Article

# Zinc Chloride-Catalyzed Synthesis of Carbamates: An Application for the Synthesis of the Anti-Alzheimer's Drug Rivastigmine

Manoj Gayke, Nirbhay Hirapara, Hanuman Narode, Siddhanath D. Bhosle, Rajesh S. Bhosale, and Jhillu Singh Yadav*
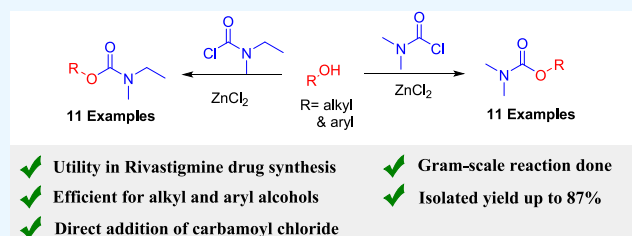
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**ABSTRACT:** Herein, we report a synthetic protocol for the synthesis of carbamates by employing zinc chloride as a catalyst from carbamoyl chlorides and aromatic/aliphatic alcohols. The developed protocol successfully utilizes the gram-scale synthesis of the FDA-approved rivastigmine drug and its derivative. The utility of zinc chloride over other catalysts such as zinc dust and zinc acetate exhibits a 49−87% yield of carbamates.



- ✔ Utility in Rivastigmine drug synthesis
- ✔ Efficient for alkyl and aryl alcohols
- ✔ Direct addition of carbamoyl chloride
- ✔ Gram-scale reaction done
- ✔ Isolated yield up to 87%

## INTRODUCTION

Carbamates (urethanes) are conventional scaffolds in agricultural, pharmaceutical, and material science due to their diverse activities.[1,2] Carbamate plays a key function in polyurethane polymers, which are often used in synthetic fibers, surface coatings, adhesives, foams, and composites in the manufacturing of paints.[3−9] Extensive application of carbamate compounds began in 1959 when the first carbamate pesticide "carbaryl" was approved in the United States[10] (Figure 1).

In particular, carbaryl is utilized as an alternative to organophosphate insecticides[11] and propoxur is commonly used to manage domestic pests.[12] Pesticides like carbofuran are employed in the cultivation of maize, rice, and cotton crops.[13] FDA-approved carbamate-containing drug molecules, such as (R)-bambuterol, have the potential to be used in the treatment of cognitive decline and post-traumatic stress disorder (PTSD),[14] while pyridostigmine is commonly used to treat myasthenia gravis.[15] On the other hand, rivastigmine acts as an acetylcholinesterase (AChE) inhibitor.[16]

A review of the literature revealed that carbamate synthesis can be accomplished using a variety of synthetic methods.[17−21] In most of these methods, carbamate synthesis is executed by the direct use of hazardous starting materials such as isocyanates,[22−25] phosgene, or carbon monoxide.[26] To tackle these issues, it would be ideal to design an efficient, nontoxic, user-friendly, and inexpensive methodology for the production of carbamate. The use of inexpensive catalysts or mediators attracts great attention as they could provide economically superior alternatives and/or distinct reaction outcomes. In this context, a few contemporary synthetic methods of carbamate synthesis have been illustrated in Scheme 1.

The interaction of propargyl alcohols with carbon dioxide in supercritical carbon dioxide (scCO$_2$) is used for carbamate synthesis (Scheme 1a),[27] albeit supercritical conditions are necessary. In another method, zinc acetate was employed as a catalyst in the presence of aromatic amines, CO$_2$, and silicate esters (Scheme 1b)[28] although it required a higher temperature and longer reaction time. Furthermore, the employment of corresponding amines, alcohols, and carbon dioxide with distinct bases or catalysts (Scheme 1c)[29−34] could generate a high carbamate yield, although the use of bases restricts functional group tolerance. The use of amines with disubstituted carbonates in the presence of NaH generates corresponding carbamates (Scheme 1d);[35−39] however, NaH limits functional group tolerance. A recently reported method to synthesize carbamates utilizing formamide and alcohol undergoes dehydrogenative synthesis of carbamates (Scheme 1e),[40] which is an inexpensive method as it required a higher temperature.

In the present work, we developed a synthetic protocol for the production of carbamates, which revealed the use of zinc chloride as an efficient catalyst to activate the carbamoyl chlorides, which were further treated with corresponding alcohols (Scheme 1f). The present developed synthetic protocol was successfully employed in the gram-scale production of FDA-approved rivastigmine (**11b**) and its derivative (**11a**). Over the last two decades, our research group extensively engaged in the development of zinc-mediated functional group transformations such as alkylation of cyclic secondary amine,[41] amide synthesis,[42] thiol ester synthesis,[43] acylation of ylides at α-carbon,[44] regioselective
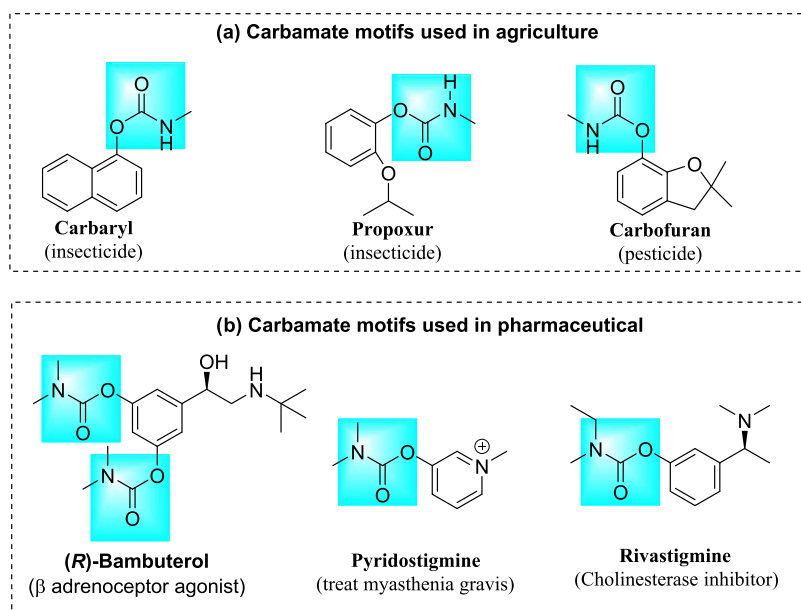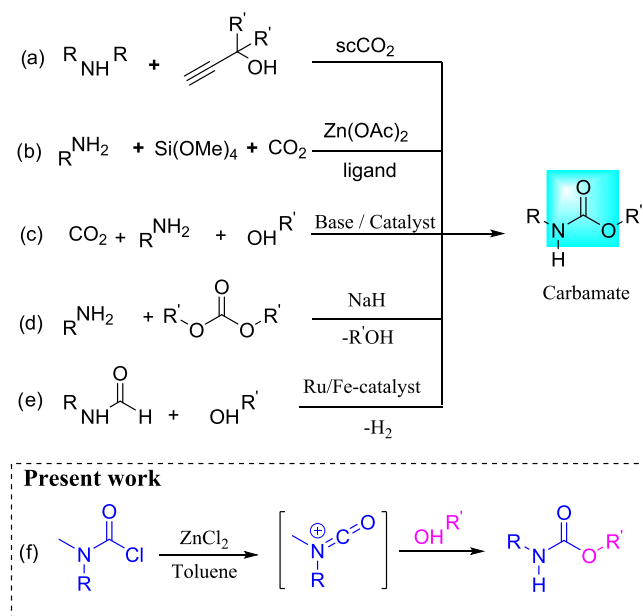
**Figure 1.** Examples of commercially available carbamate molecules.

