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Original Article

Study on the Synthesis and Hypolipidemic Activities of Coumarin Oxime Esters Derivatives

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ABSTRACT

Aim: The major objective of this research was to synthesize and evaluate the hypolipidemic Activities of Coumarin Oxime esters and develop the possible target. **Materials and Methods:** Using salicylaldehyde and ethyl acetoacetate as raw materials, coumarin-3-carboxylic acid was synthesized by Knoevenagel reaction, and then reacted with hydroxylamine hydrochloride to form oxime, which was then dehydrated and condensed with niacin and acetylsalicylic acid respectively to obtain six coumarin oxime ester target compounds. MS and HNMR were MS and HNMR were employed to confirm the structures of the examined compounds. to validate the chemical structures of the investigated synthetics. The hypolipidemic effect of these compounds was evaluated by experimental mice models. The interaction of small-molecules and possible targets was assessed by Discovery Studio (v4.5). **Results:** The optimal reaction condition for oxime was as follows: n (3-acetyl coumarin): n (pyridine) = 1:30, the yield was 76.8%. The optimal reaction condition for synthesis oxime ester was as follows: the reaction time was 48 hr, the yield was 57.2%. The results of enzyme immunosorbent assay showed that the substances C1 and C4 both demonstrated specific lipid-lowering properties and were able to considerably decrease the triglyceride and total cholesterol levels in mice. Coumarin oxime nicotinate has a stronger effect on reducing serum triglyceride, while coumarin oxime aspirin has a stronger effect on reducing total cholesterol. The docking result indicated the 3QNT may be the possible hypolipidemic target of C1 with binding energy of -1.65 kcal/mol. **Conclusion:** It can be concluded that coumarin oxime esters would be carefully explored and developed as hypolipidemic drugs. The future research work should emphasis on the alteration of the coumarin oxime backbone at the mean time keeping the right-hand side of the nicotinic acid and aspirin structures.

Keywords: Coumarin, Oxime esters, Synthesis, Hypolipidemic, Targets.

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INTRODUCTION

Due to poor lifestyles and dietary habits, the prevalence of numerous cardiovascular illnesses has increased year by year alongside economic growth and rising living standards. In recent years, cardiovascular disease has developed into a "killer" that poses a danger to human health.[1,2] It has been observed that the prevalence of dyslipidemic illnesses such as hyperlipidemia and hypercholesterolemia in adults has grown dramatically over the last decade, as seen by significantly increased levels of total Triglycerides (TG) and Cholesterol (TC) in the blood.[3,4] Hyperlipidemia could readily result in huge potentially life-threatening disease, including atherosclerosis, coronary heart disease, and cerebral thrombosis.[5] The most common lipid-lowering drugs such as statins, fibrates, and nicotinic acids.[6] However, Long-term usage of these medications have shown certain toxic side-effects. For instance, statins may have negative effects on the nervous system, metabolism, and skeletal muscle. These reports are categorized as Statin-Associated Symptoms (SAS).[7,8] Damage to the liver and muscles are two of the most worrisome side effects of fibrates seen in clinical practice since their debut. Many of these reported adverse effects have also been deemed transient and manageable (e.g., gastrointestinal disorders, decreased libido, cutireaction.[9,10] Nicotinic Acids (NA) raise fasting plasma glucose levels in non-diabetic individuals. Other negative effects of NA include mild increases in liver enzymes and trioxypurine, queasiness, diarrhoea, low blood pressure, emesis,

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and the precipitation of angina in patients using vasodilators.[11,12] Hence, the hunt for lead compounds with hypolipidemic activity derived from natural active components and the creation of novel medications to efficiently limit hazardous side effects have become hot research topics in the realm of medicinal chemistry.[13]

