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DESIGN AND SYNTHESIS NOVEL COMPOUNDS OF ORTHO-COUMARIC ACID DERIVATES AS ANTI-THROMBOTIC CANDIDATE

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ABSTRACT

It has been reported that aspirin and P2Y inhibitors have emerged as the preferred therapeutic agents for managing vaso-occlusive illness due to their anti-thrombotic properties. However, complaints about the side effects of these drugs are still being reported. Ongoing research is being conducted on the design and development of novel antithrombotic agents to obtain good health and well-being. *ortho*-Coumaric acid derivates were designed using the ChemDraw program, while a physicochemical prediction study was carried out by the Swiss ADME program, and the MOE platform was operated to predict the activity of the *ortho*-Coumaric derivates against cyclooxygenase-1. The structural modification of carboxylic acid and phenolic moieties generated ester and thiourea derivatives, thereby increasing the S score of these derivatives, was compared to *ortho*-coumaric acid. All derivatives have adequate oral absorption (55-85%). Microwave-assisted nucleophilic acyl substitution was operated to produce thiourea derivatives of *ortho*-coumaric acid using *ortho-methoxy cinnamic* acid, one of the *ortho*-coumaric acid derivates, as the starting material for reacting with substituted aniline. This method produced novel compounds in yields of 60-70 percent, depending on the substituent of the aniline compound. The structure of all product reactions was confirmed by UV & IR spectrophotometer, ^{1}HNMR, ^{13}CNMR, and HR-ESI-MS spectrometer. The thiourea moiety of *ortho*-coumaric derivates interacts similarly with aspirin. The majority of *ortho*-coumaric derivates have a higher level of interaction with cyclooxygenase-1 compared to *ortho*-coumaric acid. All of the derivatives exhibited favorable characteristics for oral absorption. Therefore, it may be inferred that these derivatives possess potential as agents with anti-thrombotic properties.

Keywords: *ortho-coumaric* Acid, Chemoinformatic, Anti-Thrombotic Agents, COX-1, MOE Platform, Good Health and Well-Being

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INTRODUCTION

Multiple sources of data indicate that thrombotic illness has emerged as a significant health concern. This health condition begins with a hematological disturbance, resulting in the development of pathological blood clots in the body, ultimately leading to mortality. Until recently, aspirin and P2Y inhibitors, as anti-platelet agents, are reported to be the gold standard for the treatment of vaso-occlusive disease. Nevertheless, due to new discoveries about the detrimental consequences of the medication, including thrombocytopenia and neutropenia, thrombotic thrombocytopenic purpura, and aplastic anemia, the practicality of its use in clinical settings has been restricted. Subsequently, throughout the past several decades, there have been reports indicating the emergence of resistance to certain platelet-aggregating drugs. Therefore, it is essential to continue searching for novel anti-platelet agent candidates.[1,2,3]

Cyclooxygenase-1 (COX-1) as a protein that is significant in platelet aggregation, is expressed by some tissues and regulates basal prostaglandin points. Drugs that alter prostaglandin production diminish inflammatory responses, including platelet aggregation.

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When platelet activation occurs, free arachidonic acid is released from the phospholipid membrane, which is further converted to prostaglandin (PG) G2 by the enzyme COX-1. Next, PGG2 is transformed into PGH2 and Thromboxane A2 (TxA2). Following TxA2's binding to TP receptors, the Gq protein is activated, changing platelet shape, degradation, and aggregation.[4] Aspirin is one example of a COX-1 inhibitor that only blocks the TxA2 route; it has no effect on the P2Y pathway. Therefore, our research seeks to design pharmaceutical molecules with anti-thrombotic properties, specifically targeting the inhibition of the COX-1 enzyme. Plenty of studies on the anti-inflammatory qualities of Kaempferia galangal and its cinnamic components led to the interest in developing cinnamic acid derivatives as anti-platelet medicines.[5] The objective of this work is to investigate the interaction between 17 derivatives of *ortho*-coumaric acid or *ortho-methoxy cinnamic* acid (MCA) and COX-1 receptors and synthesize the potential compounds of MCA. The Molecular Operating Environment (MOE) will be employed to analyze these interactions, to assess their potential as novel anti-platelet agents. The bond energy between each ligand and the target receptor will be computed by this software and shown as the S score. The MOE approach was selected due to its superior accuracy compared to other current methods. On top of that, this study adopts silico modeling to forecast the physicochemical characteristics and pharmacokinetic profiles of these molecules, considering the significance of pharmacokinetic features in medication development.[6]

