Synthesis of New Functionally Substituted 9-Azabicyclo[4.2.1]nona-2,4,7-trienes by Cobalt(I)-Catalyzed [6π + 2π]-Cycloaddition of N-Carbocholesteroxyazepine to Alkynes

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Abstract: Catalytic [6π + 2π]-cycloaddition of N-carbocholesteroxyazepine with functionally substituted terminal alkynes and 1,4-butylenediol was performed for the first time under the action of the Co(acac)₂(dppe)/Zn/ZnI₂ three-component catalytic system. The reaction gave previously undescribed but promising 9-azabicyclo[4.2.1]nona-2,4,7-trienes (in 79–95% yields), covalently bound to a natural metabolite, cholesterol. The structure of the synthesized azabicycles was confirmed by analysis of one- and two-dimensional (¹H, ¹³C, DEPT ¹³C, COSY, NOESY, HSQC, HMBC) NMR spectra.

Keywords: cycloaddition; N-carbocholesteroxyazepine; alkynes; 9-azabicyclo[4.2.1]nona-2,4,7-trienes; cobalt(II) acetylacetonate

1. Introduction

Although some 9-azabicyclo[4.2.1]nonane derivatives were described for the first time back in the 1970s [1–5], they are still attracting the attention of synthetic chemists [6–15], largely related to their pronounced biological activity and high pharmacological potential [14]. The 9-azabicyclo[4.2.1]nonane cage is a key structural component of several important natural and synthetic alkaloids (anatoxin-a [6–14], pinnamine [13,16,17], bis-homoepibatidine [18,19], and UB-165 [20–27]), possessing properties of nicotinic acetylcholine receptor agonists in the central and vegetative nervous systems (Figure 1). Therefore, various analogues containing the 9-azabicyclo[4.2.1]nonane cage are actively being studied by pharmaceutical scientists as potential medicinal agents for the treatment of severe neurological disorders such as Parkinson’s and Alzheimer’s diseases, schizophrenia, and depression [21–29].

According to previously published data, an efficient method for the synthesis of 9-azabicyclo[4.2.1]nonane cages is based on the cycloaddition reactions of N-substituted azepines catalyzed by transition metal complexes [30]. However, these reactions have been studied rather superficially, being addressed in a few publications on the photoinduced cyclo-codimerization of tricarbonyl(η⁶-N-carboalkoxyazepine)chromium(0) [31–36] and tricarbonyl(η⁶-N-cyanoazepine)chromium(0) [37] with alkenes and alkynes. Meanwhile, data on catalytic versions of these reactions are scarcely reported in the literature, except for two examples of Cr(0)-catalyzed cycloaddition of N-carbomethoxyazepine [34] and N-carbothoxyazepine [38] to ethyl acrylate (Scheme 1). Hence, the catalytic cycloaddition of N-substituted azepines is an alternative approach to the synthesis of 9-azabicyclo[4.2.1]nonanes, and therefore, these reactions require further thorough investigation.

We previously reported [39–41] the development of an efficient one-pot synthesis of some substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes and 9-azabicyclo[4.2.1]nona-2,4-dienes based on the cobalt(I)-catalyzed cycloaddition of N-carbethoxy(phenoxy)azepines to alkynes, 1,3-diynes, and 1,2-diynes (Scheme 2).
Figure 1. Some biologically active azacycles containing the 9-azabicyclo[4.2.1]nonane skeleton.

Scheme 1. Chromium(0)-promoted and chromium(0)-catalyzed \([6\pi + 2\pi]\) cycloadditions of \(N\)-substituted azepines in the synthesis of 9-azabicyclo[4.2.1]nonadi(tri)enes.
In order to further develop the above promising trend towards new 9-azabicyclo[4.2.1]nonanes, and in view of the high relevance of the development of biologically active substances for the synthesis of new-generation pharmaceutical agents, we set ourselves the task of preparing 9-azabicyclo[4.2.1]nona-2,4,7-trienes containing a natural compound fragment in their molecules. It is well known that half of the currently existing medicinal drugs have been, and continue to be, developed on the basis of natural compounds’ skeletons and their numerous synthetic analogues. As the natural compound for the present work, we chose cholesterol, which performs very important functions in the human body [42–51]. Cholesterol is a structural component of cell membranes and provides their stability, participates in the biosynthesis of steroid sex hormones and corticosteroids, serves as a basis for the formation of bile acids and vitamin D, and also protects red blood cells from the action of hemolytic poisons. Thus, to our knowledge, the present study is the first to report on the catalytic \( [6\pi + 2\pi] \)-cycloaddition of \( N \)-carbocholesterolylazepine to alkynes in order to access new 9-azabicyclo[4.2.1]nona-2,4,7-trienes containing, additionally, cholesterol building blocks (Scheme 2). To this end, we emphasize here the novelty of our planned investigation, since we succeeded in preparing, for the first time, an \( N \)-carbocholesterolylazepine system.

**2. Results**

Keeping this task in mind, we set the goal to prepare the starting monomer, \( N \)-carbocholesterolylazepine. First, we carried out the reaction of commercial cholesteryl chloroformate with sodium azide, providing, in quantitative yield, cholesteryl azidoformate 1 in the conditions depicted in Scheme 3. Please see the Supplementary Figures S1–S6.