Coumarins are a series of heterocyclic chemicals belonging to the benzopyrone family and are extensively distributed in higher plants of the Rutaceae, Umbelliferae, Asteraceae, Leguminosae, Rhamnaceae, Solanaceae and others.[14,15] Nowadays, coumarins are significant lead molecules in the development of new drugs. Several different biological functions, such as anti-bacterial, anti-neoplastic, anti-inflammatory, anti-coagulant, anti-glycemic, and antioxidation, have been attributed to coumarins in scientific studies.[16-21] Furthermore, coumarins and their derivatives have minimal toxicity, and their target organ toxicity is species-specific and non-genotoxic, which is correlated with the species' capacity to metabolize and detoxify. There is a definite threshold range for the harmful effects of coumarins and their derivatives, with toxic effects occurring only at dosages exceeding therapeutic levels and no hepatotoxic or carcinogenic effects in humans from daily use.[22,23] Unfortunately, the poor water solubility of coumarins and inclusion of a lactone ring in their molecular structure render them unstable under alkaline circumstances, restricting their therapeutic use.[24]

Niacin has been discovered to be effective as a vasodilator for the treatment of hyperlipidemia and as a vitamin for the prevention and treatment of pellagra and other niacin deficient illnesses Clinical studies have shown the effectiveness of lipid-lowering medications like[25] niacinamide and acipimox, which employ niacin as the parent nucleus for structural alteration.[26] Some medications, such as aspirin and its, are used as adjuncts with statins to treat hyperlipidemia and have an anticoagulant action that delays the onset of atherosclerosis.[7,27,28] For these reasons, to overcome the hypolipidemic activity of coumarins and enhance their shortcomings, this study synthesizes coumarin oxime analogues by changing the structure of coumarins in accordance with the collocation concept of medicinal chemistry. To develop active and stable coumarin-like lead compounds with hypolipidemic properties, the coumarin skeleton was esterified with nicotinic acid and aspirin to design and manufacture coumarin oxime ester derivatives, and preliminary tests on their hypolipidemic activities were conducted in this study. To further understand the possible biological mechanism of coumarin oxime ester, we selected seven common lipid-lowering medicine targets and performed corresponding drug-target docking investigations in this work.

MATERIALS AND METHODS

Chemistry

General: All chemical reagents were acquired from Sigma and are of the reagent grade. The chemicals were purified using column chromatography by silica-gel 60. (200-300 mesh, Merck). The amount of silica-gel that was utilized was about fifty to one hundred times more than the weight that was loaded onto the column. Thin-Layer Chromatography (TLC) was then used to supervise the eluates. A Mariner System 5304 mass spectrometer was employed to collect ESI Mass Spectra (MS), and a Bruker DPX 400 spectrometer was applied to capture 1H spectra.

Synthetic principles

Hexahydropyridine and glacial acetic acid were used to catalyze the aldol-type condensation of ethyl acetoacetate with active methylene and salicylaldehyde to create dehydrate 3-acetylcoumarin (Knoevenagel reaction). Later, hydroxylamine hydrochloride and 3-acetylcoumarin interacted to create coumarin-oxime. The required compound is created by reacting coumarin-oxime with nicotinic acid (derivatives)/aspirin (derivatives) and dehydrating it before condensing it with EDCI and DMAP. The synthetic approach was as described in Figure 1.

Methods for compound synthesis

Synthesis of 3-acetyl-2H-chromen-2-one (A)

Piperidine (0.005 mol) and ethyl acetoacetate (0.045 mol) were dissolved in 27 mL of anhydrous EtOH and agitated for 30 min at ambient temperature. The solution was stirred for a further 2 hr at 85°C after the addition of salicylide (0.041 mol) and glacial acetic acid (2 drops). TCL [EA: PE = 1: 2 as developing solvents] was used to monitor reactions. When the chemical reaction was finished, it returned to indoor temperature, and then a conical flask was filled with the reaction solution. the reaction solution was poured into a conical flask. 30 mL distilled water is then poured in. The concoction was ice-baked until the crystals had completely precipitated and filtered. 50% ethanol (8 mL × 2) was used to rinse the solid. The organic solvent was combined and a light-yellow solid of 5.78g was produced once the solvent was exhausted. Yield 75.0%.