**Scheme 1. Existing Synthetic Strategies of Carbamates**[a]



[a](a−e) Contemporary synthetic methods of carbamate synthesis. (f) The present study focuses on carbamate synthesis in the presence of the ZnCl2 catalyst employing carbamoyl chloride and related alcohols.

acylation,[45] carbamate formation from carbonate chloride,[1] chemoselective s-alkylation,[46] N-sulfonylation of amine,[47] benzoxazole synthesis,[48] and urea bond formation.[49]

## ■ RESULTS AND DISCUSSION

In the course of the development of a synthetic protocol for carbamate production, schematic optimization was conducted. At first, carbamoyl chloride was treated with 4-nitrophenol (**1**) in toluene without a catalyst at room temperature, and it was found that the reaction did not proceed (Table 1; entry 1). However, in reflux temperature, it was observed a low yield (31%) of targeted carbamate product formation (Table 1;

**Table 1. Optimization of the Reaction Conditions**[a]



| sr. no. | catalyst (equiv) | temp. (°C) | time (h) | yield (%) | alcohol recovered (%) |
|---|---|---|---|---|---|
| 1 | | 30 | 30 | | 97 |
| 2 | | 110 | 30 | 31 | 62 |
| 3 | ZnCl2 (0.1) | 30 | 16 | 30 | 63 |
| 4 | ZnCl2 (0.25) | 30 | 14 | 41 | 46 |
| **5** | **ZnCl2 (0.5)** | **30** | **12** | **81** | **12** |
| 6 | ZnCl2 (0.75) | 30 | 11 | 85 | 11 |
| **7** | **ZnCl2 (1)** | **30** | **11** | **86** | **9** |
| 8 | ZnCl2 (1) and AcOH (1) | 30 | 12 | 80 | 11 |
| 9 | ZnCl2 (1) and NH4Cl (1) | 30 | 12 | 81 | 12 |
| 10 | Zn metal (1) | 110 | 30 | 55 | 39 |
| 11 | Zn(OAc)2·2H2O (1) | 110 | 36 | traces | 79 |

[a]The bold entries show the suitable protocol for the synthesis of carbamate.

entry 2). To study the role of the selected zinc chloride catalyst in carbamate formation, it was systematically conducted with an increasing equivalence of catalyst in the reaction mixture. Initially, 0.1 equiv of zinc chlorides was loaded at room temperature, and it was observed that the targeted carbamate product was formed with a low yield of 30% (Table 1; entry 3). Furthermore, consecutive loadings of zinc chloride at room temperature such as 0.25, 0.5, 0.75, and 1 equiv, when used, yielded their carbamates 41, 81, 85, and 86%, respectively. When the catalyst concentration was 0.25 equiv loaded, it resulted in a slight increase in carbamate yield formation (Table 1; entry 4). However, when 0.5 equiv of catalyst was loaded, the carbamate formation had an excellent yield (Table 1; entry 5). There was no discernible increase in carbamate yield when the catalyst concentration was increased from 0.75

to 1 equiv (Table 1; entries 6 and 7). To study the impact of additives on carbamate formation, acetic acid and ammonium chloride were examined (Table 1; entries 8 and 9). The findings revealed that there were no additional effects of additives on carbamate yield. Finally, to test the efficacy of various zinc catalysts, carbamoyl chloride was treated with 4-nitrophenol (1) in the presence of zinc metal and carbamate was obtained with a moderate yield (55%) (Table 1; entry 10). However, when treated with zinc acetate (dihydrate), TLC revealed traces of the compound (Table 1; entry 11).

Additionally, the use of nonpolar solvents such as xylene, toluene, benzene, and DCM, as well as polar solvents like THF, 1,4-dioxane, ethyl acetate, DMSO, DMF, and acetonitrile at room temperature (Table 2), in the process was

**Table 2. Optimization of Solvents for Optimal Condition[a]**

| sr. no. | solvent | temperature (°C) | time (h) | yield (%) |
|---|---|---|---|---|
| 1 | xylene | 30 | 13 | 55 |
| **2** | **toluene** | **30** | **12** | **86** |
| 3 | benzene | 30 | 16 | 76 |
| 4 | DCM | 30 | 18 | 43 |
| 5 | THF | 30 | 15 | 70 |
| 6 | 1,4-dioxane | 30 | 24 | |
| 7 | ethyl acetate | 30 | 14 | 59 |
| 8 | DMSO | 30 | 24 | |
| 9 | DMF | 30 | 24 | |
| 10 | ACN | 30 | 16 | 56 |

[a]The bold entries show the suitable protocol for the synthesis of carbamate.

investigated to determine the effect of the solvent on yield formation. Toluene was found to be the optimum solvent for carbamate production (Table 2; entry 2).

Following the optimization study, further investigation was performed for the substrate scope, such as different alcohols (substituted aromatic and aliphatic) and carbamoyl chlorides (N,N-dimethyl carbamoyl chloride and N-ethyl,N-methyl carbamoyl chloride) in distinct carbamate formations (Scheme 2). It was observed that the aromatic alcohols (1−8), as well as aliphatic alcohols (9 and 10), were better suitable in the optimized reaction conditions for distinct carbamate formations. The formed novel carbamates were fully characterized with standard spectroscopic techniques such as ^{1}H, COSY, NOSY ^{13}C, NMR, mass, HRMS, and IR. The treatments of p-nitrophenol (1) with carbamoyl chlorides in the presence of zinc chloride gave a maximum yield of compounds 1a,[50] 86%, and 1b,[51] 87% (Schemes 2 and 3). Again without any substitution on aromatic alcohols, such as phenol (2), compound 2a[50] had a good yield of 76% and 2b[52] had a yield of 72% (Schemes 2 and 3).

The electron-withdrawing *para* and *meta* substituents of aromatic alcohol such as p-hydroxy acetophenone (3) and m-hydroxy acetophenone (4) with carbamoyl chlorides at 110 °C yielded products 3a[53] at 72%, 3b[54] at 73% and 4a[55] at 63%, 4b[56] at 62%, respectively (Schemes 2 and 3). In comparison to *meta*-substituted hydroxyl, *para*-substituted hydroxyl yields more.