Next, thermolysis of cholesteryl azidoformate 1 in benzene at 125 °C (in an autoclave) gave the target \( N \)-carbocholesterolylazepine 2 with a yield of 60% (Scheme 4). Please see the Supplementary Figures S7–S12.
Scheme 3. Synthesis of cholesteryl azidoformate.

Scheme 4. Synthesis of N-carbocholesteroxyazepine.

With N-carbocholesteroxyazepine 2 in our hands, we investigated its cycloaddition to the terminal alkynes 3a–t. Thus, we found that the desired [6π + 2π]-cycloaddition process occurred, being catalyzed by the Co(acac)₂(dppe)/Zn/ZnI₂ (dppe-1,2-bis(diphenylphosphino)ethane) system [52–57] under developed conditions (10 mol% Co(acac)₂(dppe), 30 mol% Zn, and 20 mol% ZnI₂ in DCE (1,2-dichloroethane) as solvent, for 20 h at 60 °C) to afford substituted 9-azabicyclo[4.2.1]nona-2,4,7-trienes 4a–t with 79–95% yields (Scheme 5). The adducts were formed as two N-(CO)O-cholesteryl rotamers [33,34,39–41] in a 1:1 ratio, arising due to hindered rotation of the substituent around the CN bond. Please see the Supplementary Figures S13–S12.

Scheme 5. Cycloaddition of N-carbocholesteroxyazepine to alkynes. Reaction conditions: 2 (1 mmol), 3 (1.5 mmol), Co(acac)₂(dppe) (0.10 mmol), Zn (0.3 mmol), ZnI₂ (0.20 mmol), DCE (3 mL), 60 °C, 20 h. Yields calculated based on effective amounts of material isolated by column chromatography.

| R         | 4a (R: +Bu, 91%) | 4b (R: Ph, 89%) | 4c (R: o-MePh, 87%) | 4d (R: p-BuPh, 81%) | 4e (R: p-FPh, 86%) | 4f (R: SiMe₃, 85%) | 4g (R: (CH₂)₂OH, 79%) | 4h (R: (CH₂)₂OH, 89%) | 4i (R: (CH₂)₂CN, 86%) | 4j (R: (CH₂)₂CN, 92%) | 4k (R: (CH₂)₂Br, 88%) | 4l (R: (CH₂)₂COOEt, 90%) | 4m (R: (CH₂)₂SBr, 81%) | 4n (R: (CH₂)₂SBr, 88%) | 4o (R: (CH₂)₂SBr, 85%) | 4p (R: (CH₂)₂OH, 82%) | 4q (R: 2-phthalimidoethyl, 87%) | 4r (R: 2-phthalimidoethyl, 95%) | 4s (R: 1-naphthyl, 84%) | 4t (R: 9-phenanthrenyl, 79%) |
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It is well known that at elevated temperatures, the transition from one rotamer to another is accelerated. Therefore, we studied the exchange process between rotamers upon heating and calculated the energy barrier at an operating temperature of 333 K. The investigation of the temperature dependence of the NMR spectra of compound 4r in C7D8 at 333 K has shown the presence of coalescence of a number of characteristic signals in the 13C NMR spectrum—for example, the signal of the carbamide carbon atom C(10) (Figure 2). In this case, at room temperature, double signals of the carbamide carbon atom C(10) are observed with a difference of 0.05 ppm (δ) or 25 Hz in accordance with the frequency scale. The value of the energy barrier at 333 K (Tcoal.), calculated using the approximate formula or the Eyring equation (1) [58], was about 17 kcal/mol, which corresponds to the values of the barriers to hindered rotation around the amide bond. Please see the Supplementary Figures S118–S121.

\[ \Delta G^\ddagger = 19.14T_{coal.} \left( 9.97 + \log \frac{T_{coal.}}{\delta \nu} \right) \]  

(1)

![Figure 2](image-url)  
**Figure 2.** Fragments of temperature-dependent 13C NMR spectra of 4r in C7D8.

Our experiments clearly demonstrated the Co(acac)2(dppe)/Zn/ZnI2 three-component catalytic system [52–57] being not only tolerant but equally efficient for a large variety of the substituents (alkyl, phenyl, p-halophenyl, alcohol, nitrile, ester, sulfide, phthalimide, cycloalkane, naphthalene, and phenanthrene) in the starting alkynes.

In identical conditions, N-carbocholesteroxazepine 2 reacted as well with symmetrical disubstituted 1,4-butyne-1,6-diol 5 to give the [6π + 2π]-cycloadduct, 9-azabicyclo[4.2.1]nona-2,4,7-triene 6 (80% yield) as a 1:1 mixture of two N-(CO)O-cholesteryl-rotamers (Scheme 6). Please see the Supplementary Figures S113–S117.
3. Materials and Methods

3.1. General Procedures

Briefly, 1H, 13C spectra were measured in CDCl3 on a Bruker Avance-500 spectrometer (500 MHz for 1H; 125 MHz for 13C). High-resolution mass spectra (HRMS) were measured on an instrument (MaXis impact, Bruker Daltonik GmbH, Bremen, Germany) using a time-of-flight mass analyzer (TOF) with electrospray ionization (ESI). In experiments on selective collisional activation, the activation energy was set at the maximum abundance of fragment peaks. A syringe injection was used for solutions in MeCN (flow rate: 5 µL/min). Nitrogen was applied as a dry gas; the interface temperature was set at 180 °C. All solvents were dried and freshly distilled before use. All reactions were carried out under a dry argon atmosphere. Cholesteryl chloroformate, sodium azide, the terminal alkynes, alkynols, and ZnI2 were purchased from commercial sources and used without further purification. Co(acac)2(dppe), ethyl pent-4-ynoate, 5-bromopent-1-yn, and sulfanyalkynes were synthesized according to procedures described in the literature [59–61]. For column chromatography, silica gel from Acros Organics (Thermo Fisher Scientific, Geel, Belgium) (0.060–0.200 mm) was used.