Synthesis of (*E*)-3-(1-(hydroxyimino) ethyl)-2*H*-chromen-2-one (B)

Absolute ethyl alcohol (40 mL), pyridine (0.018 mol), and hydroxylamine hydrochloride (0.018 mol) were combined and agitated at 50°C for 30 min. Then 3-acetyl-2H-chromen-2-one (0.006 mol) was introduced, and the solution was refluxed for 3 hr. TCL [EA: PE = 1: 2 as developing solvents] was used to monitor reactions. The concoction was watered down with ice-water, and the solution was refrigerated overnight for recrystallization. 0.94 g yellow solid was obtained after filtering and washing the resultant precipitate with 3×4 mL of cold ethanol. Yield: 76.8%.

General synthesis of coumarin-oxime esters (C)

Relevant acids (3.29 mmol), EDCI (3.32 mmol), and DMAP (7.3 mmol) were supplied to a dry round-bottom flask. The admixture

was swirled for 30 min at ambient temperature. Compound B (3.26 mmol) was appended and reacted overnight at 0°C. The filtrate was watered down. The strata were divided, the organic phase was rinsed with sated $NaCl_{aq}$ and dehydrated by anhydrous Na_2SO_4. With lower pressure, organic phase was consolidated. The acquired crude substance was isolated by silica-gel column. This approach for coupling has efficiently accommodated different substituents and produced coupling products.

Biology

Animals: Kunming mice purchased from Anhui Medical University (Experimental animal number: SCXK (Anhui) 2017-001).

Kits: Triglyceride (TG) Test Kit (Nanjing Jiancheng Institute of Biological Engineering), Total Cholesterol (T-CHO) Test Kit (Nanjing Jiancheng Institute of Biological Engineering).

Lipid-lowering activity in Animal Models

A minimum of 7 days was allowed for adaptation after arrival. The 90 mice were randomized into nine groups at random: a blank group, a model control group, a 3-acetylcoumarin administration group, relevant coumarin derivants administration group (6 groups). 10 mice from each group were given the corresponding drugs at a dose of 100 mg/kg (0.2 mL/10g) by gavage, while the model control group was given the same amount of lysate once a day for 6 d. Within 20 hr before the last dose, the mice were injected intraperitoneally with 75% (v/v) egg yolk emulsion (0.5 mL/each). The experimental hyperlipidemia model was created by intraperitoneal injection of 75% (v/v) egg yolk emulsion (0.5 mL/each) into mice (fasted for 16 hr before the final dose). 1 hr after the final administration, blood was centrifuged and serum was separated (another group was taken without serum containing only reagents), and enzymatic testing was used to assess total cholesterol (TC) and triglyceride (TG) levels.

Docking analysis

Employing Discovery Studio (v4.5) with the graphical user interface DS-CDOCKER protocol, chemicals were docked into the 3D X-ray structures of typical lipid-lowering targets. Chem3D extreme 12.0 (Chemical Structure Drawing Standard; Cambridge Soft company, USA) was applied to create the 3D geometries of the abovementioned chemicals, and energy consumption was reduced by employing MMFF94 with 5000 iterations and a minimal RMS gradient of 0.10. These PDB numbers for the crystal structures of lipid-lowering targets were obtained from the RCSB Protein Data Bank. These proteins had their bound fluids and ligands removed, and the polar hydrogen had been added.