EXPERIMENTAL

Drug-likeness

ortho-Coumaric acid and its derivates structure (Table-1) were drawn by the ChemDraw program, translated into SMILES format, and processed using Swiss-ADME webserver to predict their drug-likeness properties. A number of characteristics, including torque, molecular mass, log P, and the capacity of molecules to provide and receive hydrogen, were anticipated.[7]

Molecular Docking

The receptors used COX-1 (PDB. 1EQH) downloaded in PDB file format from the RCSB protein data bank website (https://www.rcsb.org/) and Flurbiprofen (FLP) as a native ligand (Figure 1). Before the docking was started, the docking study was validated by re-docking the receptor to the original ligand. The validation is accepted if the root mean square deviation (RMSD) value is <2.0 Å. The docking method was established by the Molecular Operating Environment (MOE) platform version 2022.02. Using the triangle matcher algorithm, the docking investigation was carried out in the ligand atom site by determining the affinity dG in ten positions for every molecule. The interaction energy between the ligand and receptor was represented by the S score, which was the result of this docking study.[8,9]

Synthesis

15 mmol MCA was dissolved in 5 ml of benzene and then one drop of pyridine and thionyl chloride was added in a quantity of 2.4 equivalents and the mixture was refluxed overnight in the presence of nitrogen gas. The mixture was dried using the rotary evaporator until *o*-methoxy cinnamoyl chloride (MCC) was produced. 7.5 mmol MCC was dissolved in dichloromethane, reacted with ammonium thiocyanate (10 mmol), and one drop of PEG 400 was added to the mixture. Subsequently, the mixture was irradiated in a microwave at 132W for 1.5 min. After that, 7.5 mmol aniline derivatives were added and irradiated for 2 min. The mixture was further acidified to remove the pyridine with a 2N HCl solution. Next, the 10% $NaHCO_3$ solution was added to neutralize the crude product and washed with distilled water. The precipitate was filtered and purified by recrystallization using appropriate solvents.[10]

