

Concise syntheses and some biological activities of DL-2,5-di-O-methyl-*chiro*-inositol, DL-1,4-di-O-methyl-*scyllo*-inositol, and DL-1,6-dibromo-1,6-dideoxy-2,5-di-O-methyl-*chiro*-inositol

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Abstract

The regio- and stereospecific synthesis of O-methyl-*chiro*-inositols and O-methyl-*scyllo*-inositol was achieved, starting from *p*-benzoquinone. After preparing dimethoxy conduritol-B as a key compound, regiospecific bromination of the alkene moiety of dimethoxy conduritol-B and acid-catalyzed ring opening of dimethoxydiacetate conduritol-B epoxide with Ac₂O afforded the desired new *chiro*-inositol derivatives and *scyllo*-inositol derivative, respectively. Spectroscopic methods were employed for the characterization of all synthesized compounds. The novel inositols (**11–17**) had effective inhibition profiles against human carbonic anhydrase isoenzymes I and II (hCA I and II) and acetylcholinesterase (AChE). The novel inositols **11–17** were found to be effective inhibitors against AChE, hCA I, and hCA II enzymes. K_i values were calculated in the range of 87.59 ± 7.011 to 237.95 ± 17.75 μM for hCA I, 65.08 ± 12.39 to 538.98 ± 61.26 μM for hCA II, and 193.28 ± 43.13 to 765.08 ± 209.77 μM for AChE, respectively. Also, due to the inhibitory effects of the novel inositols **11–17** against the tested enzymes, these novel inositols are potential drug candidates to treat some diseases such as glaucoma, epilepsy, leukemia, and Alzheimer's disease.

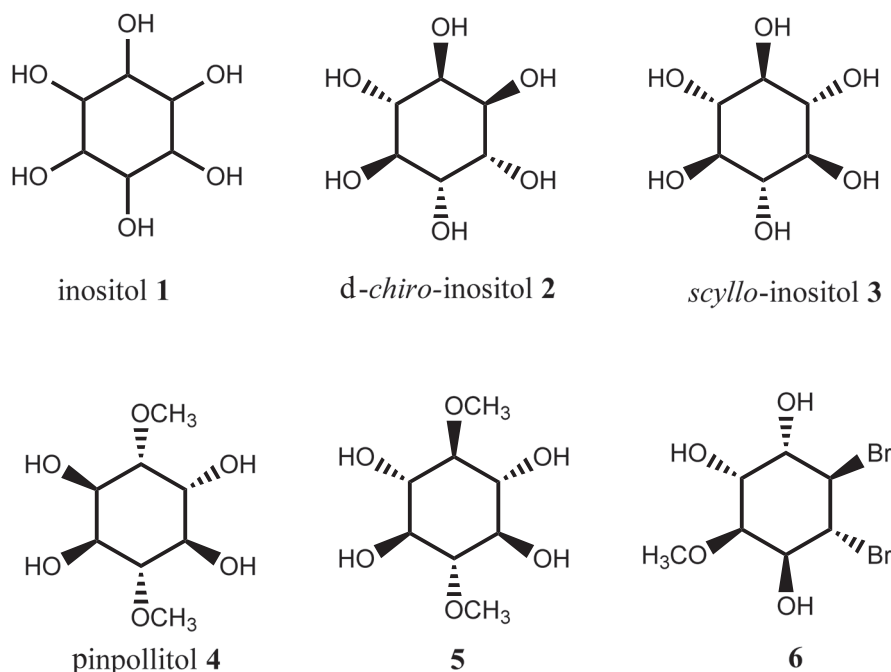
KEYWORDS

acetylcholinesterase, carbonic anhydrase, *chiro*-inositol, methoxyinositol, stereospecific synthesis

1 | INTRODUCTION

Inositol **1** and its derivatives (Figure 1) are an important class of biologically active natural products. In theory, there are nine possible inositols, of which six (*myo*-, *D-chiro*-, *L-chiro*-, *scyllo*-, *neo*-, and *muco*-inositols) are known to occur in nature.^[1–3] Recently, biological activities of *chiro*-inositol, *scyllo*-inositol, and their derivatives have been extensively studied. Isolation of one or more methyl esters of these compounds from plants has been reported, and these methyl inositols are presumed to have important functions in plant biology.^[4] *chiro*-Inositol is a naturally occurring inositol isomer in which *D-chiro*-inositol **2** has been effectively employed in the management of polycystic

ovary syndrome (PCOS).^[5–8] Moreover, *myo*-inositol and *D-chiro*-inositol, which are inositol isomers, have been shown to possess insulin-mimetic properties and found to act as second messengers in the insulin intracellular pathway.^[9,10] Recently, accumulating evidence has suggested that one of the most important mechanisms of PCOS pathogenesis is insulin resistance.^[11] It is known that some physiological activities of *myo*-inositol and *D-chiro*-inositol determine the dosages and timing of inositol supplementation in the treatment of PCOS.^[12] In addition, the combined administration of *myo*-inositol and *D-chiro*-inositol allows treatment for PCOS. For this reason, the use of such inositol isoforms as insulin sensitizers has gained increasing attention due to their safety profile and effectiveness.^[12–14]