RESULTS AND DISCUSSION

Optimisation of the oxime synthesis process

As an acid binding agent, sodium bicarbonate was utilized to prepare compound B, however the yield was only 14.6%. The yield increased when pyridine was added as the acid binding

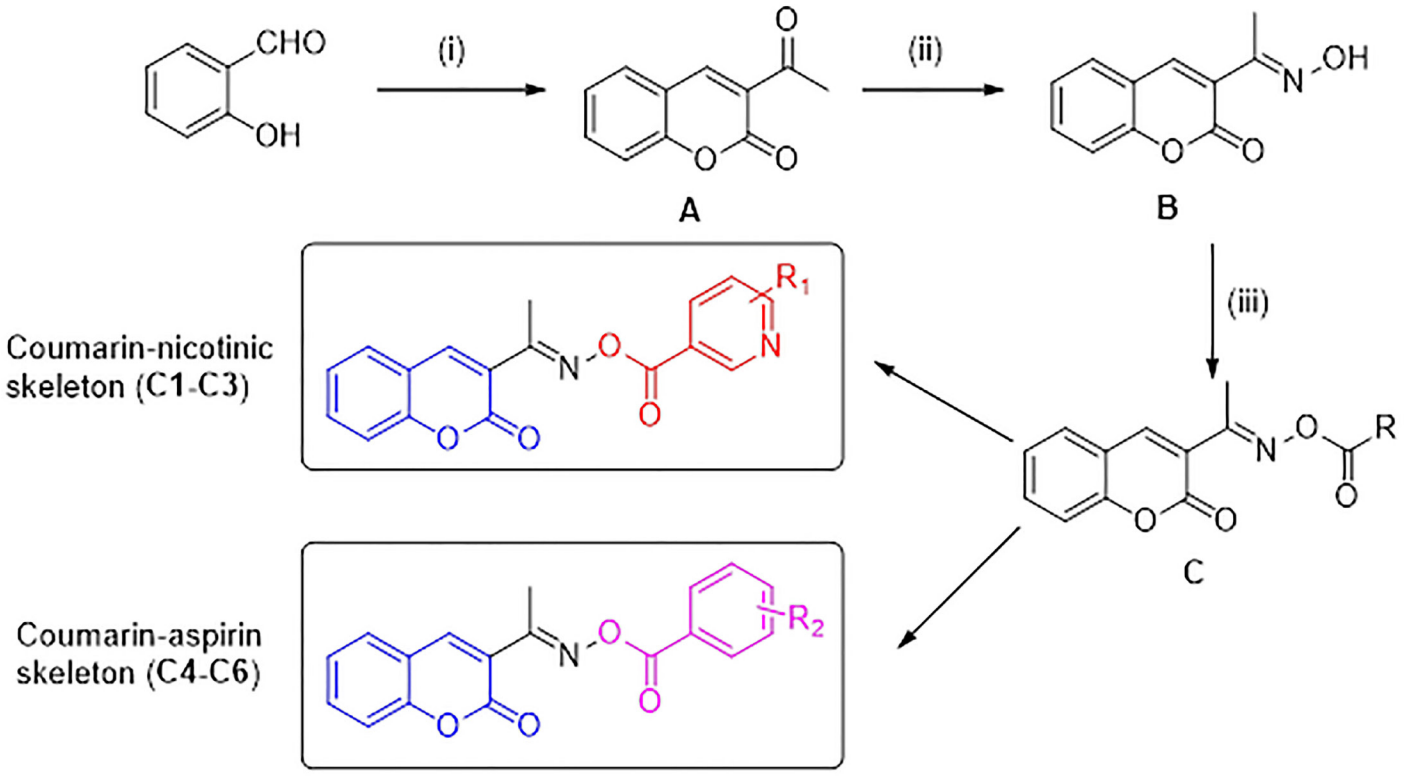

Figure 1: Synthesis pathway of the designed chemicals.

