70 (t, 2H), 2.85 (s, 3H), 3.29-3.33 (d, 1H), 6.99 (1H), ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 13.87, 23.20, 25.9, 23.28, 49.80, 58.77, 122.60, 127.11, 135.83, 136.04, 162.47, 165.42. Anal. calcd. (found) % for $C_{13}H_{21}N_3O_2S$ (*m.w.* 283.39): C, 55.10 (55.01); H, 7.47 (7.39); N, 14.83 (14.73); O, 11.29 (11.18); S, 11.31 (11.21); ESI-MS: 284.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid ethylamide (1c): Yield: 72%; m.p.: 112-114 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (aliph. C-H *str.*), 2956.56 (N-H *str.*), 1671.20 (C=O *str.* of amide), 1627.81 (C=O *str.* of amide); 1557.41 (Ar-C=C *str.*), 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.97 (t, 6H), 1.26-1.27 (d, 3H), 1.45 (m, 2H); 2.15 (s, 3H); 2.5-2.6 (t, 2H), 3.0-3.1 (q, 2H), 3.74 (q, 1H), 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 13.87, 23.20, 25.9, 23.28, 49.80, 58.77, 122.60, 127.11, 135.83, 136.04, 162.47, 165.42. Anal. calcd. (found) % for $C_{15}H_{25}N_3O_2S$ (*m.w.* 311.44): C, 56.54 (56.46); H, 7.79 (7.75); N, 14.13 (14.04); O, 10.76 (10.65); S, 10.78 (10.69); ESI-MS; 298.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid isopropylamide (1d): Yield: 69%; m.p.: 97-99 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (N-H *str.*), 2956.56 (aliph. C-H *str.*), 1671.20 (C=O *str.* of amide), 1627.81 (C=O *str.* of amide), 1557.41, (Ar C=C *str.*), 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.92 (t, 3H), 1.26-1.27 (d, 3H), 1.45 (m, 2H), 2.15 (s, 3H), 2.5-2.6 (t, 2H), 3.74 (q, 1H), 4.17 (1H, m), 6.99 (1H), ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 12.20, 14.87, 21.01, 22.77, 33.8, 40.8, 50.80, 58.77, 122.60, 127.11, 135.83, 136.04, 162.47, 165.42. Anal. calcd. (found) % for $C_{15}H_{25}N_3O_2S$ (*m.w.* 311.44): C, 57.85 (57.63); H, 8.09 (7.98); N, 13.49 (13.41); O, 10.27 (10.23); S, 10.30 (10.21); ESI-MS: 312.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid phenethylamide (1e): Yield: 75%; m.p.: 142-145 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (N-H *str.*),



Scheme-I

3030.30 (arom. C-H *str.*), 2956.56 (aliph. C-H *str.*), 1671.20, 1627.81 (C=O *str.* of amide), 1557.41 (Ar C=C *str.*), 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.92 (t, 3H), 1.26-1.27 (d, 3H), 1.45 (m, 2H), 2.15 (s, 3H), 2.5-2.6 (t, 2H), 2.83 (t, 2H), 3.37 (t, 2H), 3.74 (q, 1H), 6.26-6.28 (d, 3H), 6.6 (d, 2H), 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 14.87, 21.01, 22.77, 33.80, 50.80, 62.2, 125.9, 127.7, 128.6, 131, 112.7, 139.1, 144.3, 161.3, 172.7. Anal. calcd. (found) % for $C_{20}H_{27}N_3O_2S$ (*m.w.* 373.51): C, 64.31 (64.23); H, 7.29 (7.21); N, 11.25 (11.19); O, 8.57 (8.51); S, 8.58 (8.51); ESI-MS: 374.

4-Methyl-3-(2-propylamino-popionylamino)thiophene-2-carboxylic acid benzylamide (1f): Yield: 68%; m.p.: 133-135 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98 (N-H *str.*), 3030.30: arom. C-H *str.*), 2956.56 (aliph. C-H *str.*), 1671.20 (C=O *str.*