3.2. Synthesis of Cholesteryl Azidoformate

A mixture of cholesteryl chloroformate (2.25 g, 5 mmol) and sodium azide (1.14 g, 17.5 mmol) in dry acetone (97 mL) was heated at 40 °C for 6 h with vigorous stirring. After this period, the reaction mixture was left to reach room temperature, when minerals were filtered off. The organic filtrate was concentrated under reduced pressure to dryness to provide crude cholesteryl azidoformate 1 (2.278 g, 100% yield with respect to cholesteryl chloroformate) as a white solid. This material was used as is in the next experiments without further purification.

3.3. Synthesis of N-Carbocholesteroxyazepine

A solution of cholesteryl azidoformate 1 (2.28 g, 5 mmol) in dry benzene (106 mL) was heated in an autoclave at 125 °C for 2 h with stirring, under autogenous pressure. After this period, the cooled reaction solution was stripped of benzene under reduced pressure. Chromatographic purification over silica gel (petroleum ether/ethyl acetate 20:1) afforded the target product 2 (1.517 g, 60% yield with respect to cholesteryl azidoformate) as a yellow solid.

3.4. Cycloaddition of N-Carbocholesteroxyazepine to Alkynes

Zinc powder (0.020 g, 0.3 mmol) was added to a solution of Co(acac)2(dppe) (0.066 g, 0.1 mmol) in DCE (1.5 mL) for 3a–f, h, j–l, n–p, r–t (in 1 mL DCE for 3g, i, m, q, 5) in a Schlenk tube under a dry argon atmosphere, and the mixture was stirred at room temperature for 2 min. Next, N-carbocholesteroxyazepine (0.505 g, 1.0 mmol), the alkyne (1.5 mmol) in DCE (1.5 mL) for 3a–f, h, j–l, n–p, r–t (in 2 mL trifluoroethanol for 3g, i, m, q, 5), and dry ZnI2 (0.064 g, 0.2 mmol) were added successively. After heating at 60 °C for 20 h, the reaction
was stopped by the addition of petroleum ether and stirring in air for 10 min to deactivate the catalyst. After filtration through a short pad of silica, the volatiles were removed under vacuum. Chromatographic purification over silica gel (petroleum ether/ethyl acetate 5:1 as eluent for 4a–p, s, t, 6; petroleum ether/ethyl acetate 2:1 for 4q, r) afforded the target products 4a–t, 6.

3.5. Characterization of the Products

Cholesteryl azidoformate (1): Yield 100% (2.278 g), white solid, m. p. = 96–97 °C, [α]D17 = 30.4 (c 0.48, CHCl3). 1H NMR (500 MHz, CDCl3): δH 5.42 (d, J = 3.5 Hz, 1H), 4.57–4.66 (m, 1H), 2.35–2.47 (m, 2H), 1.80–2.08 (m, 5H), 1.24–1.73 (m, 11H), 1.07–1.23 (m, 7H), 0.99–1.06 (m, 5H), 0.93 (d, J = 6.4 Hz, 4H), 0.88 (d, J = 6.3 Hz, 6H). HRMS (ESI-TOF): calcd. for C28H45N3O2Na [M + Na]+ 758.3360, found 758.3360.

N-Cardocholesteroxazepine (2): Yield 60% (1.517 g), yellow solid, m. p. = 124–125 °C, [α]D23 = 13.9 (c 0.50, CHCl3), Rf = 0.40 (petroleum ether/ethyl acetate 20:1). 1H NMR (500 MHz, CDCl3): δH 6.07 (s, 2H), 5.91 (s, 1H), 5.84 (s, 1H), 5.55 (s, 1H), 5.47 (s, 1H), 5.40 (s, 1H), 4.59–4.68 (m, 1H), 3.32–4.47 (m, 2H), 1.92–2.08 (m, 3H), 1.80–1.91 (m, 2H), 1.23–1.69 (m, 11H), 1.08–1.22 (m, 7H), 0.99–1.07 (m, 5H), 0.93 (d, J = 6.3 Hz, 4H), 0.88 (d, J = 6.5 Hz, 6H). HRMS (ESI-TOF): calcd. for C34H51NO2Na [M + Na]+ 528.3817, found 528.3824.