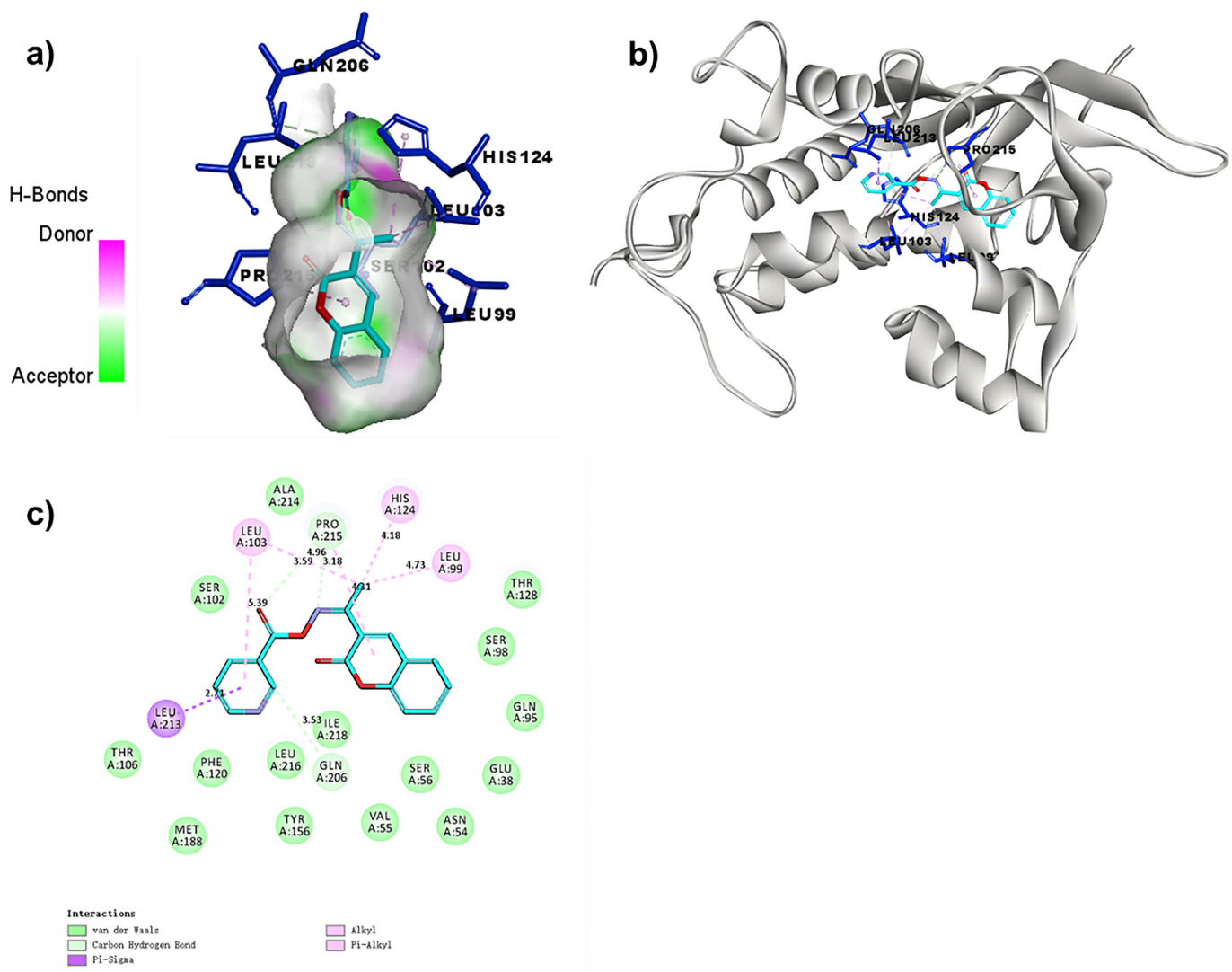

Figure 2: Docking investigations provide three interaction maps for compound C1: a) The hydrogen bond interaction graph, b) the 3D graph, c) the 2D diagram.

Table 1: Effect of compound B and pyridine ratio on isolate yield[a].

n(compound B): n(pyridine)	Isolate yield%
1:10	24.1%
1:20	46.3%
1:30	76.8%

[a]Reaction circumstances: The temperature of reaction is 50°C and the time is 3 hr.

Table 2: Effect of reaction time on yield[a].