of amide), 1627.81 (C=O *str.* of amide), 1557.41 (Ar C=C *str.*), 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 10.90-0.92 (t, 3H); 1.26-1.27 (d, 3H), 1.45 (m, 2H) ; 2.15 (s, 3H), 2.5-2.6 (t, 2H), 3.37 (t, 2H), 3.74 (q, 1H), 6.26-6.28 (d, 3H), 6.6 (d, 2H), 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 14.87, 21.1, 22.77, 43.8, 50.80, 62.2, 125.9, 126.9, 128.5, 130, 112.7, 139.1, 144.3, 161.3, 172.7. Anal. calcd. (found) % for $C_{19}H_{25}N_3O_2S$ (*m.w.* 359.49): C, 63.48 (63.41); H, 7.01 (6.97); N, 11.69 (11.61); O, 8.90 (8.83); S, 8.92 (8.84); ESI-MS; 360.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid cyclohexyl methylamide (1g): Yield: 67%; m.p.: 117-119 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98: N-H *str.*), 2956.56 (aliph. C-H *str.*), 1671.20, 1627.81 (C=O *str.* of amide), 1557.41 (Ar C=C *str.*), 1430.20 (C-C *str.*), 1222.79 (C-S *str.*); ^{1}H NMR (DMSO-d_6, δ ppm): 0.90-0.92 (t, 3H); 1.26-1.27 (d, 3H); 1.45 (m, 2H), 1.5-1.6 (m, 10H), 2.1 (m, 1H), 2.15 (s, 3H), 2.5-12.6 (t, 2H); 3.37 (t, 2H); 3.74 (q, 1H); 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 14.87, 21.01, 22.77, 25.5, 26.0, 30.7, 49.80, 62.20, 125.9, 126.9, 128.5, 131, 112.7, 139.1, 144.3, 161.3, 172.7. Anal. calcd. (found) % for $C_{19}H_{31}N_3O_2S$ (*m.w.* 365.53): C, 62.43 (62.37); H, 8.55 (8.49); N, 11.50 (11.42); O, 8.75 (8.69); S, 8.77 (8.70); ESI-MS: 366.

4-Methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid 4-methoxybenzylamide (1h): Yield: 62%; m.p.: 137-139 ºC; IR (KBr, ν_{max}, cm^{-1}): 3299.98: N-H *str.*), 3030.30 (arom. C-H *str.*), 2956.56 (aliph. C-H *str.*), 1671.20, 1627.81 (C=O *str.* of amide), 1557.41 (Ar C=C *str.*), 1222.79 (C-S *str.*), 1030.20 (C-O *str.* of ether); ^{1}H NMR; 0.90-0.92 (t, 3H):1.26-1.27 (d, 3H); 1.45 (m, 2H), 2.15 (s, 3H):2.3 (s, 3H)2.52.6 (t, 2H); 13.37 (t, 2H); 3.74 (q, 1H); 6.26-6.28 (d, 2H); 6.6 (d, 2H); 6.99 (1H); ^{13}C NMR (DMSO-d_6, δ ppm): 11.41, 14.87, 21.01, 55.08, 22.77, 43.3, 49.80, 62.2, 114.1, 130.5, 131, 112.7, 130.2, 144.3, 158.6, 161.6, 172.7. Anal. calcd. (found) % for $C_{20}H_{27}N_3O_3S$ (*m.w.* 389.51): C, 61.67 (61.61); H, 6.99 (6.92); N, 10.79 (10.71); O, 12.23 (12.18); S, 8.23 (8.16); ESI-MS: 390.

Antimicrobial activity: Using the broth microdilution method [21], the antibacterial activity of the synthesized compounds synthesized from 4-methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid was investigated. This methodology entailed subjecting the compounds to rigorous assessment with the aim of discerning their ability to impede the microbial growth. The compounds synthesized with *n*-propylamine and isopropylamine showed the lowest MIC values against *P. aeruginosa* MTCC-1688 and *S. aureus* MTCC-96, while the compound synthesized with methylamine (**1g**) had the lowest MIC against *E. coli* MTCC-443. Additionally, the compound synthesized with benzylamine (**1f** and **1h**) exhibited the poor MIC against *B. subtilis* MTCC-441 and *S. aureus* MTCC-96, respectively.

Structure activity relationship (SAR): The antimicrobial activity of different amines with varying alkyl chain lengths and aromatic substituents was investigated against a range of bacterial and fungal strains.

Molecular docking study: Molecular docking studied was carried out using Autodock Vina version 1.2.3 and Biovia Discovery Studio. A molecular docking study was conducted on *S. aureus* tyrosyl-tRNA synthetase protein (PDB ID: 1JIJ) to investigate the binding affinities of thiophene derivatives.

RESULTS AND DISCUSSION

Methyl 3-amino-4-methyl thiophene-2-carboxylate as starting compound reacts with 2-bromopropionyl bromide in acetone using K_2CO_3 followed by reaction with propylamine to get methyl 4-methyl-3-[1-(propylamino)ethyl]thiophene-2-carboxylate (articaine base) (**M1**), which was hydrolyzed by NaOH to get articaine acid. The reaction of thionyl chloride with 4-methyl-3-(propylamino)thiophene-2-carboxylic acid (articaine acid) (**M2**) followed by reaction with various amine to obtain novel thiophene compounds. In the IR spectra, the absorption bands at 2956.56, 222.79, 1671.20 & 1627.81, 1557.41 cm^{-1} appeared due to aliphatic C-H *str.*, C-S *str.*, C=O *str.* of amide and Ar C=C *str.*, respectively. In ^{1}H NMR, the compounds shows δ 0.90-0.97 ppm, which corresponds to the protons on the methyl group attached to the thiophene ring. A peak at δ 1.26-1.27 ppm is associated to the methyl proton (CH_3) attached to the propylamide group. Similarly, a singlet signal at δ 2.15 ppm is associated to the methyl proton (CH_3) attached to the thiophene ring.