The change in the electron-withdrawing substituent of aromatic alcohol like aldehyde showed an increase in the productivity of carbamate. The treatment of p-hydroxybenzaldehyde (5) and o-hydroxybenzaldehyde (6) with carbamoyl chlorides in the presence of zinc chloride gave maximum yields

of 5a[53] at 82%, 5b[54] at 80% and 6a[57] at 84%, 6b at 81%, respectively (Schemes 2 and 3). However, with the substrate having both electron-withdrawing and -donating functionality of 4-hydroxy-3-methoxybenzaldehyde (7), a poor yield of carbamate was obtained. The utility of the developed protocol was checked with 4-hydroxy-3-methoxybenzaldehyde (7), and low yields of 7a[57] at 49% and 7b at 51% at 110 °C were found (Schemes 2 and 3). To assess the effect of the electron-donating group of aromatic alcohols, 3-methoxyphenol (8) was treated with carbamoyl chlorides in the presence of zinc chloride, which obtained 78% of 8a[58] and 80% of 8b (Schemes 2 and 3). The selection of higher temperatures in the synthesis of carbamates (3a,b; 4a,b; and 7a,b) was due to the low yield formation of the resultant carbamates at room temperature. The scopes of aliphatic substrates were also evaluated. Benzyl alcohol (9) when treated with carbamoyl chlorides yielded 9a[59] at 76% and 9b at 79% (Schemes 2 and 3). 4-(3-Chlorophenyl)but-1-ol (10) was reacted with carbamoyl chlorides in the presence of zinc chloride and isolated 73% yield of 10a and 77% yield of 10b (Schemes 2 and 3). These outcomes exhibit that the current methodology is useful for various carbamate syntheses using distinct alcohols (aromatic and aliphatic) and has the potential for the synthesis of therapeutic active drug molecules.

The plausible mechanism of zinc chloride-mediated carbamate formation is depicted in Figure 2. Initially, the zinc chloride coordinates with 2 moles of carbamoyl chloride to form a complex (1), followed by the participation of a lone pair of nitrogen to produce an in situ isocyanate intermediate (2) and as a byproduct that released 2 mol of Cl⁻ and ZnCl₂ which is further used in the cycle. Furthermore, the intermolecular nucleophilic addition of alcohol to the reactive isocyanate (2) intermediate resulted in the formation of the unstable intermediate (3). Finally, Cl⁻ abstracts the proton from the obtained intermediate (3) to generate the carbamate motif (4) and liberate HCl as a by-product.

The developed synthetic protocol was successfully employed for the synthesis of the FDA-approved drug rivastigmine and its derivative (Scheme 4). A review of the literature revealed that carbamate synthesis (11b) was accomplished using carbamoyl chloride in the presence of various bases or catalysts.[60−64] The enantiomerically enriched scaffold (S)-3-(1-(dimethylamino)ethyl)phenol (11)[65] was treated with N-ethyl,N-methyl carbamoyl chloride at 110 °C for 13 h to isolate an 80% yield of the rivastigmine (11b)[66] drug molecule with 91.23% ee. Rivastigmine derivative 11a[67] synthesis was achieved via the treatment of phenol 11 with N,N-dimethyl carbamoyl chloride at 110 °C for 13 h to isolate 78% yield with 97.44% ee.

## ■ CONCLUSIONS

In summary, we were able to effectively employ inexpensive zinc chloride as a catalyst for the direct synthesis of carbamate utilizing carbamoyl chloride and corresponding alcohols. Notably, both aromatic and aliphatic alcohols can achieve maximum yield of carbamates, in the presence of either electron-withdrawing and/or -donating substituents. Other functional groups (nitro, keto, aldehyde, alkoxy, ter-amine, and halide) were not affected, showing that the reaction is chemoselective for carbamate synthesis. The present methodology offers a novel approach to carbamate synthesis, which is a simple, highly efficient, and inexpensive process. The developed protocol has potential use in polyurethane,

