ORIENTAL JOURNAL OF CHEMISTRY
An International Open Access, Peer Reviewed Research Journal
www.orientjchem.org
ISSN: 0970-020 X
CODEN: OJCHEG
2025, Vol. 41, No.(3):
Pg. 808-815

Synthesis of Novel Cholesteryl Carbamate Derivatives

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http://dx.doi.org/10.13005/ojc/410312

(Received: February 19, 2025; Accepted: May 11, 2025)

ABSTRACT

Nine novel cholesterol-derived carbamate derivatives, were synthesised by reacting cholesteryl chloroformate with various amines, including urea, acetamide, acrylamide, thiocarbazide, 4-methylthiosemicarbazide, aniline, p-methoxy benzylamine, 4-aminoquinaldine and piperidine. The derivatives contain diverse functional groups, such as carbamate linkages, sulphur-containing moieties, aromatic rings and aliphatic amines. The use of 4-dimethyl amino pyridine (DMAP) as a catalyst reduced the reaction time from 24 h to 12 hours. The reactions proceeded under mild conditions, with yields varying based on the nature of the amine. Secondary aliphatic amines afforded the highest yields, followed by hydrazine-based carbamates. The synthesised compounds were characterised using NMR spectroscopy, mass spectrometry. These cholesteryl carbamates provide a versatile platform for further modifications and show potential applications in chemical sensing, biomaterials and drug delivery.

Keywords: Cholesteryl chloroformate, Cholesteryl carbamates, 4-dimethyl amino pyridine (DMAP), Hydrazine-based carbamates, Cholesterol-based sensors.

INTRODUCTION

Cholesterol is a vital biological molecule that plays a central role in maintaining cell membrane integrity, steroid hormone synthesis and metabolic regulation. Its rigid polycyclic structure, combined with its amphipathic nature, makes cholesterol[1] an attractive scaffold for chemical modifications, enabling the design of derivatives with novel functionalities and reactivities. In recent years, cholesterol derivatives[2] have gained attention for their potential applications in biomedical research, chemical sensing, and materials science, due to their unique combination of hydrophobic and hydrophilic regions, as well as their biocompatibility[3-10].

Among cholesterol derivatives, carbamates[11-12] have emerged as important class of compounds due to their stability, tunable properties, and bioactive potential. These molecules exhibit excellent chemical and proteolytic stability, making them resistant to enzymatic degradation, an essential property for drug stability and prolonged activity. Additionally, carbamate-bearing molecules serve as peptide bond surrogates in many FDA-approved drugs, owing to their structural resemblance to amide bonds. This similarity allows them to maintain biological activity while enhancing membrane permeability and intercellular drug delivery. Modifying cholesterol frameworks with carbamate linkages enables fine tuning of chemical and physical

properties, allowing for precise functionalisation suited for targeted applications.

However, despite these promising attributes, the systematic synthesis and exploration of cholesterol-based carbamates with diverse functional groups remain relatively limited. Previous studies focus on simple amine-functionalized carbamates, with limited investigation of more complex derivatives incorporating amides and semicarbazides. Additionally, existing methods often suffer from long reaction times (>24 h), poor selectivity and less yields, limiting their practicality for large scale applications.

To address these limitations, this study focuses on the synthesis and characterisation of structurally diverse cholesterol-based carbamate derivatives[13-17] by reacting cholesteryl chloroformate with a range of amines, amides and semicarbazides. The incorporation of 4-dimethylaminopyridine (DMAP) as an organocatalyst, facilitates the process, significantly reducing reaction times, which typically exceeds 24 h in conventional methods.

DMAP is a highly nucleophilic acylation catalyst, that accelerates carbamate formation[18], via the formation of a reactive acyl pyridinium intermediate, which facilitates rapid acyl group transfer to nucleophiles. This mechanism not only reduces reaction time but also allows milder reaction conditions and improved product yields. Additionally, the nucleophilic nature of DMAP enhances selectivity and minimises side reactions leading to cleaner product profiles.

By systematically varying the functional groups and reaction conditions, we aim to develop structurally diverse carbamates with optimised properties, providing insights into their potential applications in materials science and bioactive compound development. This approach not only enhances reaction efficiency and selectivity but also offers a deeper mechanistic understanding of the role of catalysis in cholesteryl carbamate synthesis, paving the way for broader applications in medicinal chemistry and material science.