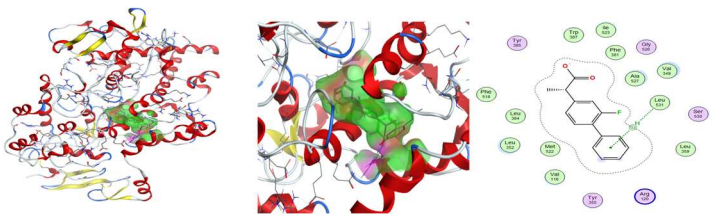
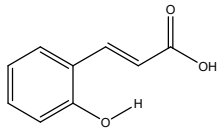
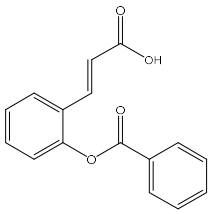
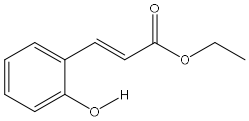
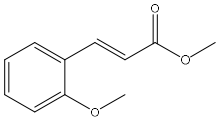
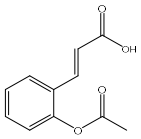
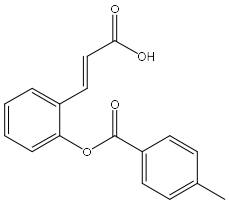
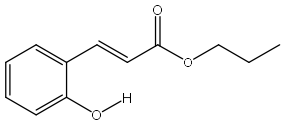
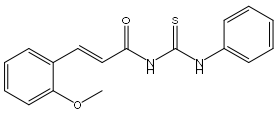
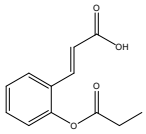
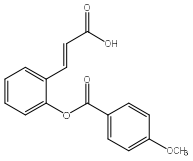
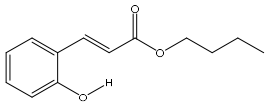
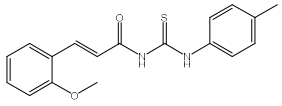
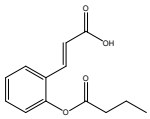
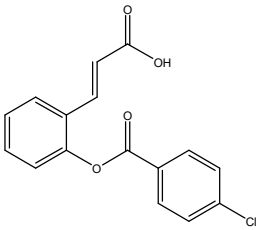
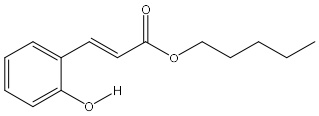
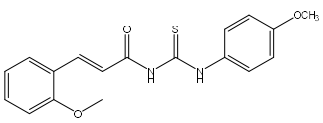
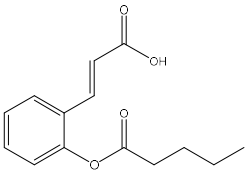
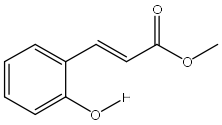
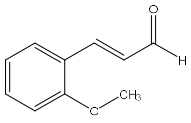
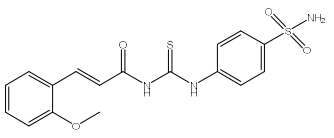


Fig.-1: Structure of COX-1 Receptor (PDB ID: 1EQH chain A) (left) and its Native Ligand (FLP) (right)

Table-1: Chemical Structures of *ortho*-Coumaric Acid Derivates

 CA1	 CA6	 CA11	 CA16
 CA2	 CA7	 CA12	 CA17
 CA3	 CA8	 CA13	 CA18
 CA4	 CA9	 CA14	 CA19
 CA5	 CA10	 CA15	 CA20

RESULTS AND DISCUSSION

Drug-likeness

The drug-likeness character can be evaluated using Lipinski's rule of five. The result is every CA derivative meets the criteria (Table-2). Therefore, it is anticipated that CA derivatives can be administered orally and are well absorbed by the gastrointestinal tract. The assessment of drug-likeness has significant importance within the field of drug development since it relies on the analysis of chemical structures and physicochemical features.[11,12] The Lipinski rule encompasses many criteria for evaluating the drug-likeness

of a molecule. These criteria include a molecular weight below 500, a computed octanol/water partition coefficient (log P) less than or equal to 5, a minimum of 5 hydrogen bond donors (HBD), and a minimum of 10 hydrogen bond acceptors (HBA). The SWISS ADME program is utilized to identify shared properties among drugs or to compare the properties of drugs (positive sets) with those of other compounds (e.g., negative sets, often chemical reagents). Consequently, physicochemical properties such as lipophilicity, solubility, permeability, metabolic stability, and affinity are commonly evaluated, yielding the results presented in Table-2.