**Scheme 2. Substrate Scope with *N,N*-Dimethyl Carbamoyl Chloride**[a]
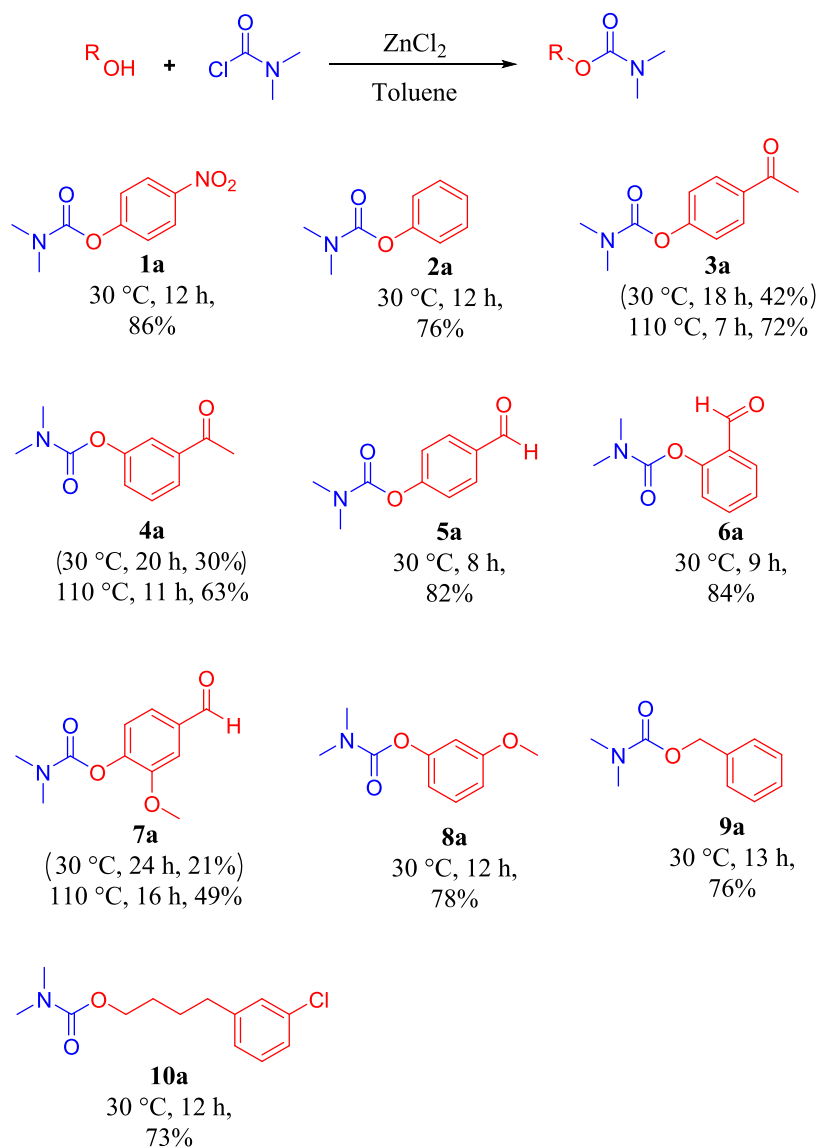


[a]Reaction conditions: **1–10** (1.0 mmol) of alcohols, (1.0 mmol) of *N,N*-dimethyl carbamoyl chloride, and (0.5 mmol) of zinc chloride; isolated yields were reported.
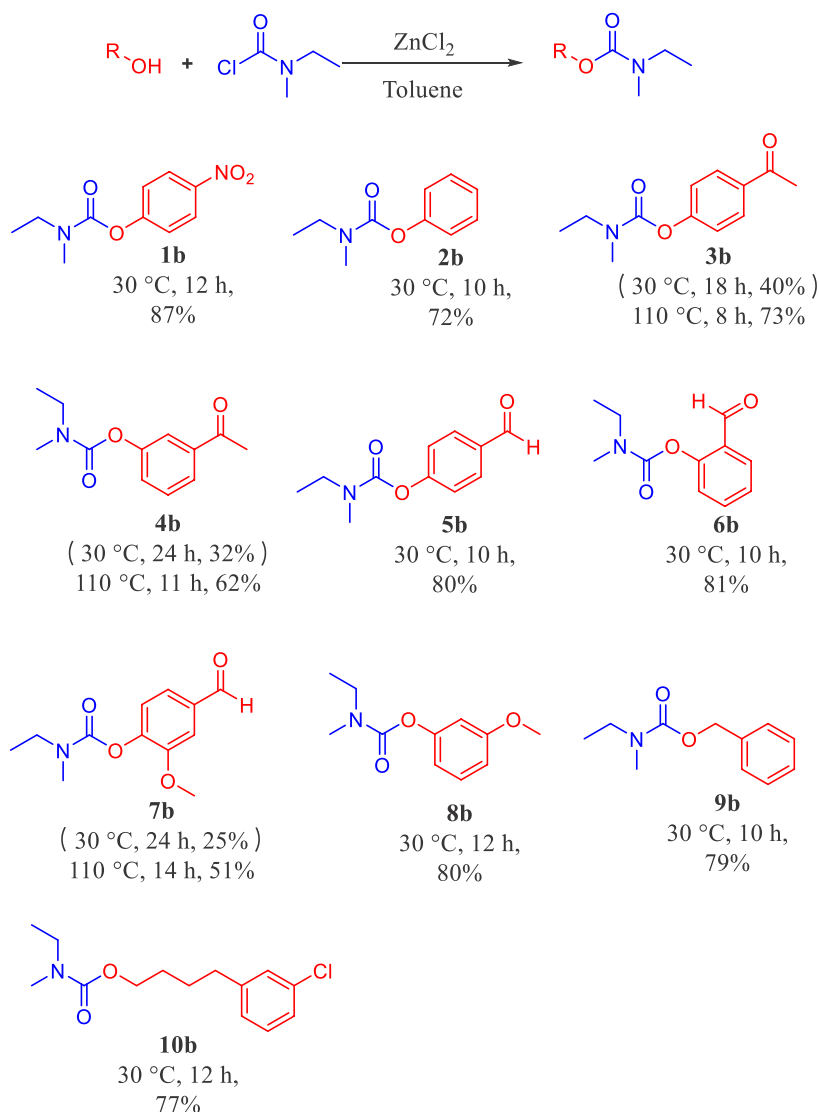
pharmaceutical, and agrochemical industries. With the objective being to demonstrate the efficient and inexpensive method demonstrated, the utility of the current methodology in the preparation of rivastigmine drug molecules is proven.

## ■ EXPERIMENTAL SECTION

All chemicals were purchased from different suppliers, like carbamoyl chloride was purchased from Sigma-Aldrich. All corresponding alcohols and zinc catalyst were purchased from Tokyo Chemicals, Loba Chemie, and Avra synthesis. Reaction-grade solvents were purchased from Finar Limited. All chemicals were used as supplied without further purification, except for the solvents, which were refined further by standard methods to eliminate residues of undesirable contaminants. ESI-MS data were obtained with a Waters mass spectrometer. IR spectra were measured with a Shimadzu 1900 FTIR spectrometer. The enantiomeric excess was determined by Water's HPLC analysis on a chiral cellulose-C column. ^{1}H, ^{13}C, COSY, and NOSY NMR were recorded at room temperature in a deuterated solvent on a Bruker Avance 400 MHz spectrometer with tetramethylsilane as the internal standard. The chemical shifts are based on the CDCl$_3$ peaks at $\delta$ = 7.26 ppm for proton NMR and at $\delta$ = 77.00 ppm (t) for carbon NMR. Column chromatography was performed with silica gel (60–120 mesh), and thin-layer chromatography was performed using Merck precoated aluminum TLC plates 60F-254.

**General Procedure A for the Synthesis of Carbamates.** Under N$_2$ protection, zinc chloride (1.79 mmol) and carbamoyl chloride (3.58 mmol) were added to (10 vol) anhydrous toluene and agitated at room temperature for 10 min. The corresponding alcohol (3.58 mmol) was added to the agitated reaction mass and stirred at room temperature until the reaction was completed. After completion of the reaction (as indicated by TLC), the reaction mass was quenched with water and the layers were separated. The organic layer was washed with water and dried over sodium sulfate; the reaction mixture was concentrated under reduced pressure to obtain the

**Scheme 3. Substrate Scope with *N*-Ethyl,*N*-Methyl Carbamoyl Chloride[a]**

titled compounds. All of the crude compounds were purified by column chromatography over silica gel (60−120 mesh) (hexane-ethyl acetate) to afford the pure product.

**General Procedure B for the Synthesis of Carbamates.** Under N₂ protection, zinc chloride (1.79 mmol) and carbamoyl chloride (3.58 mmol) were added to (10 vol) anhydrous toluene and agitated at room temperature for 10 min. The corresponding alcohol (3.58 mmol) was added to the agitated reaction mass and stirred at 110 °C until the reaction was completed. After completion of the reaction (as indicated by TLC), the reaction mass was allowed to cool at room temperature, and then, the reaction mass was quenched with water and the layers were separated. The organic layer was washed with water and dried over sodium sulfate; the reaction mixture was concentrated under reduced pressure to obtain the titled compounds. All of the crude compounds were purified by column chromatography over silica gel (60−120 mesh) (hexane-ethyl acetate) to afford the pure product.

**Procedure C for the Synthesis of Rivastigmine (11b) and Its Intermediate (11a).** Under N₂ protection, zinc

chloride (15.12 mmol) and *N*-ethyl,*N*-methyl carbamoyl chloride or *N*,*N*-dimethyl carbamoyl chloride (30.25 mmol) were added in anhydrous toluene (10 mL) and agitated over a mechanical stirrer at room temperature for 10 min. Then, 30.25 mmol of (*S*)-3-(1-(dimethylamino)ethyl)phenol (**11**) was added to the agitated reaction mass and allowed to reflux temperature until the reaction was completed. To check the completion of the reaction, an aliquot for TLC was taken and it was dissolved in methanol; after completion of the reaction, toluene was condensed under a vacuum and the residue was dissolved in ethyl acetate and washed with water. Then, it was dried over sodium sulfate and concentrated under reduced pressure to obtain the crude product. The crude was purified by column chromatography over silica gel (MDC/MeOH = 95:5) to afford the desired product rivastigmine (**11b**) or its derivative (**11a**).