MATERIALS AND METHODS

All chemicals and solvents used in this study were of analytical or HPLC grade and obtained from reputed commercial sources. They were used without further purification unless otherwise specified. Cholesteryl chloroformate (98% purity) was procured from Sigma-Aldrich and served as the precursor for synthesizing cholesteryl carbamate derivatives. Dichloromethane (DCM), HPLC grade, was obtained from Fisher Scientific and used as a solvent for reactions and extractions. 4-dimethyl aminopyridine (DMAP), used as a catalyst for carbamate formation, was procured from Sigma-Aldrich (99% purity), anhydrous methanol (99% purity), and chloroform were purchased from VWR (Van Waters and Rogers) and used in work-up procedures. Anhydrous sodium sulphate, used to remove moisture during extractions, was obtained from Fisher Scientific. Silica gel (60-120 mesh) for column chromatography was supplied by Acros Organics and used for purification of the synthesized compounds.

Reaction progress was monitored using thin layer chromatography (TLC) on pre-coated silica gel plates and product purification was achieved through column chromatography, employing methanol/ chloroform mixture as the eluent. Melting points were measured using capillary tubes and are reported uncorrected. The ^{1}H NMR spectra were acquired on Varian or Agilent 400 MHz spectrometers at 300 K, in $CDCl_3$. Tetramethyl silane (TMS) was used as the internal standard, and chemical shifts were reported in δ (ppm) scale. All coupling constants and chemical shifts were determined from the ^{1}H NMR spectra. The ^{13}C NMR spectra were recorded using the same instrument, operating at 100 MHz High-resolution mass spectra (HRMS) were obtained using Waters G2-XS Q-TOF mass spectrometer, while electrospray ionisation (ESI) mass spectra were obtained using Agilent Mass Spectrometer.

Synthesis

General Procedure for the Synthesis of cholesteryl carbamate derivatives C1-C9 (Scheme1)

In dry DCM, one equivalent of the amine (e.g. A1) was added, followed by triethyl amine (0.03 mL,1.2 equivalents) at 0°C under a nitrogen atmosphere. A pre-prepared solution of cholesteryl chloroformate (B) (1 equivalent) in dry DCM (10 mL), was introduced gradually over 1 h while maintaining the temperature at 0°C. To facilitate complete addition, the reaction mixture was stirred at 0°C for 30 minutes. Subsequently, 4-dimethylaminopyridine (DMAP) was introduced as a catalyst (0.1 equivalent), and the reaction mixture was continuously stirred at room

temperature for (8-12 h) to allow completion. Upon completion of the reaction, as confirmed by TLC, the mixture was extracted using deionized water (3×10 mL). The organic layer was separated, dried over anhydrous sodium sulphate, and concentrated under reduced pressure to obtain a crude residue. The crude product was dissolved in a minimal quantity of DCM, followed by dropwise addition of methanol to induce precipitation. The precipitate formed was then collected by filtration, dried under vacuum in a desiccator, and further purified by column chromatography using silica gel (60-120 mesh) and a methanol/chloroform mixture as the eluent. This refined process yielded the final purified cholesteryl carbamate derivative (C1).

The general procedure described above was applied to all amines A1-A9 used in the study: urea, acetamide, acrylamide, thiocarbazide, 4-methylthiosemicarbazide, aniline, p-methoxy benzylamine, 4-aminoquinaldine, and piperidine. Each amine was treated in 1:1 molar ratio with cholesteryl chloroformate, and the reactions proceeded smoothly under the same conditions. The respective carbamate derivatives (C1-C9), were obtained in yields ranging from 70% to 90%, depending on the amine employed.