Table-2: The Physicochemical Properties of *ortho*-Coumaric Acid Derivates

Code	MW	LogP	Bond Rotation	HBA	HBD	TPSA	Lipinski Rule	Bioav. Score
CA1	164.16	1.40	2	3	2	57.53	Yes	0.85
CA2	206.19	1.67	4	4	1	63.60	Yes	0.85
CA3	220.22	2.01	5	4	1	63.60	Yes	0.85
CA4	234.25	2.33	6	4	1	63.60	Yes	0.85
CA5	248.27	2.73	7	4	1	63.60	Yes	0.85
CA6	268.26	2.87	5	4	1	63.60	Yes	0.85
CA7	282.29	3.22	5	4	1	63.60	Yes	0.85
CA8	298.29	2.86	6	5	1	72.83	Yes	0.85
CA9	302.71	3.42	5	4	1	63.60	Yes	0.85
CA10	178.18	1.82	3	3	1	46.53	Yes	0.55
CA11	192.21	2.09	4	3	1	46.53	Yes	0.55
CA12	206.24	2.52	5	3	1	46.53	Yes	0.55
CA13	220.26	2.77	6	3	1	46.53	Yes	0.55
CA14	234.29	3.11	7	3	1	46.53	Yes	0.55
CA15	162.19	2.03	3	2	0	26.30	Yes	0.55
CA16	176.21	2.31	3	2	0	26.30	Yes	0.55
CA17	312.39	3.26	7	2	2	82.45	Yes	0.55
CA18	326.41	3.56	7	2	2	82.45	Yes	0.55
CA19	342.41	3.23	8	3	2	91.68	Yes	0.55
CA20	391.46	2.11	8	5	3	150.99	Yes	0.55

All substances that were subjected to testing have demonstrated favorable characteristics for oral absorption. AMES toxicity of CA-17-CA19 generated negative results, according to Nofianti et al. (2019), suggesting that none of the test chemicals is expected to trigger genetic alterations. Additionally, it stated that the products' LD50 was above 0.477, indicating that they are safe for use in humans due to their high levels.[13]

Molecular Docking

A molecular docking study was performed using the MOE platform in order to predict affinity between CA derivates with COX-1 enzyme. These processes were carried out in the COX-1 enzyme's crystal structure (PDB ID: 1EQH) chain A. The procedure underwent validation, resulting in an average root mean square deviation (RMSD) of 1.04. The S Score findings of CA derivatives are depicted in Fig.-2.

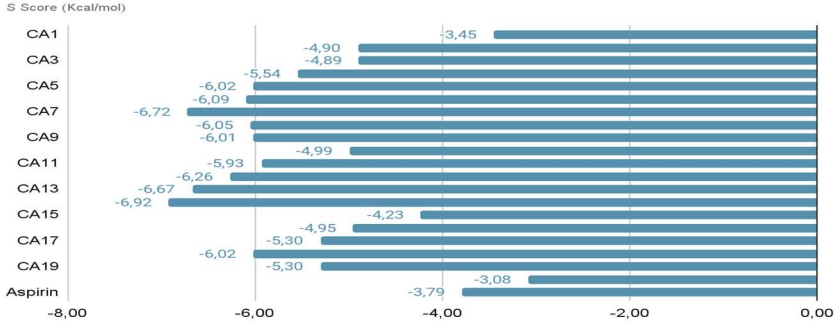


Fig.-2: Barchart of the S Score *o*-Coumaric Acid Derivates and Aspirin by MOE Platform and PDB ID 1EQH (x= S score, y=sample)

According to the findings shown in Fig.-2, it is evident that thiourea derivatives of CA have potential as anti-thrombotic agents. Therefore, these compounds will be synthesized. Their interactions were visually represented in Fig.-3.