*4-Nitrophenyl Dimethylcarbamate (1a).* The reaction was performed as described in general procedure A using 4-nitrophenol (**1**) (0.5 g, 3.59 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 4-nitro-
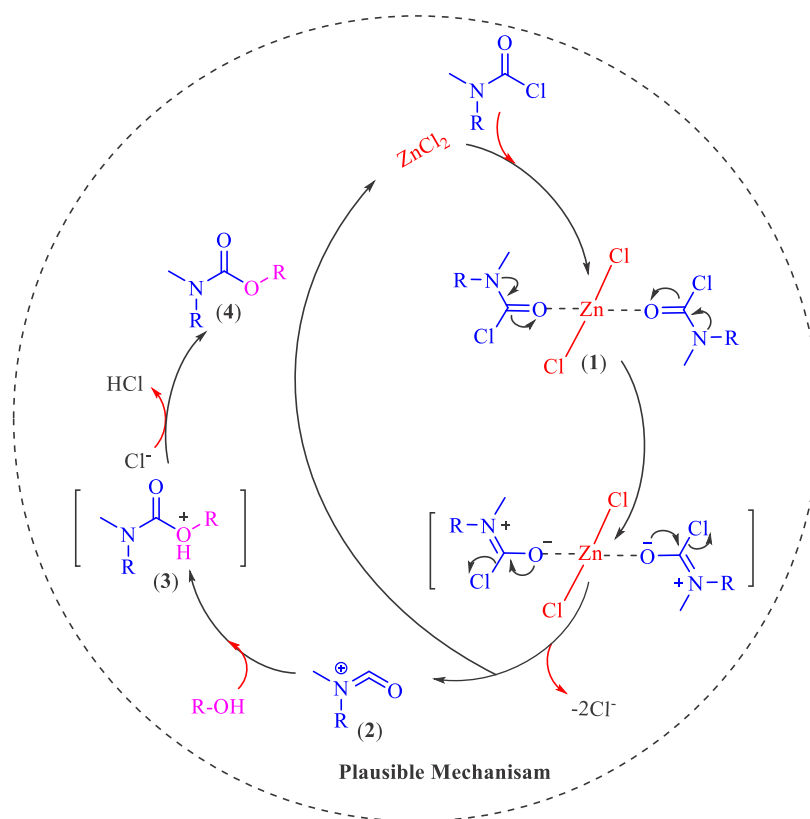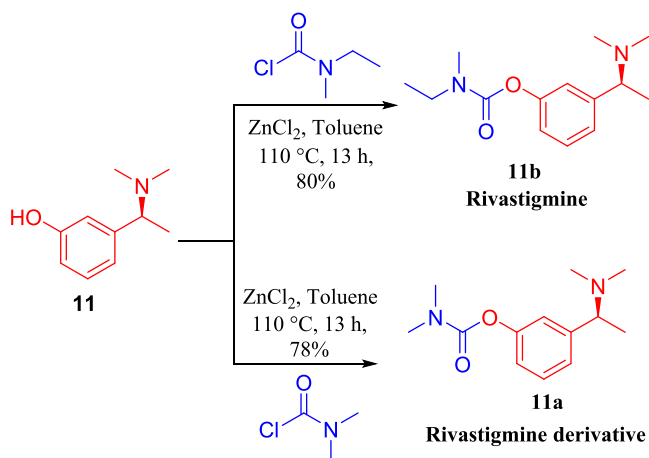
**Figure 2.** Plausible mechanism of carbamate synthesis catalyzed by zinc chloride.

**Scheme 4. Synthesis of Rivastigmine and Its Derivative**



phenyl dimethylcarbamate (**1a**) (0.65 g, 86%) as a brown solid. MP 43−45 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.26 (d, $J$ = 9.2 Hz, 2H), 7.32 (d, $J$ = 9.2 Hz, 2H), 3.14 (s, 3H), 3.05 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 156.45, 153.47, 144.77, 125.09, 122.30, 36.88, 36.62; FTIR (KBr) ν: 2939, 2769, 1735, 1608, 1523, 1392, 1346, 1222, 1157 cm$^{-1}$; ESI-MS $m/z$ calcd. for [C$_9$H$_{10}$N$_2$O$_4$]$^+$ 211.19; found, 209.11 and 208.18 [M − H and 2H]$^-$.

*Phenyl Dimethylcarbamate (2a).* The reaction was performed as described in general procedure A using phenol (**2**) (0.5 g, 5.31 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave phenyl dimethylcarbamate (**2a**) (0.67 g, 76%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.42−7.35 (m, 2H), 7.22 (t, $J$ = 7.4 Hz, 1H), 7.14 (d, $J$ = 7.6 Hz, 2H), 3.12 (s, 3H), 3.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 155.00, 151.58, 129.27, 125.22, 121.81, 115.38, 36.73, 36.49; FTIR (CCl$_4$) ν: 3043, 2935, 1724, 1481, 1388, 1207 cm$^{-1}$; ESI-MS $m/z$ calcd. for [C$_9$H$_{11}$NO$_2$]$^+$ 166.08; found, 166.00 [M + H]$^+$.

*4-Acetylphenyl Dimethylcarbamate (3a).* The reaction was performed as described in general procedure B using 1-(4-hydroxyphenyl)ethan-1-one (**3**) (0.5 g, 3.67 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave 4-acetylphenyl dimethylcarbamate (**3a**) (0.55 g, 72%) as a white solid. MP 49−50 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.98 (d, $J$ = 8.8 Hz, 2H), 7.23 (d, $J$ = 8.7 Hz, 2H), 3.13 (s, 3H), 3.04 (s, 3H), 2.60 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 197.04, 155.37, 154.09, 134.10, 129.85, 121.75, 36.80, 36.57, 26.63; (KBr) ν: 3051, 2943, 1728, 1674, 1589, s 1454, 1396, 1261, 1211 cm$^{-1}$; ESI-MS $m/z$ calcd. for [C$_{11}$H$_{13}$NO$_3$]$^+$ 208.09; found, 208.18 [M + H]$^+$.

*3-Acetylphenyl Dimethylcarbamate (4a).* The reaction was performed as described in general procedure B using 1-(3-hydroxyphenyl)ethan-1-one (**4**) (0.5 g, 3.67 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 3-acetylphenyl dimethylcarbamate (**4a**) (0.48 g, 63%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.81−7.76 (m, 1H), 7.71−7.68 (m, 1H), 7.45 (t, $J$ = 7.9 Hz, 1H), 7.33 (m, 1H), 3.11 (s, 3H), 3.01 (s, 3H), 2.58 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 197.23, 154.55, 151.78, 138.36, 129.45, 126.70, 125.12, 121.65, 36.77, 36.50, 26.72; FTIR (CCl$_4$) ν: 2935, 1728, 1689, 1589, 1477, 1388, 1261, 1192, 1151 cm$^{-1}$; ESI-MS $m/z$ calcd. for [C$_{11}$H$_{13}$NO$_3$]$^+$ 208.09; found, 208.11 [M + H]$^+$.

*4-Formylphenyl Dimethylcarbamate (5a).* The reaction was performed as described in general procedure A using 4-

hydroxybenzaldehyde (**5**) (0.5 g, 4.09 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave 4-formylphenyl dimethylcarbamate (**5a**) (0.65 g, 82%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 9.95 (s, 1H), 7.90−7.85 (m, 2H), 7.30−7.26 (m, 2H), 3.09 (s, 3H), 3.01 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 191.09, 156.39, 153.86, 133.38, 131.11, 122.30, 36.78, 36.56; FTIR (CCl$_4$) $\nu$: 3032, 2939, 2827, 2731, 1728, 1708, 1597, 1489, 1388, 1219 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{11}NO_3]^+$ 194.07; found, 194.12 $[M + H]^+$.

*2-Formylphenyl Dimethylcarbamate (6a).* The reaction was performed as described in general procedure A using 2-hydroxybenzaldehyde (**6**) (0.5 g, 4.09 mmol). Purification by column chromatography (hexane/ethyl acetate, 3:2) gave 2-formylphenyl dimethylcarbamate (**6a**) (0.67 g, 84%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 10.20 (s, 1H), 7.87 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.39−7.30 (m, 1H), 7.60 (m, 1H), 7.24 (dd, $J$ = 8.2, 0.8 Hz, 1H), 3.16 (s, 3H), 3.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 188.88, 154.23, 153.02, 135.20, 129.86, 128.50, 125.80, 123.69, 36.93, 36.64; FTIR (CCl$_4$) $\nu$: 3042, 2935, 2858, 2754, 1728, 1701, 1604, 1581, 1477, 1454, 1384 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{11}NO_3]^+$ 194.07; found, 194.00 $[M + H]^+$.