Antimicrobial activity and structure-activity relationship (Antimicrobiol-SAR): Compound 4-methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid phenethylamide (**1e**) exhibited high activity against *E. coli* MTCC-443 and *S. aureus* MTCC-96, with an MIC of 8.0. However, it has lower activity against *P. aeruginosa* MTCC-1688 and *B. subtilis* MTCC-441, with MICs of 32.0 and 8.0, respectively.

All the synthesized thiophene derivatives display varying antimicrobial effectiveness, indicating the crucial role of amine selection. Gram-negative strains *viz. P. aeruginosa* and *E. coli*, are more susceptible to the thiophenes than Gram-positive strains (*S. aureus* and *B. subtilis*), suggesting stronger activity against Gram-negative bacteria (Table-1). Novel thiophenes generally exhibit lower potency against the fungal strain *A. niger*, indicating limited antifungal activity. Structural differences, such as alkyl or aromatic group variations, contribute to variations in antimicrobial activity. Isopropylamine and *n*-propylamine show relatively higher potency against the studied bacterial strains. Compared to the standard antibiotics, synthesized thiophenes generally have higher MIC values, indicating inferior effectiveness.

Molecular docking studies: The results revealed that the final compound bearing a phenylethylamine derivative exhibited the highest binding affinity followed by cyclohexyl methylamine and benzylamine derivatives (Fig. 1). The starting material exhibited a binding affinity of -6 kcal/mol, which increased through the reaction stages. The **M1** molecule showed a binding affinity of -5.1 kcal/mol and upon completion of the second stage, compound **M2** exhibited a binding affinity of -5.3 kcal/mol. Significantly, all the compounds displayed binding affinities exceeding -6 kcal/mol indicating a consistent increase in binding affinity from the starting material to the final compounds. Several compounds exhibited binding affinities higher than the reference drug ampicillin (-7 kcal/mol), notably compounds **1e**, **1f** and **1g**. Among these, compound **1e** demonstrated the

TABLE-1
ANTIMICROBIAL ACTIVITY DATA OF NOVEL THIOPHENE DERIVATIVES

Compounds	Amine used	MIC of bacterial strains (µg/mL)				
		Gram-negative strains		Gram-positive strains		Fungal strains
		P. aeruginosa MTCC-1688	*E. coli* MTCC-443	*S. aureus* MTCC-96	*B. subtilis* MTCC-441	*A. niger* MTCC-282
1a	*n*-Propyl amine	4.0	1.0	16.0	16.0	32.0
1b	Methyl amine	8.0	8.0	32.0	16.0	256.0
1c	Ethyl amine	8.0	2.0	32.0	32.0	128.0
1d	Isopropyl amine	2.0	2.0	8.0	8.0	32.0
1e	Phenyl ethylamine	8.0	8.0	32.0	8.0	64.0
1f	Benzylamine	16.0	8.0	64.0	64.0	64.0
1g	Cyclohexane methyl amine	8.0	4.0	16.0	8.0	128.0
1h	4-Methoxy benzylamine	16.0	8.0	32.0	16.0	128.0
Streptomycin		0.5	0.25	0.25	0.25	–
Kanamycin		–	–	–	–	4.0