Characterisation of cholesteryl carbamate derivatives C1-C9: The synthesized derivatives (C1-C9) were analysed using ^{1}H and ^{13}C nuclear magnetic resonance (NMR) and mass spectrometry (MS) techniques, as described below:

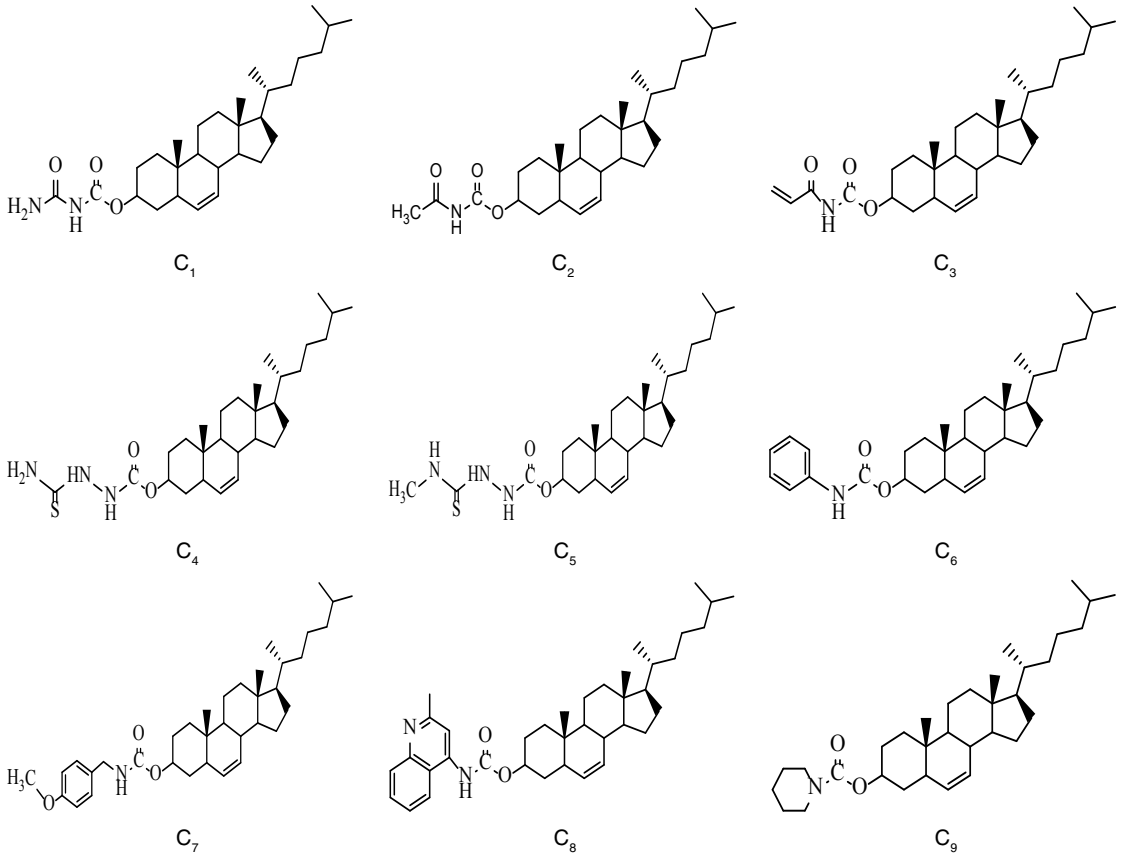


Fig. 1. Structures of synthesized cholesteryl carbamate derivatives (C1-C9)

3-Carbamoyloxy-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetra decahydro-cyclopenta[a]phenanthrene (C1)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.09 (s, 1H, NH), 6.78 (s, 2H, NH_2), 5.48 (m, 2H, C5-H and C6-H, olefinic protons), 4.70 (m, 1H, OCO-CH adjacent to carbamate), 2.24-1.30 (m, 42H, CH, CH_2, CH_3 aliphatic protons). MS (ESI): calculated for $C_{29}H_{48}N_2O_3$[M]:472.36; found at m/z 470.54[M-H].

3-Acetylcarbamoyloxy-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-tetra decahydrocyclopenta[a]phenanthrene (C2)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (s, 1H, NH carbamate), 6.50 (m, 2H, C5-H, and C6-H, olefinic protons), 5.35 (m, 1H, OCO-CH, carbamate linkage), 3.00 (s, 3H, CH_3), 2.40-0.68 (m, 42H, Aliphatic protons), ^{13}C NMR (101 MHz, $CDCl_3$, δ): 164.3 (C=O, acetyl), 149.0 (NH-CO-O), 140.72, 121.64, 71.67(C-O, methine), 56.69, 56.07, 50.57, 50.05, 42.24, 42.10, 39.70, 39.44, 37.17, 36.43, 36.11, 35.77, 31.83, 31.46, 28.16, 27.14, 24,22, 23.75, 22.74, 22.49, 21.01, 19.32, 18.63, 11.78 (cholesterol backbone and side chain). MS (ESI): Calculated for $C_{30}H_{49}NO_3$[M]:471.37; found at m/z 471.86.