Cholesteryl [15S,6R*]-7-butyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate with Cholesteryl [1R,6S*]-7-butyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4a): Yield 91% (0.535 g), yellowish solid, m. p. = 94–95 °C, [α]D17 = 17.6 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. Rf = 0.45 (petroleum ether/ethyl acetate 5:1). 1H NMR (500 MHz, CDCl3): δH 6.13–6.73 (m, 4H), 5.84–5.99 (m, 4H), 5.33–5.59 (m, 2H), 5.20 (d, J = 11.5 Hz, 2H), 4.94 (d, J = 5.1 Hz, 1H), 4.88 (d, J = 5.1 Hz, 1H), 4.77 (d, J = 3.5 Hz, 1H), 4.73 (d, J = 3.4 Hz, 1H), 4.43–4.52 (m, 2H), 2.23–2.39 (m, 4H), 1.93–2.05 (m, 4H), 1.76–1.89 (m, 6H), 1.23–1.61 (m, 30H), 1.05–1.22 (m, 14H), 0.99–1.04 (m, 10H), 0.93 (d, J = 6.5 Hz, 8H), 0.90–0.92 (m, 6H), 0.89 (d, J = 2.2 Hz, 6H), 0.88 (d, J = 2.2 Hz, 6H). HRMS (ESI-TOF): calcd. for C34H51NO2Na [M + Na]+ 528.3817, found 528.3824.

Cholesteryl [15S,6R*]-7-phenyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate with Cholesteryl [1R,6S*]-7-phenyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4b): Yield 89% (0.541 g), yellowish solid, m. p. = 155–156 °C, [α]D17 = 18.5 (c 0.18, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. Rf = 0.47 (petroleum ether/ethyl acetate 5:1). 1H NMR (500 MHz, CDCl3): δH 7.47 (d, J = 7.4 Hz, 4H), 7.35 (t, J = 7.5 Hz, 4H), 7.24–7.30 (m, 2H), 6.30–6.47 (m, 4H), 5.88–6.02 (m, 5H), 5.60 (d, J = 4.8 Hz, 1H), 5.53 (d, J = 5.0 Hz, 1H), 5.39 (s, 2H), 5.01 (d, J = 2.3 Hz, 1H), 4.97 (d, J = 2.3 Hz, 1H), 4.47–4.62 (m, 2H), 2.21–2.46 (m, 4H), 1.79–2.08 (m, 10H), 1.24–1.71 (m, 22H), 1.08–1.23 (m, 14H), 0.98–1.07 (m, 10H), 0.94 (d, J = 6.4 Hz, 8H), 0.90 (d, J = 1.3 Hz, 6H), 0.89 (s, 6H), 0.70 (s, 6H). HRMS (ESI-TOF): calcd. for C34H51NO2Na [M + Na]+ 610.4600, found 610.4606.
Cholesteryl (1S*,6R*)-7-(o-tolyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate equivalent with Cholesteryl (1R*,6S*)-7-(o-tolyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4c): Yield 87% (0.541 g), yellowish solid, m. p. = 115–116 °C, [α]D18 = 10.4 (c 0.49, CHCl₃), exists as two N-(CO)-cholesteryl rotamers. Rf = 0.44 (petroleum ether/ethyl acetate 5:1).

1H NMR (500 MHz, CDCl₃): δH 7.13–7.28 (m, 8H), 6.35–6.46 (m, 2H), 6.15–6.26 (m, 2H), 5.97–6.06 (m, 4H), 5.52 (d, J = 1.5 Hz, 1H), 5.49 (d, J = 2.0 Hz, 1H), 5.33–5.43 (m, 4H), 5.01 (dd, J = 5.1 Hz, J = 2.3 Hz, 1H), 4.96 (dd, J = 5.1 Hz, J = 2.3 Hz, 1H), 4.48–4.57 (m, 2H), 2.21–2.43 (m, 10H), 1.78–2.07 (m, 10H), 1.23–1.65 (m, 22H), 1.07–1.22 (m, 14H), 0.98–1.07 (m, 10H), 0.94 (d, J = 6.5 Hz, 8H), 0.90 (d, J = 2.1 Hz, 6H), 0.88 (d, J = 2.1 Hz, 6H), 0.70 (s, 6H) ppm.

13C NMR (125 MHz, CDCl₃): δC 153.4 (2C), 139.9 (2C), 138.3 (2C), 137.6 (2C), 136.8 (2C), 134.1 (2C), 132.1 (2C), 130.6, 130.56, 129.8, 129.7, 127.9, 127.8, 126.5, 125.8, 124.7 (2C), 124.2 (2C), 122.4, 122.37, 118.6 (2C), 74.6, 74.55, 62.9 (2C), 60.9, 60.7, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.8 (2C), 39.5 (2C), 38.6, 38.5, 37.0, 36.95, 36.6 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 28.2 (4C), 28.0 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.1 (2C), 20.6, 20.57, 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for C₄₃H₃₉NO₂Na [M + Na]+ 644.4443, found 644.4457.

Cholesteryl (1S*,6R*)-7-(4-fluorophenyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate

Cholesteryl (1S*,6R*)-7-(4-bromophenyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate
Cholesteryl (1S*,6R*)-7-(2-cyanoethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4g): Yield 79% (0.455 g), yellowish solid, m. p. = 134–135 °C, \([\alpha]_D^{18} = -16.9\) (c 0.49, CHCl₃), exists as two N-(CO)O-cholesteryl rotamers. \(R_f = 0.50\) (petroleum ether/ethyl acetate 5:1).

\[\text{M} \rightarrow \text{Na}^+\] HRMS (ESI-TOF): calcd. for C₂₁H₃₆NO₂SiNa \([M + Na]^+\) 626.4369, found 626.4376.