Reaction time (h)	Isolate yield%
12	15.8%
24	36.9%
48	57.2%

[a] Reaction conditions: The reaction temperature is 0°C.

agent. The effect of the reaction ratio of 3-acetylcoumarin and pyridine on the yield was investigated and found that the yield increased with the increase of the amount of pyridine. Effect of compound B and pyridine ratio on isolate yield of products are showed in Table 1.

Optimisation of oxime ester synthesis processes

In the preparation of coumarin oxime nicotinate and coumarin oxime aspirin ester, it was discovered that the reaction must be properly regulated at 0°C. Increasing the reaction temperature, the reaction was partial and extremely low quantities of byproducts were readily formed. Reaction time was shown to be a significant factor in determining coumarin oxime nicotinate production, and it was discovered that yield rose as reaction time increased. Table 2 presents the findings regarding the influence of reaction time on the amount of coumarin oxime nicotinate that was separated.

Six coumarin-oxime esters have been isolated by column chromatography on silica gel. All isolated products were identified further by ^{1}H NMR and MS for characterization (Table 3).

Table 3: isolated yields, ^{1}H NMR and MS Data for the isolated coumarin-oxime esters.

Sl. No.	Chemical structure	Isolated yield	^{1}H NMR Data (400 MHz, DMSO)	MS Data
C1	image3	57.2%	9.22 (s, 1H), 8.91-8.86 (m, 1H), 8.45-8.41 (m, 1H), 8.36 (s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.69 (dd, *J* = 10.9, 4.8 Hz, 1H), 7.63 (dd, *J* = 7.6, 5.1 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 2.46 (s, 3H).	HRMS (ESI$^+$): 309.0806; calcd mass for $[C_{17}H_{13}N_2O_4]^+$ 309.0870.
C2	image4	68.5%	8.93-8.88 (m, 1H), 8.44-8.79 (m, 1H), 8.36 (s, 1H), 7.91(d, *J* = 7.8 Hz, 1H), 7.71(dd, *J* = 11.0, 4.6 Hz, 1H), 7.83(dd, *J* = 7.5, 4.8Hz, 1H), 7.45(d, *J* = 8.4 Hz, 1H), 7.41(t, *J* = 7.5 Hz, 1H), 2.42 (s, 3H).	HRMS (ESI$^+$): 344.0369; calcd mass for $[C_{19}H_{23}N_2O_2]^+$ 344.0378.
C3	image5	71.9%	8.17-8.12 (m, 1H), 8.33-8.28(m, 1H), 8.36 (s, 1H), 7.89(d, *J* = 7.7 Hz, 1H), 7.70(t, *J* = 11.5 Hz, 1H), 6.58(dd, *J* = 7.7, 5.0Hz, 1H), 7.45(d, *J* = 8.3 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 2.44 (s, 3H).	HRMS (ESI$^+$): 325.0775; calcd mass for $[C_{19}H_{23}N_2O_2]^+$ 325.0780.
C4	image6	74.2%	8.36 (s, 1H), 8.07 (t, *J* = 11.6 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.76-7.66 (m, 2H), 7.50-7.45 (m, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 2.37 (s, 3H), 2.28 (s, 3H).	HRMS (ESI$^+$): 388.0814; calcd mass for $[C_{19}H_{23}N_2O_2]^+$ 388.0796.
C5	image7	68.3%	8.37 (s, 1H), 8.10(t, *J* = 7.7 Hz, 1H), 7.87(d, *J* = 7.6 Hz, 1H), 7.59(d, *J* = 7.5 Hz, 1H), 7.38(d, *J* = 7.4 Hz, 1H), 7.21(s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.31(d, *J* = 7.8 Hz, 1H), 2.35 (s, 3H).	HRMS (ESI$^+$): 359.0280; calcd mass for $[C_{19}H_{23}N_2O_2]^+$ 359.0375.
C6	image8	61.2%	8.37 (s, 1H), 8.08(dd, *J* = 11.3, 5.0 Hz, 1H), 7.88(d, *J* = 7.6Hz, 1H), 7.84(d, *J* = 7.4 Hz, 1H), 7.39-7.34(m, 2H), 6.92(d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.6Hz, 1H), 7.33(d, *J* = 7.9 Hz, 1H), 2.37(s, 3H).	HRMS (ESI$^+$): 324.0797; calcd mass for $[C_{19}H_{23}N_2O_2]^+$ 324.0827.