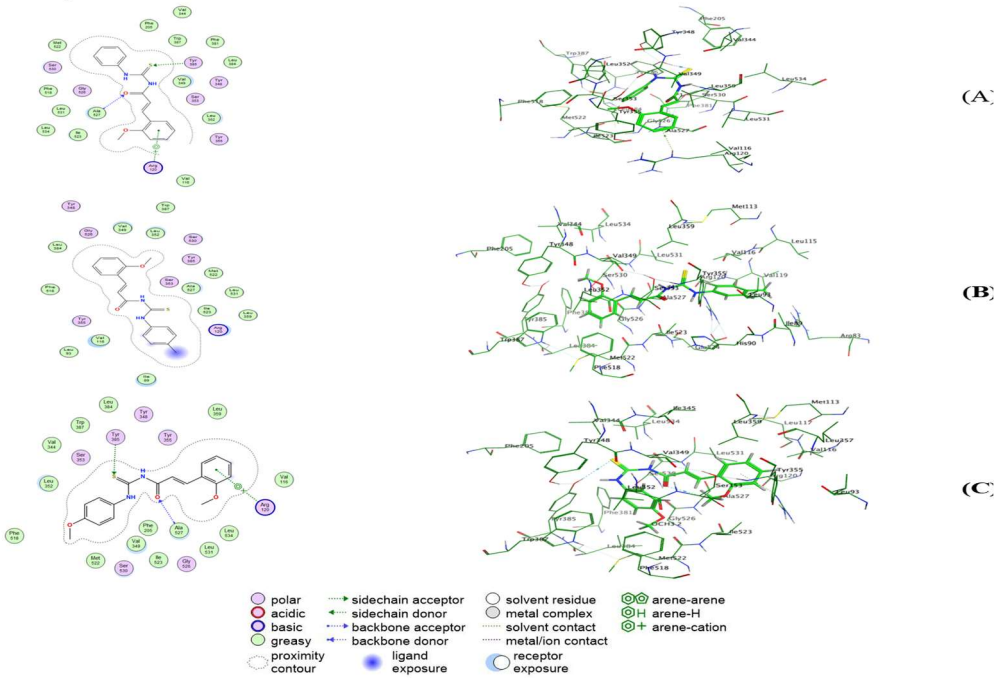


Fig.-3: Interaction between *o*-coumaric Acid Derivates and COX-1 Receptor (A) CA17 (B) CA18 (C) CA19

Molecular docking and virtual screening methodologies are efficient, cost-effective, and dependable techniques employed in the identification of prospective protein targets and the discovery of novel pharmaceuticals via rational drug design (RDD) or computer-assisted drug design (CADD). RDD or CADD are now used to quickly annotate and evaluate large pharmacology libraries.[14] Validation is conducted in order to demonstrate that the methodology employed produces accurate outcomes in accordance with the true value.[15] Many platforms can be used in molecular docking, such as the MOE platform, which makes more poses from the ligand to search favorable binding configurations with receptors. All of the poses were calculated using the London dG scoring function and represented by the S score.[16] S score is estimated by equation (1).

$$\Delta G_{LdG} = c + E_{flex} + \sum_{h-bonds} c_{hb} f_{hb} + \sum_{metal-lig} c_m f_m + \sum_{atomsi} \Delta D_i \qquad (1)$$

E flex represents the estimation of ligand entropy. Then, c, c hb, and c m are constants. Meanwhile, *f*_hb and *f*_m serve as metrics for assessing geometric imperfections in protein-ligand and metal-ligand interactions. Figure-3 illustrates that all derivatives of CA containing a thiourea moiety have comparable interactions with aspirin, particularly in their interaction with serine, a residue located at the active site responsible for the acetylation of the acetyl group in aspirin, leading to its antithrombotic activity.[17] In addition to serine, an inhibitor of the COX-1 enzyme, there exists a distinctive interaction with tyrosine, a crucial amino acid involved in the mediation of arachidonic acid conversion.[18] The visualization of ligand-receptor interaction showed that the most contributing interaction with amino acids is hydrophobic interaction. Nevertheless, the presence of hydrogen-bond interactions also played a role in determining the affinity between the ligand and receptor, thereby influencing their activity. Thiourea group is an important pharmacophore in many drugs, exhibiting promising potential as non-anionic antiplatelet agents. The presence of the thiourea group has been observed to possess inhibitory effects on the generation of tyrosyl radicals within the thromboxane A2 (TxA2) pathway.[19,20]

Synthesis

One of the CA derivates that has anti-thrombotic activity is *o-methoxy cinnamic* acid (MCA), so this compound was used as a starting material in the synthesis process. **Figure-4** illustrates the schematic representation of the synthetic process for thiourea derivatives employing microwave radiation as the primary energy source.