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\delta_{1H} 6.25–6.36 (m, 4H), 5.85–5.91 (m, 4H), 5.28–5.38 (m, 4H), 4.95 (d, \(J = 5.0\) Hz, 1H), 4.91 (d, \(J = 5.1\) Hz, 1H), 4.78 (s, 1H), 4.75 (d, \(J = 4.8\) Hz, 1H), 4.88 (d, \(J = 4.9\) Hz, 1H), 4.75 (d, \(J = 2.8\) Hz, 1H), 4.52 (s, 1H), 4.39–4.50 (m, 2H), 3.60 (s, 4H), 2.10–2.37 (m, 8H), 1.91–2.04 (m, 4H), 1.65–1.90 (m, 10H), 1.21–1.60 (m, 22H), 1.04–1.19 (m, 14H), 0.97–1.03 (m, 10H), 0.91 (d, \(J = 6.4\) Hz, 8H), 0.87 (d, \(J = 1.6\) Hz, 6H), 0.86 (s, 6H), 0.67 (s, 6H) ppm. \[\text{M} \rightarrow \text{Na}^+\] HRMS (ESI-TOF): calcd. for C₂₃H₄₇NO₃Na \([M + Na]^+\) 598.4236, found 598.4238.

Cholesteryl (1S*,6R*)-7-(3-hydroxypropyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4h): Yield 89% (0.525 g), yellowish solid, m. p. = 142–143 °C, \([\alpha]_D^{18} = -17.2\) (c 0.49, CHCl₃), exists as two N-(CO)O-cholesteryl rotamers. \(R_f = 0.52\) (petroleum ether/ethyl acetate 5:1).

\[\text{M} \rightarrow \text{Na}^+\] HRMS (ESI-TOF): calcd. for C₂₃H₄₇NO₃Na \([M + Na]^+\) 612.4392, found 612.4389.

Cholesteryl (1S*,6R*)-7-(2-cyanoethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate with Cholesteryl (1R*,6S*)-7-(2-cyanoethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4i): Yield 86% (0.503 g), white solid, m. p. = 168–169 °C, \([\alpha]_D^{23} = -23\) (c 0.51, CHCl₃), exists as two N-(CO)O-cholesteryl rotamers. \(R_f = 0.48\) (petroleum ether/ethyl acetate 5:1).

\[\text{M} \rightarrow \text{Na}^+\] HRMS (ESI-TOF): calcd. for C₂₃H₄₇NO₃Na \([M + Na]^+\) 612.4392, found 612.4389.
Cholesteryl (1R*,6S*)-7-(3-cyanopropyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate with C3H4O (CDCl3): δH 6.23–6.38 (m, 4H), 5.29–5.32 (m, 2H), 4.92 (d, J = 5.1 Hz, 1H), 4.88 (d, J = 5.1 Hz, 1H), 4.80 (d, J = 3.5 Hz, 1H), 4.76 (d, J = 3.4 Hz, 1H), 4.42–4.51 (m, 2H), 2.18–2.42 (m, 12H), 1.92–2.05 (m, 4H), 1.75–1.91 (m, 1OH), 1.22–1.62 (m, 22H), 1.06–1.21 (m, 14H), 0.99–1.05 (m, 10H), 0.92 (d, J = 6.4 Hz, 8H), 0.88 (d, J = 2.0 Hz, 6H), 0.87 (d, J = 2.1 Hz, 6H), 0.68 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δC 153.2 (2C), 139.8 (2C), 138.4 (2C), 137.8 (2C), 134.4, 134.2, 125.1 (2C), 123.6 (2C), 122.4, 122.37, 119.2 (2C), 117.5, 117.2, 74.5 (2C), 62.0, 61.9, 60.2, 60.1, 56.7 (2C), 56.1 (2C), 50.2 (2C), 42.3 (2C), 39.7 (2C), 38.6, 38.4, 37.0, 36.9, 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (2C), 31.87 (2C), 28.2 (2C), 28.1, 28.0 (2C), 25.6, 25.5, 24.3 (2C), 24.1, 24.07, 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 18.4 (2C), 18.7 (2C), 16.4, 16.3, 11.9 (2C) ppm. HRMS (ESI-TOF): calcld. for C40H37NO7Na [M + Na]^+ 621.4396, found 621.4406.

Cholesteryl (1S*,6R*)-7-(3-bromopropyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (2k): Yield 88% (0.574 g), yellowish viscous oil, [α]D18 +18.8 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. Rf = 0.50 (petroleum ether/ethyl acetate 5:1).