3-(Acryloyloxy)-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl) tetra decahydrocyclopenta[a]phenanthrene (C3)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (s, 1H, NH carbamate),7.75 (dd,1H), 7.00 (dd,1H), 6.50 (dd, 1H), 5.35 (m, 2H, C5-H and C6-H, olefinic protons), 3.50 (m, 1H, OCO-CH, carbamate linkage), 2.40-0.65 (m, 42 H, CH, CH_2, CH_3 aliphatic protons). MS (ESI): calculated for $C_{31}H_{49}NO_3$ [M]:483.37; found at m/z 483.57.

3-(Carbamothiohydrazinyl-1-carboxylate)-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methyl-heptan-2-yl)tetradecahydrocyclopenta[a] phenanthrene (C4)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.70 (s, 2H, NH_2, thiourea), 8.19 (d, 1H, CSNH), 6.59 (d, 1H, NH), 5.40 (m, 2H, C5-H and C6-H, olefinic protons), 4.60 (m, 1H, OCO-CH, carbamate linkage), 3.8-0.62 (m, 42 H, CH, CH_2, CH_3 aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 182.00 (C=S, thiourea), 170.50 (C=O, carbamate), 80.00 (C-O, methine), 39.42, 34.94, 34.83, 34.74 34.49, 33.79, 31.90, 31.61, 31.46, 30.40, 30.27, 30.14, 30.09, 30.01, 29.67, 29.48, 29.34, 29.13, 28.92, 27.05, 22.66, 14.09 (cholesterol backbone and side chain). MS(ESI): calculated for $C_{29}H_{49}N_3O_2S$ [M]:503.35; found at m/z 502.21 [M-H].

3-(Methylcarbamothioyl)hydrazinyl-1-carbo-xylate-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetradecahydro- cyclopenta[a] phenanthrene (C5)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.40 (s, 1H, NH), 9.7 (d, 1H, NH, carbamate), 7.20 (s, 1H, NH, thiourea), 5.40 (m, 2H, C5-H, C6-H olefinic protons), 4.70 (m, 1H, OCO-CH, carbamate linkage), 3.30 (s, 3H, CH_3 attached to thiourea), 2.60-0.62 (m, 42 H m, CH, CH_2, CH_3 aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 170.10 (C=O, carbamate), 140.74, 140.73 (C=S, thiourea), 121.72 (C adjacent to thiourea), 121.68, 71.79 (C-O, methine), 66.57, 39.07, 37.08, 31.91, 31.42, 30.54, 30.17, 30.02, 29.68, 29.35, 27.07, 22.68, 19.71, 19.17, 14.11, 13.72 (cholesterol backbone and aliphatic side chain). MS (ESI): calculated for $C_{30}H_{52}N_3O_2S$ [M+H] : 518.37; found at m/z 518.37.

3-(Phenylcarbamoyloxy)-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)tetra decahydrocyclopenta[a]phenanthrene (C6)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.19 (s, 1H, NH, carbamate), 7.4–7.0 (m, 5H, aromatic protons phenyl group), 5.4 (m, 2H, C5-H, C6-H olefinic protons), 4.60 (m, 1H, OCO-CH, proton adjacent to carbamate carbonyl linkage), 2.62-0.62 (m, 42 H aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 154.95 (C=O, carbamate), 147.19, 106.49 (aromatic carbons, phenyl group), 56.12, 39.49, 39.21, 31.91, 30.27, 29.69, 29.51, 29.35, 28.00, 25.40, 24.28, 23.80, 22.80, 22.68, 22.55, 18.69, 14.11, 11.84 cholesterol backbone and side chain). MS (ESI): calculated for $C_{34}H_{51}NO_2$ [M]:505.39; found at m/z 505.25.