*4-Formyl-2-Methoxyphenyl Dimethylcarbamate (7a).* The reaction was performed as described in general procedure B using 4-hydroxy-3-methoxybenzaldehyde (**7**) (0.5 g, 3.28 mmol). Purification by column chromatography (hexane/ethyl acetate, 3:2) gave 4-formyl-2-methoxyphenyl dimethylcarbamate (**7a**) (0.36 g, 49%) as a white solid. MP 69−70 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 9.91 (s, 1H), 7.50−7.39 (m, 2H), 7.25 (d, $J$ = 7.8 Hz, 1H), 3.11 (s, 3H), 3.88 (s, 3H), 3.00 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 191.22, 153.83, 152.48. 145.88, 134.67, 124.79, 123.76, 110.75, 56.14, 36.84, 36.65; FTIR (KBr) $\nu$: 3012, 2939, 2839, 2731, 1732, 1643, 1608, 1462, 1388, 1276, 1153 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{11}H_{13}NO_4]^+$ 223.08; found, 223.21 $[M + H]^+$.

*3-Methoxyphenyl Dimethylcarbamate (8a).* The reaction was performed as described in general procedure A using 3-methoxyphenol (**8**) (0.5 g, 4.02 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 3-methoxyphenyl dimethylcarbamate (**8a**) (0.61 g, 78%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.28 (d, $J$ = 7.9 Hz, 1H), 6.77 (m, 1H), 6.73 (m, 1H), 6.70 (t, $J$ = 2.3 Hz, 1H), 3.81 (s, 3H), 3.12 (s, 3H), 3.03 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 160.39, 154.83, 152.54, 129.58, 114.02, 111.27, 107.69, 55.39, 36.71, 36.47; FTIR (CCl$_4$) $\nu$: 2939, 1724, 1600, 1481, 1450, 1394, 1269, 1157 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{13}NO_3]^+$ 196.09; found, 196.24 $[M + H]^+$.

*Benzyl Dimethylcarbamate (9a).* The reaction was performed as described in general procedure A using phenylmethanol (**9**) (0.5 g, 4.62 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave benzyl dimethylcarbamate (**9a**) (0.63 g, 76%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.35−7.41 (m, 4H), 7.34 (d, $J$ = 2.6 Hz, 1H), 5.15 (s, 2H), 2.95 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 156.50, 137.01, 128.47, 127.93, 127.85, 67.02; FTIR (CCl$_4$) $\nu$: 3036, 2939, 1763, 1708, 1620, 1400, 1280, 1184 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{13}NO_2]^+$ 180.09; found, 180.29 $[M + H]^+$.

*4-(3-Chlorophenyl)Butyl Dimethylcarbamate (10a).* The reaction was performed as described in general procedure A using 4-(3-chlorophenyl)butan-1-ol (**10**) (0.5 g, 2.70 mmol). Purification by column chromatography (hexane/ethyl acetate,

4:1) gave 4-(3-chlorophenyl)butyl dimethylcarbamate (**10a**) (0.51 g, 73%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.14−7.26 (m, 3H), 7.03−7.11 (m, 1H), 4.10 (t, $J$ = 6.1 Hz, 2H), 2.92 (s, 6H), 2.65 (t, $J$ = 7.2 Hz, 2H), 1.67−1.73 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 156.77, 144.24, 134.08, 129.58, 128.50, 126.62, 126.01, 65.03, 36.35, 35.93, 35.16, 28.63, 27.51; FTIR (CCl$_4$) $\nu$: 2939,1705, 1585, 1477, 1396, 1265, 1188 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for $[C_{13}H_{18}ClNNaO_2]^+$ 278.0923, found 278.0916 $[M + Na]^+$; ESI-MS $m/z$ calcd. for $[C_{13}H_{18}ClNO_2]^+$ 256.10; found, 256.26 $[M + H]^+$.

*4-Nitrophenyl Ethyl(Methyl)Carbamate (1b).* The reaction was performed as described in general procedure A using 4-nitrophenol (**1**) (0.5 g, 3.59 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 4-nitrophenyl ethyl(methyl)carbamate (**1b**) (0.70 g, 87%) as a white solid. MP 59−61 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 8.22−8.35 (m, 2H), 7.27−7.35 (m, 2H), 3.47 (dd, $J$ = 24.3, 7.2 Hz, 2H, rotamer), 3.07 (d, $J$ = 29.9 Hz, 3H, rotamer), 1.25 (m, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 156.48, (153.15, rotamer), (152.99, rotamer), 144.73, 144.69, 125.06, 125.03, 122.27, (44.36, rotamer), (44.29, rotamer), (34.41, rotamer), (33.98, rotamer), (13.26, rotamer), (12.38, rotamer); FTIR (KBr) $\nu$: 3068, 2978, 2939, 2453, 1732, 1600, 1523, 1481, 1396, 1346, 1222, 1153 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{12}N_2O_4]^+$ 225.08; found, 225.21 $[M + H]^+$.

*Phenyl Ethyl(Methyl)Carbamate (2b).* The reaction was performed as described in general procedure A using phenol (**2**) (0.5 g, 5.31 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave phenyl ethyl(methyl)-carbamate (**2b**) (0.69 g, 72%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.38 (t, $J$ = 7.9 Hz, 2H), 7.11−7.25 (m, 3H), 3.42−3.54 (m, 2H, rotamer), 3.06 (d, $J$ = 30.2 Hz, 3H, rotamer), 1.24 (dt, $J$ = 19.9, 7.2 Hz, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 151.57, 129.23, 125.13, 121.79, 44.09, (34.26, rotamer), (33.82, rotamer), (13.23, rotamer), (12.49, rotamer); FTIR (CCl$_4$) $\nu$: 2974, 2935, 1724, 1455, 1366, 1207, 1162 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{10}H_{13}NO_2]^+$ 180.09; found, 180.15 $[M + H]^+$.

*4-Acetylphenyl Ethyl(Methyl)Carbamate (3b).* The reaction was performed as described in general procedure B using 1-(4-hydroxyphenyl)ethan-1-one (**3**) (0.5 g, 3.67 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave 4-acetylphenyl ethyl(methyl)carbamate (**3b**) (0.60 g, 73%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.94−8.00 (m, 2H), 7.23 (dd, $J$ = 8.6, 4.7 Hz, 2H), 3.46 (dq, $J$ = 25.1, 7.1 Hz, 2H, rotamer), 3.05 (d, $J$ = 30.7 Hz, 3H, rotamer), 2.60 (s, 3H), 1.23 (m, $J$ = 19.8, 7.1 Hz, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 197.02, 155.39, (153.76, rotamer), (153.58, rotamer), 134.04, 134.00, 129.83, 129.80, 121.73, 44.20 (34.32, rotamer), (33.91, rotamer), 26.60, (13.25, rotamer), (12.43, rotamer); FTIR (CCl$_4$) $\nu$: 2974, 2935, 1728, 1685, 1465, 1400, 1269, 1215, 1157 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{12}H_{15}NO_3]^+$ 222.11; found, 222.27 $[M + H]^+$.