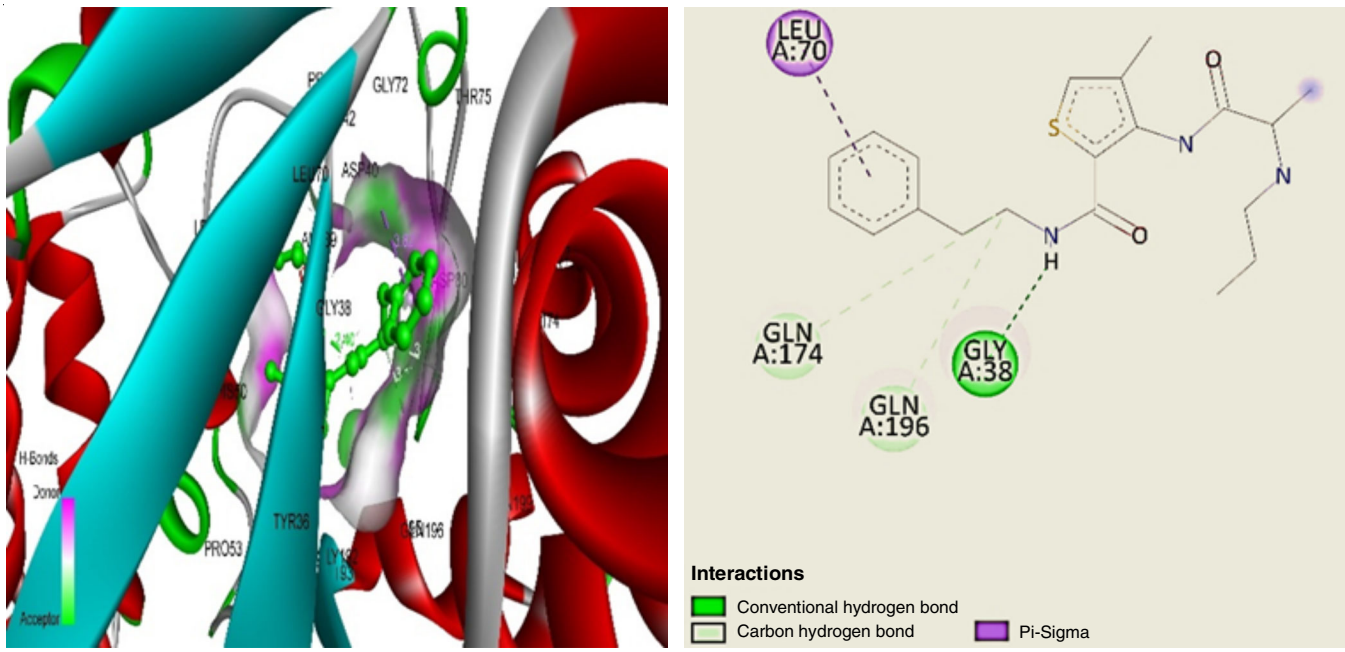


Fig. 1

highest binding affinity followed by compounds **1g**, **1f** and **1h**.

The results revealed important structure-activity relationships that can guide the design and development of more potent antimicrobial agents. Firstly, the alkyl chain length of the amines showed a significant effect on their antimicrobial activity. Amines with shorter alkyl chains, such as *n*-propylamine and isopropylamine, exhibited lower MIC values against the tested strains. This suggests that a shorter alkyl chain may enhance antimicrobial activity, possibly by facilitating better interactions with the microbial targets. Moreover, amines with aromatic substituents, such as phenyl ethylamine and 4-methoxy benzylamine, demonstrated moderate antimicrobial activity. These aromatic groups likely contribute to the interactions between the compounds and the bacterial or fungal targets, potentially influencing the potency of the compounds.

Interestingly, the position of the amino group on the amine structure was found to influence the antimicrobial potency. For instance, compounds such as 4-methyl-3-(2- propylamino-propionylamino)thiophene-2-carboxylic acid propylamide and 4-methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid isopropylamide, which have similar structures but differ in the position of the amino group, exhibited varying antimicrobial activity. The compound with the isopropylamine substitution showed lower MIC values against the tested strains, indicating that the position of the amino group can impact antimicrobial potency. Furthermore, modifications to the amine side chain were observed to affect antimicrobial activity. The addition of ethyl group in 4-methyl-3-(2-propylamino-propionylamino)thiophene-2-carboxylic acid ethylamide led to slightly higher MIC values compared to *n*-propyl and isopropylamine substitutions. This indicates that specific side chain modifications can influence the potency of the compounds. These findings provide valuable insights into the structure-activity relationship of amines as antimicrobial agents. By understanding the impact of alkyl chain length, aromatic substituents, amino group position and side chain modifications, researchers can design and optimize novel compounds with enhanced antimicrobial potency.

Conclusion

In conclusion, few novel thiophene derivatives were synthesized through a multi-step synthetic route starting from methyl 4-methyl-3-amino thiophene and successfully characterized through mass spectra, NMR and IR spectroscopy, confirming their structural integrity. Our bioactivity evaluation revealed varying levels of antimicrobial activity against tested bacterial and fungal strains. Compounds synthesized with *n*-propylamine and isopropylamine displayed the lowest MIC values against *P. aeruginosa* and *S. aureus*, indicating their potential as effective antimicrobial agents. However, further optimization is needed to enhance their potency compared to standard antibiotics. This research provides valuable insights into the synthesis and bioactivity of these thiophene derivatives, emphasizing the importance of structural features for antimicrobial potency.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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