3-[(4-Methoxybenzyl)carbamoyloxyl]-(10S, 13R,17R)-10,13-dimethyl-17-((R)-6-methyl -heptan-2-yl) tetradecahydrocyclopenta[a] phenanthrene(C7)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.20 (d, 2H, ArH), 6.85 (d, 2H ArH), 5.38 (m, 2H, olefinic protons, C5-H and C6-H, olefinic protons), 4.50 (m, 1H, OCO-CH, carbamate linkage), 4.30 (d, 2H, benzyl CH), 3.80 (s, 3H, OCH), 2.40-0.60 (m, 43 H, aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.60 (C=O, carbamate), 139.80–114.00 (aromatic carbons, methoxybenzyl), 74.47 (C-O, methine), 56.10 (OCH , methoxy group), 55.29, 49.99, 44.47, 42.30, 39,71, 39.50, 38.54, 36.77, 36.55, 36.14, 35.77, 31.89, 28.22, 28.15, 28.00, 24.27, 23.81, 22.81, 22.55, 21.02, 19.32, 18.69, 11.84 (cholesterol backbone and side chain). HRMS (ESI+): calculated for $C_{36}H_{56}NO_3$ [M+H]:550.4260; found at m/z 550.4226.

3-[(2-Methylquinolin-4-yl)carbamoyloxyl-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methyl-heptan-2-yl)tetradecahydrocyclopenta[a] phenanthrene (C8)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20 (d,1H, ArH, quinoline C3-H), 8.04 (s, 1H, NH, carbamate), 8.02 (d, 1H, ArH, quinoline), 7.65-6.50 (m, 3H, ArH, quinoline), 5.40 (m,2H, C5-H and C6-H, olefinic protons), 4.68 (m, 1H, OCO-CH, carbamate linkage), 2.71 (s, 3H, CH_3 methyl on quinoline), 2.5-0.20 (m, 42H, CH, CH_2, CH_3 aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 159.93, (C=O, carbamate), 152.52, 140.82, 139.26, 129.54, 125.43, 123.05, 121.62 (aromatic carbons, quinoline), 118.56,114.05, 108.99 (C5-H and C6-H, olefinic protons) 71.78 (C-O, methine), 56.74, 50.12 (CH_2, quinoline), 50.11 (tertiary C-N), 42.30, 39.76, 39.70, 39.50, 37.24, 36.91, 36.58, 36.48, 36.17, 35.78, 31.42, 29.69, 28.22, 28.00, 24.28, 23.82, 22.81, 22.69, 22.55, 21.07, 18.70, 14.12, 11.85 (cholesterol backbone and side chain). HRMS (ESI+): calculated for $C_{38}H_{55}N_2O_2$ [M+H] : 571.4263; found at m/z 571.4550.

3-(Piperidine-1-carboxylate)-(10S,13R,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl) tetradecahydrocyclopenta[a]phenanthrene (C9)

^{1}H NMR (400 MHz, $CDCl_3$, δ): 5.40 (m, 2H, C5-H, C6-H, olefinic protons), 4.75 (m, 1H, OCO-CH, carbamate linkage), 3.40 (m, 4H, CH , piperidine), 2.49 (m, 6H, CH , piperidine) 2.47-0.40 (m, 42 H, aliphatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.13 (C=O, carbamate), 83.03 (OCO-CH), 56.66, 56.60, 49.96, 49.89, 44.66 (piperidine carbons), 42.28, 39.72, 39.63, 39.50, 38.69, 37.55, 37.03, 36.73, 36.57, 36.46, 36.15, 35.76, 31.86, 31.76, 28.22, 27.99, 27.33, 25.66, 24.43, 24.24, 23.80, 22.80, 22.55, 21.01, 18.69, 11.83 (cholesterol backbone and side chain). HRMS (ESI+): calculated for $C_{33}H_{56}NO$ $[M+H]^+$:498.4311; found at m/z 498.4364.