1H NMR (500 MHz, CDCl3): δH 6.24–6.38 (m, 4H), 5.87–6.01 (m, 4H), 5.33–5.39 (m, 2H), 5.28 (d, J = 6.1 Hz, 2H), 4.94 (d, J = 5.1 Hz, 1H), 4.89 (d, J = 5.1 Hz, 1H), 4.79 (d, J = 3.2 Hz, 1H), 4.75 (d, J = 3.0 Hz, 1H), 4.43–4.52 (m, 2H), 3.33–3.43 (m, 4H), 2.19–2.42 (m, 8H), 1.93–2.07 (m, 8H), 1.75–1.92 (m, 6H), 1.22–1.62 (m, 22H), 1.06–1.22 (m, 14H), 0.99–1.05 (m, 10H), 0.93 (d, J = 6.5 Hz, 8H), 0.89 (d, J = 2.3 Hz, 6H), 0.88 (d, J = 2.2 Hz, 6H), 0.69 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δC 153.3 (2C), 139.9 (2C), 138.4 (2C), 138.0 (2C), 135.3, 135.1, 124.9 (2C), 123.6 (2C), 122.4, 122.35, 116.9, 116.6, 74.5 (2C), 62.2, 62.1, 60.3, 60.2, 56.7 (2C), 56.1 (2C), 50.2 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0, 36.9, 36.6 (2C), 36.2 (2C), 35.8 (2C), 32.8, 32.77, 31.9 (4C), 31.2, 31.1, 28.2 (3C), 28.16, 28.0 (2C), 25.2, 25.1, 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcld. for C29H25BrNO7Na [M + Na]^+ 674.3548, found 674.3558.

Cholesteryl (1S*,6R*)-7-(3-ethoxy-3-oxopropyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate with C3H4O (CDCl3): δH 6.23–6.37 (m, 4H), 5.26–5.30 (m, 2H), 4.94 (d, J = 5.1 Hz, 1H), 4.77 (d, J = 3.4 Hz, 1H), 4.73 (d, J = 3.3 Hz, 1H), 4.42–4.51 (m, 2H), 1.3 (d, J = 7.1 Hz, 4H), 1.22–1.60 (m, 22H), 1.06–1.21 (m, 14H), 0.99–1.05 (m, 10H), 0.92 (d, J = 6.4 Hz, 8H), 0.88 (d, J = 2.0 Hz, 6H), 0.87 (d, J = 2.1 Hz, 6H), 0.68 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δC 172.6, 172.5, 153.3 (2C), 139.9 (2C), 138.3 (2C), 138.1 (2C), 135.6, 135.5, 124.9 (2C), 123.7 (2C), 122.4, 122.3, 116.3, 116.2, 74.4, 74.4, 62.2 (2C), 60.5 (2C), 60.2, 60.1, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0, 36.9, 36.5 (2C), 36.2 (2C), 35.8 (2C), 32.9 (2C), 31.9 (4C), 28.2 (3C), 28.16, 28.0 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 22.0, 21.9, 21.0 (2C), 19.4 (2C), 18.7 (2C), 14.2 (2C), 11.8 (2C) ppm. HRMS (ESI-TOF): calcld. for C34H34NO6Na [M + Na]^+ 654.4498, found 654.4515.
H(1H), 4.79 (d, J = 3.4 Hz, 1H), 4.75 (d, J = 3.7 Hz, 1H), 4.43–4.52 (m, 2H), 2.59–2.71 (m, 4H), 2.19–2.52 (m, 8H), 1.99 (dd, J = 25.1 Hz, J = 15.0 Hz, 4H), 1.74–1.92 (m, 6H), 1.40–1.62 (m, 12H), 1.34 (d, J = 3.4 Hz, 2H), 1.22–1.29 (m, 4H), 1.06–1.21 (m, 14H), 0.99–1.05 (m, 10H), 0.93 (d, J = 6.5 Hz, 8H), 0.88 (d, J = 2.1 Hz, 6H), 0.87 (d, J = 1.9 Hz, 6H), 0.69 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δ 153.3 (2C), 139.9 (2C), 138.3 (2C), 138.1 (2C), 135.8, 136.5, 124.9 (2C), 123.7 (2C), 122.4, 122.3, 116.6, 116.4, 74.5, 74.4, 62.0, 61.9, 60.2, 60.1, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 42.2 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 36.9 (2C), 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 31.0 (6C), 28.2 (4C), 28.0 (2C), 27.4, 27.3, 26.9 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for C42H83NO2SNa [M + Na]+ 670.4633, found 670.4639.

Cholesteryl (1S*,6R*)-7-(3-tert-butylthiophenoxy)propyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate equivalent with Cholesteryl (1R*,6S*)-7-(3-tert-butylthiophenoxy)propyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4n): Yield 88% (0.583 g), yellowish solid, m. p. = 135–136 °C, [α]D18 = 23.5 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. Rf = 0.53 (petroleum ether/ethyl acetate 5:1). 1H NMR (500 MHz, CDCl3): δH 6.22–6.38 (m, 4H), 5.84–6.01 (m, 4H), 5.35 (s, 2H), 5.24 (d, J = 11.1 Hz, 2H), 4.93 (d, J = 4.8 Hz, 1H), 4.88 (d, J = 4.9 Hz, 1H), 4.78 (s, 1H), 4.74 (s, 1H), 4.42–4.52 (m, 2H), 2.50 (dd, J = 12.0 Hz, J = 6.7 Hz, 4H), 2.19–2.38 (m, 8H), 1.92–2.07 (m, 4H), 1.70–1.91 (m, 10H), 1.41–1.63 (m, 12H), 1.22–1.40 (m, 28H), 1.06–1.21 (m, 14H), 0.98–1.05 (m, 10H), 0.88 (s, 6H), 0.87 (s, 6H), 0.69 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δC 153.2 (2C), 139.9 (2C), 138.4 (2C), 138.2 (2C), 136.3 (2C), 124.7 (2C), 123.5 (2C), 122.4, 122.3, 116.2, 116.6, 74.4 (2C), 62.2 (2C), 60.3, 60.2, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 42.0 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0, 36.95, 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (4C), 31.0 (6C), 28.4, 28.37, 28.2 (4C), 28.0 (2C), 27.6 (2C), 26.2, 26.1, 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for C43H85NO2SNa [M + Na]+ 684.4790, found 684.4810.