*p<0.05.

Analysis of hypolipidemic activity

Although the high-fat cell model has the advantages of short experimental period, high controllability and low cost compared to other models. A cellular model, on the other hand, can only depict the impact that a medicine has on certain cells and cannot take the place of the organism as a whole since an organism is a complete organism and all of its tissues and organs are related to one another.[29-31] In addition, mice are easy to breed, cheap to model, stable in blood lipids and easy to sample,[32] so they were used to establish a high ester model in this study, and blood TC and TG as a lipid-lowering criteria.

Table 4 displays the outcomes of the *in vitro* enzyme-immunosorbent assay. The lipid-lowering activity of the parent skeleton compound, 3-acetylcoumarin, was not prominent, but the activities were altered after modifying the acid on the right side. Three nicotinic acid derivatives (C1, C2 and C3), C2 and C3 exhibited inferior activity compared to the nicotinic acid without any structural modification (C1). This indicated that the introduction of the nicotinic acid backbone is effective in reducing Total Cholesterol (TC) and Triglycerides (TG). These conclusions about the alteration of the backbone are equally valid for the aspirin coumarin derivatives. The three derivatives of benzoic acid modified (C4, C5, and C6), compound C4 with

Table 4: Effect of the target compounds C1-C6 on TC and TG in hyperlipidemic mice.

Compd.	TC/(mmol/L)	TG/(mmol/L)
Blank group	1.62±1.22	0.62±0.82
Model group	5.23±1.41	1.91±0.65
3-acetyl coumarin treated group	5.08±0.79	1.70±0.74
C1 treated group	2.09±0.68*	1.08±0.97*
C2 treated group	4.56±1.14*	1.83±0.89
C3 treated group	4.97±1.24	1.78±0.91*
C4 treated group	2.39±1.31*	1.14±0.87*
C5 treated group	5.15±1.27	1.43±0.61
C6 treated group	4.52±0.65*	1.63±0.79
*p<0.05		

Table 5: Docking study of small-molecules and possible targets.

Comp.	Target	PDB code	Binding energy [kcal/mol]
C1	Wild-type LOX-1	1YPQ	1332739843.62
	Human BChE	6I0B	0.00
	Bovine rhodopsin	1L9H	0.00
	HMG-CoA reductase	3CD7	-
	Peroxisome proliferator activated receptor α (PPAR-α)	3KDU	0.00
	Niemann-Pick C1 like 1(NPC1L1)	3QNT	-1.65
C4	LOX-112	1YPQ	636579352.17
	Human BChE	6I0B	-0.00
	Bovine rhodopsin	1L9H	0.00
	HMG-CoA reductase	3CD7	9870417941.96
	Peroxisome proliferator activated receptor α (PPAR-α)	3KDU	0.00
	Niemann-Pick C1 like 1(NPC1L1)	3QNT	21.60

aspirin backbone exhibited better hypolipidemic activities than others (C5, C6). Nevertheless, there are distinctions between the activities of these two series of derivatives, primarily in that the lowering of TG is greater when nicotinic acid is introduced to the coumarin oxime structure; the lowering of TC is stronger when aspirin is introduced. Consequently, the current investigation has prompted us in the future drug-design studies, we should concentrate on the alteration of the coumarin oxime backbone at the mean time keeping the right-hand side of the nicotinic acid and aspirin structures.