RESULTS AND DISCUSSION

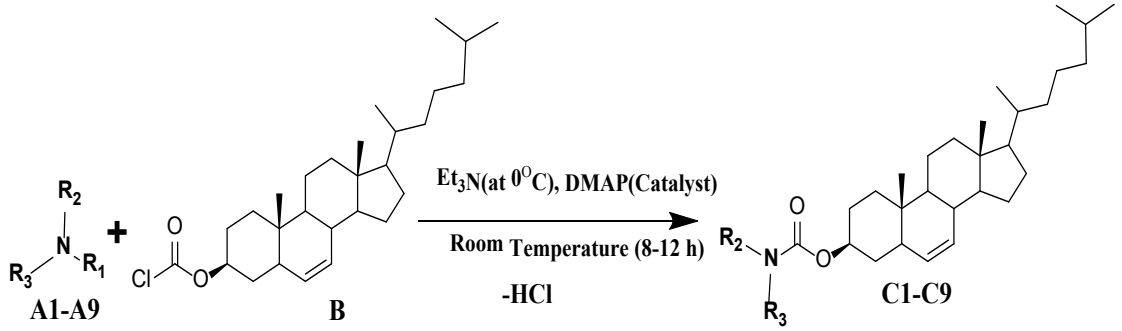
The nine cholesteryl carbamate derivatives (C1-C9) were synthesised to systematically explore the effect of different functional groups on the reactivity of cholesteryl chloroformate. This study highlights the versatility of cholesteryl chloroformate as a precursor for reactions with diverse functional group containing molecules.

As a representative example, the nucleophilic substitution reaction of cholesteryl chloroformate (B) with urea (A1) in DCM was initially carried out without using any catalyst. The reaction proceeded over an extended duration, yielding 60-70% of the product. However, upon employing 4-dimethylaminopyridine (DMAP) as a catalyst, the reaction time was reduced by half, and the yield significantly improved to 70-90%. The catalytic role of DMAP can be attributed to its ability to enhance the electrophilicity of cholesteryl chloroformate by forming an acyl pyridinium intermediate, thereby facilitating nucleophilic attack.

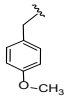
Following this optimised protocol, various NH- containing reactants, including urea, acetamide, acrylamide, thiocarbazide, 4-methylthiose-micarbazide, aniline, p-methoxybenzyl amine, 4-aminoquinaldine and piperidine (A1-A9), were reacted with cholesteryl chloroformate under mild conditions in the presence of DMAP. The reactions afforded the corresponding carbamate derivatives (C1-C9) in good to excellent yields (70-90%), demonstrating high efficiency and reproducibility of this approach. The incorporation of diverse functional groups enabled a systematic evaluation of steric and electronic influences on carbamate formation. Based on structural characteristics, the compounds were classified into amides, thiocarbazides, aromatic amines and aliphatic amines (Scheme 1, Figure 1).

The reactivity trends of cholesteryl chloroformate were analysed based on percentage yields and structural characteristics of the resulting carbamate derivatives. Amide derivatives (C1-C3) exhibited moderate reactivity, as the electron-withdrawing carbonyl group in the amide reduced the nucleophilicity of the nitrogen. Among them acetyl (C2) and acryloyl (C3) derivatives showed slightly higher reactivity than simple urea (C1). The acryloyl group, due to its conjugation and strong electron withdrawing effects, increased the electrophilicity of cholesteryl chloroformate, thereby facilitating the reaction. Thiocarbazide derivatives (C4-C5) displayed higher reactivity than amides, owing to the strong nucleophilicity of the thiocarbazide nitrogen. The presence of sulphur, with its larger atomic radius and higher polarizability, further enhanced nucleophilicity. However, the methyl substituted thiocarbazide derivative (C5), exhibited slightly reduced activity compared to (C4), indicating minor

steric hindrance from the additional methyl group. The amine derivatives (C6-C7) exhibited moderate reactivity, influenced by the delocalization of the nitrogen lone pair into the benzene ring, which reduced nucleophilicity. The phenyl derivative (C6) showed lower reactivity compared to (C7), where the presence of an electron donating group such as methoxy group, increased the yield by enhancing electron density on the nitrogen, thereby improving nucleophilicity. Aliphatic amine derivatives (C8-C9) exhibited the highest reactivity among all classes. The secondary amine derivative (C9), provided the highest yield, likely due to an optimal balance of steric and electronic factors, allowing for efficient nucleophilic attack on the cholesteryl chloroformate. While the primary amine (C8) also exhibited high reactivity, its slightly lower 80% yield suggested the occurrence of side reactions.