Cholesteryl (1S*,6R*)-7-cyclopentyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate equivalent with Cholesteryl (1R*,6S*)-7-cyclopentyl-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4o): Yield 85% (0.510 g), yellowish solid, m. p. = 125–126 °C, [α]D18 = –13.3 (c 0.50, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. Rf = 0.48 (petroleum ether/ethyl acetate 5:1). 1H NMR (500 MHz, CDCl3): δH 6.22–6.37 (m, 4H), 5.84–5.97 (m, 4H), 5.36 (d, J = 5.0 Hz, 2H), 5.22 (d, J = 11.7 Hz, 2H), 4.98 (d, J = 5.1 Hz, 1H), 4.91 (d, J = 5.1 Hz, 1H), 4.76–4.79 (m, 1H), 4.74 (dd, J = 4.9 Hz, J = 2.1 Hz, 1H), 4.42–4.53 (m, 2H), 2.56–2.66 (m, 2H), 2.17–2.40 (m, 4H), 1.75–2.05 (m, 14H), 1.64–1.73 (m, 8H), 1.22–1.63 (m, 26H), 1.06–1.21 (m, 14H), 0.99–1.05 (m, 10H), 0.93 (d, J = 6.5 Hz, 8H), 0.89 (d, J = 2.2 Hz, 6H), 0.88 (d, J = 2.1 Hz, 6H), 0.69 (s, 6H) ppm. 13C NMR (125 MHz, CDCl3): δC 153.4, 153.3, 141.7 (2C), 140.0 (2C), 138.6 (2C), 138.3 (2C), 124.2 (2C), 123.5 (2C), 122.4 (2C), 114.2 (2C), 74.3 (2C), 62.0 (2C), 60.2, 60.15, 56.7 (2C), 56.1 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 38.0, 37.9, 37.0 (2C), 36.6 (2C), 36.2 (2C), 35.8 (2C), 32.8, 32.7, 32.4, 32.2, 31.9 (4C), 28.2 (4C), 28.0 (2C), 24.9 (2C), 24.8 (2C), 24.3 (2C), 23.8 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for C41H63NO2Na [M + Na]+ 622.4600, found 622.4599.
Cholesteryl (1S*,6R*)-7-(1,3-dioxoindolin-2-yl)ethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4a): Yield 84% (0.553 g), yellowish solid, m. p. = 123–124 °C, [α]D17−17=−6.7 (c 0.31, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.55 (petroleum ether/ethyl acetate 5:1).

Cholesteryl (1S*,6R*)-7-(1,3-dioxoindolin-2-yl)ethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4b): Yield 87% (0.663 g), yellowish solid, m. p. = 127–128 °C, [α]D17=−18.7 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.56 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1R*,6S*)-7-(1,3-dioxoindolin-2-yl)ethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4a): Yield 95% (0.696 g), yellowish solid, m. p. = 122–123 °C, [α]D18=−15 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.60 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1R*,6S*)-7-(1,3-dioxoindolin-2-yl)ethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4b): Yield 95% (0.696 g), yellowish solid, m. p. = 122–123 °C, [α]D18=−15 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.60 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1S*,6R*)-7-(naphthalen-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4q): Yield 87% (0.613 g), yellowish solid, m. p. = 127–128 °C, [α]D18=−11.8 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.56 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1R*,6S*)-7-(naphthalen-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4q): Yield 87% (0.613 g), yellowish solid, m. p. = 127–128 °C, [α]D18=−11.8 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.56 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1R*,6S*)-7-(naphthalen-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4q): Yield 87% (0.613 g), yellowish solid, m. p. = 127–128 °C, [α]D18=−11.8 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.56 (petroleum ether/ethyl acetate 2:1).