The docking results of small-molecules and possible targets

The lipid-lowering mechanisms are complicated, and the involved pharmacological targets are multiple.[33-36] To further understand the possible biological mechanism of coumarin oxime ester, we selected seven common lipid-lowering medicine targets and performed corresponding drug-target docking investigations. The docking result of small-molecules and possible targets were showed in Table 5. Docking data indicated that C1 and C4 compounds had no obvious binding activities on some targets (LOX-1, HMG-CoA reductase) with binding energy over 100. Furthermore, these two compounds have a binding energy of zero for targets such as 6I0B, 1L9H, and 3KDU, suggesting that they may have interact between the target protein and small molecules. C1 had a tightly linked to 3QNT with binding energy of -1.65 kcal/mol, that indicated the 3QNT may be the possible target of C1.

Figures 2a, b, and c, sequentially, illustrate the hydrogen bond interaction diagram, the 3D optimum configuration, and the 2D graph engaging with the NPC1L1 active site. Strong Pi-Sigma interactions exist between the amino acid residue Leu 213 and the pyridine ring of C1. There are also alkyl interactions between the pyridine ring and another oxygenated six-membered heterocycle with residues Leu103 and Pro 215. Besides, the Leu103 and His124 and Leu 99 also interact with the methyl group of C1. Furthermore, Van der Waals forces also exist between several 3QNT residues and C1. All of these interactions are crucial for stabilizing its binding affinity.

In this study, 3-acetylcoumarin was synthesized from salicylaldehyde and ethyl acetoacetate by the Knoevenagel reaction. Using 3-acetylcoumarin as the lead component, the synthetic pathway of the target compounds was then identified, and the synthesis process was optimized to find the ideal reaction conditions and ultimately six end-products were generated. HNMR and MS spectroscopy were used to confirm the structures of the target chemical compounds. Preliminary biological activity studies on all the synthesized compounds were carried out and compounds C1 and C4 exhibited decent hypolipidemic activities. Drug-target calculations indicate that NPC1L1 is the most likely target for the hypolipidemic lead compound C1. Hence, it is anticipated that coumarin oxime esters would be carefully explored and developed as hypolipidemic drugs.

CONCLUSION

In conclusion, this research aimed to synthesize and evaluate the hypolipidemic activities of Coumarin Oxime esters and identify potential targets. Six coumarin oxime ester compounds were successfully obtained through a series of reactions starting from salicylaldehyde and ethyl acetoacetate. Structural confirmation was performed using MS and HNMR techniques. The hypolipidemic effects of these compounds were assessed using experimental mice models, and the interaction with possible targets was analyzed through Discovery Studio. Compounds C1

and C4 exhibited specific lipid-lowering properties, significantly reducing triglyceride and total cholesterol levels in mice. Coumarin oxime nicotinate showed a stronger effect on reducing serum triglyceride, while coumarin oxime aspirin demonstrated a stronger effect on reducing total cholesterol. Docking analysis suggested that the 3QNT target may be a potential hypolipidemic target for C1. Overall, coumarin oxime esters hold promise as hypolipidemic drugs and further research should focus on modifying the coumarin oxime backbone while preserving the functional groups on the right-hand side of the nicotinic acid and aspirin structures.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PDB: Protein data bank; **EA:** ethyl acetate; **PE:** petroleum ether; **EDCI:** 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide; **DMAP:** 4-dimethylaminopyridine; **MMFF:** Merck molecular force field; **RMS:** root-mean-square; **NMR:** Nuclear Magnetic Resonance.

SUMMARY

Six coumarin oxime esters with derivatives were produced with optimized synthesis process. The hypolipidemic activities of these compounds were also evaluated by relevant hyperlipemia mice models. Among them, two compounds with nicotinic acid (C1) and aspirin (C4) skeleton presented superior lipid-lowering activities. The docking result indicated the 3QNT may be the possible hypolipidemic target of C1 with binding energy of -1.65 kcal/mol. All these concluded that coumarin oxime esters would be carefully explored and developed as hypolipidemic drugs.

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