Scheme 1

Compound	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9
R_1	H	H	H	H	H	H	H	H	H
R_2	H	H	H	H	H	H	H	H	-
R_3									
m.p.	97°C-98°C	101°C-103°C	98°C-100°C	102°C-104°C	100°C-103°C	96°C-97°C	97°C-99°C	102°C-105°C	100°C-102°C
% Yield	70-80%	70%	70%	90%	90%	75%	80%	80%	90%

The structural integrity of the nine cholesterol-derived carbamate derivatives (C1-C9) was confirmed by NMR spectroscopy and mass spectrometry. ^{1}H NMR spectroscopy, revealed characteristic NH and carbamate functional group proton signals. The thiocarbazide derivatives exhibited distinct NH and SH peaks, confirming successful incorporation. ^{13}C NMR spectroscopy displayed characteristic carbonyl peaks (C=O) for the carbamate functionality along with expected chemical shifts for the cholesterol scaffold. However, some quaternary carbon signals, particularly those in the steroid core and the carbamate moiety, were observed with lower intensity or were not distinctly visible. This is likely due to their long relaxation times, peak broadening and overlapping signals in the complex steroidal framework, a common occurrence in cholesterol derivatives. Slight variations in the number of observed signals may also be attributed to factors such as molecular symmetry or dynamic effects. Similar challenges have been noted in previous studies on steroid-based molecules, where quaternary carbons exhibit weak intensity due to reduced magnetization transfer efficiency in conventional ^{13}C NMR experiments. Despite these limitations, the observed spectral data align well with the proposed structures, confirming successful synthesis. Mass spectrometry analysis, including High resolution mass spectrometry where applicable, further supported the molecular composition of the synthesised derivatives. For compounds where only ESI-MS data were available, the obtained m/z values were consistent with their calculated molecular weights, reinforcing structural information.

This study highlights the significant influence of functional groups on the reactivity of cholesterol-based carbamate derivatives. Electron withdrawing groups (e.g., acryloyl) enhanced electrophilicity, leading to higher reactivity.

Thiocarbazides exhibited high nucleophilicity, leading to higher reactivity. The secondary amine, piperidine (C9), showed the highest yield due to an optimal balance between steric hinderance and nucleophilicity. These derivatives offer potential applications in chemical sensing due to their tunable reactivity, and ability to interact with metal ions. as precursors in drug delivery systems. The cholesterol scaffold provides a stable yet modifiable framework for developing materials with tailored properties.

A comparative evaluation suggests that electron-donating groups (e.g., methoxy, in C7) enhance reactivity and solubility, while heterocycles (C8) may favor π-stacking or metal-ion coordination in sensing applications. The increased nucleophilicity in secondary amines (e.g., C9) translates to higher yields and may potentially improve biological membrane permeability. These cholesteryl carbamate derivatives can thus serve as molecular scaffolds for drug conjugation or as ligands in metal ion sensing. Notably, the thiourea and quinoline functionalities (C5, C8) are known for their strong metal chelation properties, suggesting their use in nickel/copper sensing platforms. The lipophilic steroid core facilitates efficient membrane interaction, while the carbamate linkage confers hydrolytic stability, making these compounds promising candidates for prodrug development and controlled-release applications.

CONCLUSION

Nine novel cholesterol derived carbamate derivatives (C1-C9) were successfully synthesised and characterised to evaluate the influence of different functional groups on the reactivity of cholesteryl chloroformate. The reactivity of the derivatives was strongly influenced by the electronic and steric properties of substituents with secondary amine C9 exhibiting the highest reactivity. A key feature of this work is the use of 4-dimethyl amino pyridine (DMAP) as a catalyst, which significantly reduced the reaction time from 24 h to 12 h enhancing reaction efficiency while maintaining high yields. Functional groups such as acryloyl (C3) and thiosemicarbazide derivatives (C4, C5) exhibited enhanced reactivity due to their electron-withdrawing and nucleophilic properties, respectively. The tunable reactivity of these derivatives suggests their potential applications in chemical sensing, bioactivity and material science. By leveraging the cholesterol scaffold, this work provides a foundation for designing functional materials with improved properties, opening avenues for further exploration in biomedical and industrial applications.

ACKNOWLEDGEMENT

We extend our gratitude to Osmania University for providing infrastructural facilities.

Conflict of interests

The authors do not have any conflict of interest.

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