*3-Acetylphenyl Ethyl(Methyl)Carbamate (4b).* The reaction was performed as described in general procedure B using 1-(3-hydroxyphenyl)ethan-1-one (**4**) (0.5 g, 3.67 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 3-acetylphenyl ethyl(methyl)carbamate (**4b**) (0.51 g, 62%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) (maximum peaks shows rotamer pattern) $\delta$ ppm: 7.77 (dt, $J$ = 7.8, 1.4 Hz, 1H), 7.64−7.72 (m, 1H), 7.44 (t, $J$ = 7.9 Hz, 1H), 7.33 (dd, $J$

= 8.0, 3.3 Hz, 1H), 3.44 (dq, $J$ = 29.0, 7.1 Hz, 2H), 3.03 (d, $J$ = 34.2 Hz, 3H), 2.58 (s, 3H), 1.22 (dt, $J$ = 23.4, 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) (maximum peaks show a rotamer pattern) $\delta$ ppm: 197.21, 154.20, 154.05, 151.77, 138.34, 129.41, 126.72, 126.67, 125.08, 125.03, 121.64, 121.58, 45.10, 44.16, 44.12, 34.28, 33.84, 26.69, 13.23, 12.42; FTIR (CCl$_4$) $\nu$: 2974, 2935, 1728, 1693, 1435, 1396, 1257, 1192, 1157 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{12}H_{15}NO_3]^+$ 222.11; found, 222.20 $[M + H]^+$.

*4-Formylphenyl Ethyl(Methyl)Carbamate (5b).* The reaction was performed as described in general procedure A using 4-hydroxybenzaldehyde (**5**) (0.5 g, 4.09 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave 4-formylphenyl ethyl(methyl)carbamate (**5b**) (0.68 g, 88%) as a white solid. MP 42−43 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: (maximum peaks show a rotamer pattern) $\delta$ ppm: 10.19 (d, $J$ = 4.9 Hz, 1H), 7.86 (dt, $J$ = 7.9, 2.5 Hz, 1H), 7.58 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.27−7.35 (m, 1H), 7.22 (t, $J$ = 7.8 Hz, 1H), 3.46 (m, $J$ = 44.7, 7.2 Hz, 2H), 3.05 (d, $J$ = 46.0 Hz, 3H), 1.23 (m $J$ = 28.3, 7.2 Hz, 3H), $^{13}$C NMR (100 MHz, CDCl$_3$) (maximum peaks show a rotamer pattern) $\delta$ ppm: 188.79, 188.65, 153.85, 153.73, 153.14, 153.02, 135.15, 135.12, 129.78, 129.54, 128.59, 128.50, 125.72, 125.68, 123.68, 123.58, 44.35, 44.23, 34.37, 33.98, 13.27, 12.40; FTIR (KBr) $\nu$: 2974, 2935, 2827, 2731, 1724, 1597, 1465, 1396, 1292, 1215, 1157 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{11}H_{13}NO_3]^+$ 208.19; found, 208.00 $[M + H]^+$.

*2-Formylphenyl Ethyl(Methyl)Carbamate (6b).* The reaction was performed as described in general procedure A using 2-hydroxybenzaldehyde (**6**) (0.5 g, 4.09 mmol). Purification by column chromatography (hexane/ethyl acetate, 3:2) gave 2-formylphenyl ethyl(methyl)carbamate (**6b**) (0.69 g, 81%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 10.21 (d, $J$ = 4.6 Hz, 1H), 7.89 (dt, $J$ = 7.8, 2.4 Hz, 1H), 7.62 (td, $J$ = 7.8, 1.8 Hz, 1H), 7.35 (t, $J$ = 7.5 Hz, 1H), 7.22−7.29 (m, 1H), 3.42−3.58 (m, 2H, rotamer), 3.09 (d, $J$ = 45.4 Hz, 3H, rotamer), 1.21−1.32 (m, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: (188.90, rotamer), (188.75, rotamer), (153.14, rotamer), (153.01, rotamer), 135.17, 132.07, 129.63, 128.50, 125.72, 123.59, (44.40, rotamer), (44.28, rotamer), (34.42, rotamer), (34.01, rotamer), (13.30, rotamer), (12.42, rotamer); FTIR (CCl$_4$) $\nu$: 2974, 2935, 2866, 2746, 1728, 1604, 1454, 1392, 1276, 1211, 1157 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for $[C_{11}H_{13}NO_3K]^+$, 246.1883; found 246.0739 $[M + K]^+$; ESI-MS $m/z$ calcd. for $[C_{11}H_{13}NO_3]^+$ 208.09; found, 208.10 $[M + H]^+$.

*4-Formyl-2-Methoxyphenyl Ethyl(Methyl)Carbamate (7b).* The reaction was performed as described in general procedure B using 4-hydroxy-3-methoxybenzaldehyde (**7**) (0.5 g, 3.28 mmol). Purification by column chromatography (hexane/ethyl acetate, 3:2) gave 4-formyl-2-methoxyphenyl ethyl(methyl)-carbamate (**7b**) (0.4 g, 51%) as a white solid. MP 72−74 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 9.93 (s, 1H), 7.41−7.50 (m, 2H), 7.24−7.30 (m, 1H), 3.90 (s, 3H), 3.39−3.56 (m, 2H, rotamer), 3.05 (d, $J$ = 39.6 Hz, 3H, rotamer), 1.18−1.31 (m, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 191.24, (153.60, rotamer), (153.43, rotamer), (152.54, rotamer), (152.46, rotamer), 146.05, 134.65, 134.59, 124.91, 123.81, 110.64, 56.12, 44.38, (34.42, rotamer), (34.01, rotamer), (12.99, rotamer), (12.38, rotamer); FTIR (KBr) $\nu$: 2970, 2939, 2889, 2835, 2731, 1728, 1651, 1597, 1465, 1392, 1273, 1207, 1153 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for

$[C_{12}H_{15}NO_4]^+$, 238.1001; found 238.1070 $[M + H]^+$; ESI-MS $m/z$ calcd. for $[C_{12}H_{15}NO_4]^+$ 238.10; found, 238.22 $[M + H]^+$.

*3-Methoxyphenyl Ethyl(Methyl)Carbamate (8b).* The reaction was performed as described in general procedure A using 3-methoxyphenol (**8**) (0.5 g, 4.02 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 3-methoxyphenyl ethyl(methyl)carbamate (**8b**) (0.68 g, 78%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.28 (d, $J$ = 7.9 Hz, 1H), 6.69−6.79 (m, 3H), 3.82 (s, 3H), 3.40−3.51 (m, 2H, rotamer), 3.05 (d, $J$ = 28.2 Hz, 3H, rotamer), 1.24 (m, $J$ = 18.5, 7.2 Hz, 3H, rotamer); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 160.39, 152.55, 129.57, 114.03, 111.21, 107.70, 55.39, 44.09, (34.26, rotamer), (33.82, rotamer), (13.23, rotamer), (12.48, rotamer); FTIR (CCl$_4$) $\nu$: 2970, 2943, 1720, 1604, 1477, 1396, 1269, 1157 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for $[C_{11}H_{15}NO_3]^+$ 210.1129; found 210.1130 $[M + H]^+$; ESI-MS $m/z$ calcd. for $[C_{11}H_{15}NO_3]^+$ 210.25; found, 210.26 $[M + H]^+$.