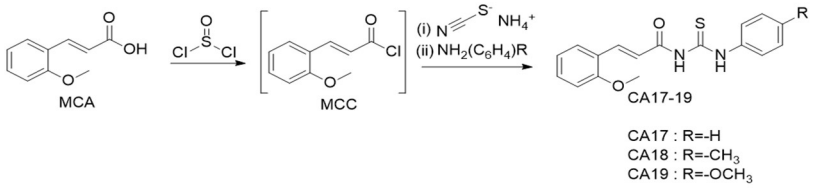


Fig.-4: Synthesis Scheme of Thiourea Derivates of CA

The physicochemical properties of the synthesis products and the spectral characteristics of those compounds are listed in the statements below:

CA17:(*E*)-3-(2-methoxyphenyl)-*N*-(phenylcarbamothioyl)acrylamide. yellow amorphous powder, mp: 166-167ºC. IR (KBr; cm^{-1}): 3177 (-N-H, amide, 2°); 3026(-N-H, amine, 2°); 1673(-C=O); 1591(-C=C-, alkene); 1514(-C=S); 1154(-CO-C); 748 (aromatic ring ortho- substituted). UV/Vis λmax (EtOH) nm (log ε): 298. ^{1}HNMR(pyr-d6;ppm) : 3.55 (3H,s); 6.89 (1H,d, *J*=16Hz); 6.90 (1H,d, *J*=8Hz); 6.94 (1H, t, *J*=8Hz); 7.33 (1H,d, *J*=7Hz); 7.35 (1H, dd, *J*= 3, 5 Hz); 7.37(2H, d, *J*=8Hz); 7.55 (1H,s); 7.98 (2H,d, *J*=6Hz); 8.41(1H,d, *J*=16Hz); 12.66 (1H,s); 13.43 (1H, s). ^{13}CNMR (pyr-d6; ppm) : 57.4; 113.9; 122.8; 123.2; 125.4; 126.6; 128.4; 130.0; 130.0; 131.0; 132.7; 134.5; 141.1; 143.6; 161.2; 170.0;182.3. HR-ESI-MS (positive) m/z : 335.0824 $[M+Na]^+$ (calcd. for $C_{17}H_{16}O_2N_2NaS$: 335.0825.

CA18:(*E*)-3-(2-methoxyphenyl)-*N*-(*p*-tolylcarbamothioyl)acrylamide. yellow amorphous powder, mp: 203-204ºC. IR (KBr; cm^{-1}): 3223 (-N-H, amide, 2°); 3025(-N-H, amine, 2°); 1679 (-C=O); 1592 (-C=C-, alkene); 1538 (-C=S); 1146 (-CO-C); 744 (aromatic ring *ortho*- substituted). UV/Vis λmax (EtOH) nm (log ε): 298. ^{1}HNMR(pyr-d6;ppm) : 2.18 (3H, s); 3.55 (3H,s); 6.89 (1H,d, *J*=8Hz); 6.90 (1H, d, *J*=16Hz); 6.94 (1H,t, *J*=7Hz); 7.15 (2H, d, *J*=8Hz); 7.32 (1H,d, *J*=8Hz); 7.34 (1H, dd, *J*=3, 6 Hz); 7.55 (1H,d, *J*=7Hz); 7.85 (2H, dd, *J*=2,8Hz); 8.41(1H,d, *J*=16Hz); 12.64 (1H,s); 13.36 (1H, s). ^{13}CNMR (pyr-d6; ppm) : 21.3; 55.9; 113.9; 122.8; 123.2; 125.4; 126.6; 112.4; 121.4; 121.7; 124.9; 130.1; 131.1; 136.5; 141.9; 159.7; 168.4;180.7. HR-ESI-MS (negative) m/z: 327.1163 $[M–H]^-$ (calcd. for $C_{18}H_{19}O_2N_2NaS$: 327.1162).