Cholesteryl (1R*,6S*)-7-(naphthalen-1-yl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (4q): Yield 87% (0.613 g), yellowish solid, m. p. = 127–128 °C, [α]D18=−11.8 (c 0.49, CHCl3), exists as two N-(CO)O-cholesteryl rotamers. \( \Delta \) = 0.56 (petroleum ether/ethyl acetate 2:1).
exists as two N-(CO)O-cholesteryl rotamers. \( R_f = 0.57 \) (petroleum ether/ethyl acetate 5:1).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_{1H} 7.97 \) (d, \( J = 4.0 \) Hz, 2H), 7.78–7.92 (m, 6H), 7.39–7.57 (m, 10H), 6.45–6.56 (m, 2H), 6.02–6.22 (m, 6H), 5.66 (d, \( J = 11.3 \) Hz, 2H), 5.58 (s, 1H), 5.48 (s, 1H), 5.36–5.45 (m, 2H), 5.11 (s, 1H), 5.06 (d, \( J = 2.2 \) Hz, 1H), 4.57 (s, 2H), 2.22–2.49 (m, 4H), 1.80–2.09 (m, 10H), 1.24–1.71 (m, 22H), 0.99–1.24 (m, 24H), 0.96 (s, 8H), 0.91 (d, \( J = 5.6 \) Hz, 12H), 0.71 (d, \( J = 5.5 \) Hz, 6H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_c 153.5 (2C), 139.9 (2C), 138.1 (2C), 137.6 (2C), 133.7 (2C), 132.8 (4C), 132.2 (2C), 130.7 (2C), 130.6 (2C), 128.4 (2C), 128.3 (2C), 127.0 (2C), 126.4 (4C), 126.0 (4C), 125.4 (2C), 125.1 (2C), 124.8 (2C), 124.4 (2C), 122.4 (2C), 119.4 (2C), 74.7 (2C), 63.6 (2C), 61.0, 60.8, 56.7 (2C), 56.2 (2C), 50.0 (2C), 42.3 (2C), 39.8 (2C), 39.6 (2C), 38.7, 38.5, 37.1 (2C), 36.6 (2C), 36.2 (2C), 35.8 (2C), 32.9 (4C), 28.3 (4C), 28.0 (2C), 24.3 (2C), 23.9 (2C), 22.9 (2C), 22.6 (2C), 21.1 (2C), 19.4 (2C), 18.8 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for \( C_{35}H_{61}NO_2Na \) [M + Na\(^+\)] = 730.4600, found 728.4612.

**Cholesteryl 7,8-bis(hydroxymethyl)-9-azabicyclo[4.2.1]nona-2,4,7-triene-9-carboxylate (6):** Yield 80% (0.473 g), white solid, m. p. = 188–189 °C, [\( \alpha \)]\(_D\)\(^{18}\) = −20.6 (c 0.34, CHCl\(_3\)), exists as two N-(CO)O-cholesteryl rotamers. \( R_f = 0.58 \) (petroleum ether/ethyl acetate 5:1).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta_{1H} 6.29–6.39 \) (m, 4H), 5.86–5.95 (m, 4H), 5.36 (d, \( J = 7.4 \) Hz, 2H), 5.09 (dd, \( J = 9.2 \) Hz, \( J = 5.2 \) Hz, 4H), 4.41–4.51 (m, 2H), 4.25–4.34 (m, 8H), 2.19–2.37 (m, 4H), 1.92–2.06 (m, 4H), 1.75–1.91 (m, 6H), 1.22–1.63 (m, 22H), 1.06–1.21 (m, 14H), 0.96–1.05 (m, 10H), 0.93 (d, \( J = 6.5 \) Hz, 8H), 0.89 (d, \( J = 2.2 \) Hz, 6H), 0.87 (d, \( J = 2.2 \) Hz, 6H), 0.69 (s, 6H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta_c 153.6 (2C), 139.7 (2C), 138.2 (2C), 138.8 (2C), 132.9 (2C), 132.6 (2C), 124.7 (2C), 124.6 (2C), 122.6, 122.5, 75.0 (2C), 61.8 (2C), 61.75 (2C), 56.7 (2C), 56.2 (2C), 54.9 (2C), 54.8 (2C), 50.0 (2C), 42.3 (2C), 39.7 (2C), 39.5 (2C), 38.6, 38.4, 37.0, 36.9, 36.5 (2C), 36.2 (2C), 35.8 (2C), 31.9 (2C), 31.86 (2C), 28.2 (2C), 28.17 (2C), 28.0 (2C), 24.3 (2C), 23.9 (2C), 22.8 (2C), 22.6 (2C), 21.0 (2C), 19.4 (2C), 18.7 (2C), 11.9 (2C) ppm. HRMS (ESI-TOF): calcd. for \( C_{35}H_{57}NO_2Na \) [M + Na\(^+\)] = 708.4635, found 709.4685.

**4. Conclusions**

In summary, we synthesized, for the first time, N-carbocholereoxyazepine and studied its [\( \pi + \pi \)-] and [\( \pi + 2\pi \)]-cycloaddition reactions with functionally substituted terminal alkynes and 1,4-butynediol under the action of the Co(acac)\(_2\)(dppe)/Zn/ZnI\(_2\) three-component catalytic system. Our strategy provided a new 9-azabicyclo[4.2.1]nona-2,4,7-triene series bearing, at C-7, a large variety of substituents in high yields (79–95%, 20 examples of feasibility). The synthesized azabicycles possess a high potential for practical application in pharmacology and medicine, as they can be used as key precursors in the targeted search for and development of innovative drugs and other practically significant compounds.

**Supplementary Materials:** The following are available online: 1D (\(^1\)H and \(^{13}\)C NMR) and 2D (NOESY, COSY, HSQC, HMBC) spectra of the products synthesized in this work.

**Author Contributions:** Conceptualization, U.M.D. and V.A.D.; methodology, validation, and execution of chemistry experiments, G.N.K. and V.A.D.; manuscript preparation, G.N.K., V.A.D., and U.M.D. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** The authors declare no conflict of interest.
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