*Benzyl Ethyl(Methyl)Carbamate (9b).* The reaction was performed as described in general procedure A using phenylmethanol (**9**) (0.5 g, 4.62 mmol). Purification by column chromatography (hexane/ethyl acetate, 7:3) gave benzyl ethyl(methyl)carbamate (**9b**) (0.71 g, 79%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.31−7.46 (m, 5H), 5.15 (s, 2H), 3.36 (q, $J$ = 7.3 Hz, 2H), 2.94 (s, 3H), 1.14 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 156.13, 137.08, 128.46. 127.88, 127.79, 66.90, 43.73, (34.02, rotamer), (33.31, rotamer), (13.07, rotamer), (12.61, rotamer); FTIR (CCl$_4$) $\nu$: 2970, 2939, 1705, 1469, 1404, 1296, 1176 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for $[C_{11}H_{15}NNaO_2]^+$ 216.0999; found 216.0997 $[M + Na]^+$; ESI-MS $m/z$ calcd. for $[C_{11}H_{15}NO_2]^+$ 194.25; found, 194.30 $[M + H]^+$.

*4-(3-Chlorophenyl)Butyl Ethyl(Methyl)Carbamate (10b).* The reaction was performed as described in general procedure A using 4-(3-chlorophenyl)butan-1-ol (**10**) (0.5 g, 2.70 mmol). Purification by column chromatography (hexane/ethyl acetate, 4:1) gave 4-(3-chlorophenyl)butyl ethyl-(methyl)-carbamate (**10a**) (0.57 g, 71%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.16−7.25 (m, 3H), 7.05−7.10 (m, 1H), 4.09−4.12 (t, 2H), 3.27−3.36 (q, 2H), 2.90 (s, 3H), 2.65 (t, $J$ = 7.1 Hz, 2H), 1.67−1.73 (m, 4H), 1.12 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 156.36, 144.25, 134.09, 129.58, 128.50, 126.62, 126.01, 64.85, 43.51, 35.15, 33.33, 28.63, 27.54, 12.81; FTIR (CCl$_4$) $\nu$: 2939, 1701, 1589, 1473, 1392, 1298, 1180 cm$^{-1}$; HRMS (ESI-TOF) $m/z$ calcd for $[C_{14}H_{20}ClNNaO_2]^+$ 292.1080; found 292.1081 $[M + Na]^+$; ESI-MS $m/z$ calcd. for $[C_{14}H_{20}ClNO_2]^+$ 270.77; found, 270.323 $[M + H]^+$.

*(S)-3-(1-(Dimethylamino)Ethyl)Phenyl Ethyl(Methyl)-Carbamate (11b).* The reaction was performed as described in the procedure C for the synthesis of rivastigmine using (S)-3-(1-(dimethylamino)ethyl)phenoll (**10**) (5 g, 30.25 mmol). Purification by column chromatography (CH$_2$Cl$_2$/MeOH, 9:1) gave (S)-3-(1-(dimethylamino)ethyl)phenyl ethyl-(methyl)carbamate (**11b**) (6.15 g, 80%) as a brown oil. HPLC: 91.23% ee. The ee was determined on a chiral cellulose-C column with *n*-hexane/2-propanol/trifluoroacetic acid/diethanolamine = 80:20:0.2:0.2, flow = 1 mL/min, wavelength = 230 nm. Retention times: 8.198 min (Figure S1). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.26−7.32 (m, 1H), 6.97−7.18 (m, 3H), 3.38−3.50 (m, 2H), 3.26 (q, $J$ = 6.7 Hz, 1H), 3.03 (d, $J$ = 29.5 Hz, 3H), 2.21 (s, 6H), 1.33−1.42 (d, 3H), 1.16−1.28 (m, 3H), 2 rotamers; $^{13}$C NMR (100 MHz,

CDCl$_3$) $\delta$ ppm: 151.54, 145.66, 128.89, 124.23, 120.77, 120.28, 65.63, 44.04, 43.19, (34.21, rotamer), (33.78, rotamer), 20.06, (13.23, rotamer), (12.48, rotamer); FTIR (CCl$_4$) $\nu$: 2974, 2943, 2874, 2820, 2769, 1724, 1465, 1392, 1230, 1165 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{14}H_{22}N_2O_2]^+$ 251.17; found, 251.31$[M + H]^+$.

*(S)-3-(1-(Dimethylamino)Ethyl)Phenyl Dimethylcarbamate (11a)*. The reaction was performed as described in the procedure C for the synthesis of rivastigmine derivative using (*S*)-3-(1-(dimethylamino)ethyl)phenoll (**10**) (1.5 g, 9.07 mmol). Purification by column chromatography (CH$_2$Cl$_2$/ MeOH, 9:1) gave (*S*)-3-(1-(dimethylamino)ethyl)phenyl ethyl(methyl)carbamate (**11b**) (1.69 g, 78%) as a yellow oil. HPLC: 97.44% ee. The ee was determined on a chiral cellulose-C column with *n*-hexane/2-propanol/trifluroacetic acid/diethanolamine = 80:20:0.2:0.2, flow = 1 mL/min, wavelength = 230 nm. Retention times: 17.562 min (Figure S2). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.31 (t, *J* = 7.9 Hz, 1H), 7.08 (s, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.03 (d, *J* = 8.7 Hz, 1H), 3.34 (q, *J* = 6.7 Hz, 1H), 3.10 (s, 3H), 3.01 (s, 3H), 2.24 (s, 6H), 1.40 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 154.94, 151.57, 144.77, 129.03, 124.44, 120.95, 120.52, 65.60, 42.95, 36.72, 36.47, 29.73, 19.76; FTIR (CCl$_4$) $\nu$: 2931, 2858, 2816, 2769, 1724, 1608, 1446, 1384, 1269, 1230, 1168 cm$^{-1}$; ESI-MS $m/z$ calcd. for $[C_{13}H_{20}N_2O_2]^+$ 237.15; found, 237.22 $[M + H]^+$.

## ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c05350.

> Characterization spectra $^1$H, $^{13}$C, NMR, IR, and mass spectra of all compounds; $^1$H, $^{13}$C, COSY, NOSY NMR, IR, HRMS, and mass spectra of novel compounds; and HPLC chromatograms for rivastigmine and it derivatives (PDF)

## AUTHOR INFORMATION

### Corresponding Author

**Jhillu Singh Yadav** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India;* Ⓞ orcid.org/0000-0002-6535-1704; Email: yadavfna@gmail.com

### Authors

**Manoj Gayke** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India*

**Nirbhay Hirapara** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India*

**Hanuman Narode** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India*

**Siddhanath D. Bhosle** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India*

**Rajesh S. Bhosale** − *Department of Chemistry, School of Science, Indrashil University, Mehsana 382715 Gujarat, India*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.2c05350

### Author Contributions

M.G. contributed to the synthesis, characterization, preparation of the supporting information, and proofreading of the manuscript. N.H. performed the synthesis and characterization of carbamate scaffolds. H.N. performed the characterization of carbamate scaffolds and preparation of the supporting information. S.D.B. performed the characterization of carbamate scaffolds and preparation of the supporting information. R.S.B. contributed to the evaluation of results, optimization of methodology, and proofreading. J.S.Y. contributed to the methodology design, final result analysis, and manuscript writing.

### Notes

The authors declare no competing financial interest.

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