CA19:(*E*)-3-(2-methoxyphenyl)-*N*-((4-methoxyphenyl)carbamothioyl)acrylamide. yellow amorphous powder, mp: 183-184ºC. IR (KBr; cm^{-1}): 3160 (-N-H, amide, 2°); 3022(-N-H, amine, 2°); 1678(-C=O); 1615 (-C=C-, alkene); 1520(-C=S); 1538(-CO-C); 760 (aromatic ring *ortho*- substituted). UV/Vis λmax (EtOH) nm (log ε): 282. ^{1}HNMR(pyr-d6; ppm) : 3.55 (3H,s); 3.63 (3H,s); 6.89 (1H,d, *J*=8Hz); 6.94 (1H, t, *J*=7Hz); 6.96 (1H,d, *J*=9Hz); 6.97 (1H, d, *J*=16Hz); 7.32 (1H, dd, *J*= 2, 9 Hz); 7.34 (1H, d, *J*=6Hz); 7.54 (1H,dd, *J*= 2,8 Hz); 7.83 (2H, d, *J*= 9Hz); 8.39 (1H,d, *J*=16Hz); 12.61 (1H,s); 13.25 (1H, s). ^{13}CNMR (pyr-d6; ppm) : 55.9; 56.0; 112.4; 114.7; 114.8; 114.9; 121.7; 123.9; 126.8; 129.9; 131.3; 133.1; 141.9; 158.9; 158.9; 159.9; 168.4; 181.2. HR-ESI-MS (negative) m/z: 343.1110 $[M – H]^-$ (calcd. for $C_{18}H_{19}O_3N_2NaS$: 343.1110. The molecular composition of CA-17 exhibited the incorporation of seventeen carbon atoms, sixteen proton entities, two nitrogen atoms, two oxygen atoms, and one sulfur atom. The confirmation structure was obtained by the analysis of HR-ESI-MS and NMR spectra. The infrared (IR) spectra exhibited the absence of broadening and upward shifts in the peaks corresponding to intermolecular hydrogen bonding involving carboxylic acid groups in MCA, change into thiocarbamothioyl groups, manifesting as a band at wavenumbers 3463 (-N-H, primer, 1°) and 3223(-N-H, amine, 2°). The alkene of CA-17 was confirmed by two signals on H = 6.89 (1H, d, J = 16 Hz) and 8.41 (1H, d, J = 16 Hz), indicating that the double bond existed in the trans isomeric form.[21] In contrast to MCA, CA-18 has a structural composition containing eighteen carbon atoms, nineteen proton entities, two nitrogen atoms, three hydrogen atoms, and one sulfur atom. The alterations were observed by the analysis of its HR-ESI-MS and NMR spectra. Alteration of the carboxylic acid moiety into thiocarbamothioyl groups was performed at IR spectra on the wave number 3177 cm^{-1} (-N-H, amide, 2°); and 3026 cm^{-1} (-N-H, amine, 2°). Two signals indicated the

presence of the alkene double bond on H = 6.90 (1H, d, J = 16 Hz) and 8.41 (2H, d, J = 16 Hz), indicating that the alkene of CA-18 was the trans isomer form.[21] The CA-19 compound showed an increase in the number of eight carbon atoms, eight hydrogen atoms, two nitrogen atoms, and one sulfur atom, as confirmed by both NMR and HR-ESI-MS spectra. This data was also verified by IR spectra, which displayed the conversion of the carboxylic acid group to a thiourea group in the form of a loss of the band at 3000–3400 cm-1 to a thiocarbamoyl group. The spectral profile of CA derivatives (CA17-CA19) is related to that of previous studies that synthesized thiourea using the meta isomer of MCA as the starting material.[10,20] All compounds are prospected as novel anti-thrombotic candidates.

CONCLUSION

The majority of CA derivatives have a higher degree of interaction with the COX-1 enzyme compared to CA. All of the derivatives exhibited favorable characteristics for oral absorption. Therefore, it may be inferred that these derivatives possess potential as anti-thrombotic agents.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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