**FIGURE 1** Selected inositol derivatives

However, both *scyllo*- and *D-chiro*-inositols have potential roles in medicine. *scyllo*-Inositol **3** has shown promise as a potential therapeutic for Alzheimer's disease (AD), by directly interacting with the amyloid β ($A\beta$) peptide to inhibit $A\beta$ fiber formation.^[15–17] ^1H nuclear magnetic resonance (NMR) spectroscopy has been used to detect *scyllo*-inositol in the brain and in cancers. *D-chiro*-Inositol can also be used for reducing hyperglycemia due to its insulin-mimetic property by restoring insulin sensitivity.^[10] Recently, their methyl inositols or methoxyinositols (pinitol),^[18,19] 1,4-di-O-methyl-*chiro*-inositol **4** (pinpollitol),^[20] 1,2-di-O-methyl-*chiro*-inositol,^[21] and 1,4-di-O-methyl-*scyllo*-inositol **5**^[16] have been synthesized from some natural compounds. Moreover, halo-substituted inositols (dimethoxydichloro compound,^[22] methoxyfluoro compound,^[23] such as methoxydibromo **6**)^[24] have also gained importance over the last decade. (+)-Pinpollitol, a dimethyl ether of *chiro*-inositol was isolated from the pollen and needles of *Pinus radiata* by Gallagher,^[25] and its structure has been proven as 1*D*-1,4-di-O-methyl-*chiro*-inositol **4**.^[26] Another dimethyl ether of *chiro*-inositol, 1*D*-1,3-di-O-methyl-*chiro*-inositol, was synthesized by Sureshan et al.^[26]

The preparation of cyclitols and their analogs is challenging due to the dense stereochemistry of the hydroxylated carbon centers. Thus, every step in the progress of the synthesis of inositols is very important. Recently, we have reported the stereospecific synthesis of some polyhydroxylated compounds.^[27–30] Consequently, regarding the previous results, we aimed to synthesize novel halogenated deoxyinositols containing methyl groups. Due to the improvements in the biological activity of various cyclitols on methoxyinositol and interesting structural features of halogenated deoxyinositols, we focused on the synthesis of dimethoxydibromo deoxyinositol.

Carbonic anhydrases (CAs) are structurally several distinct enzyme families that catalyze the transformation of carbon dioxide

(CO_2) to bicarbonate (HCO_3^-) and proton (H^+). This important reaction affects pH values and provides HCO_3^- ions in several metabolic, physiological, and biosynthetic pathways.^[31–33] The CAs are an active research area for medicinal chemists, as effective CA inhibitors (CAIs) need to be designed, which play a main role in the treatment of glaucoma, epilepsy, altitude sickness, and idiopathic intracranial hypertension.^[34–36] CAIs can constitute new therapeutics against cancer or can have capacity as antiviral and antifungal drugs. Nowadays, the inhibition act of CAs by sulfonamide molecules has also been reported to inhibit the growth and development of pathogenic microorganisms.^[37,38] Indeed, selective inhibition of CA II establishes an effective approach to fight against the disturbances caused by the detrimental effects of the CA II isoenzyme.^[39–41]

Acetylcholinesterase (AChE) is typically synthesized in muscle, nerve, and some hematopoietic cells. In inducible tissues, AChE is localized on the extracellular surface of both muscle and nerve and is arranged by tissue. The prime effect of AChE is the termination of nerve impulse conduction by the rapid hydrolysis of acetylcholine (ACh) in cholinergic synapses.^[42–44] Recently, a large spectrum of AChE inhibitors has been developed and approved to treat myasthenia gravis, Parkinson's disease (PD), senile dementia, AD, and ataxia. There are diverse drugs, for example, tacrine, donepezil, and rivastigmine, based on the duration of memory loss and cognitive dysfunction related to AD.^[45–47] Indeed, these molecules have been recorded to have some effects like gastrointestinal disturbances.^[48–50] These clinical medications can prevent ACh disruption and enhance its level in cholinergic synapses, which can increase cognitive deficits. However, the adverse and undesired effects including nausea, weight loss, and vomiting have restrained their clinical usage and efficacy. So, it is essential to develop novel AChE inhibitors with less toxic side effects and better therapeutic effects.^[51–53]

In this study, we synthesized some novel inositol derivatives (**11–17**) and determined their inhibition properties against the CA I, CA II isoenzymes, and AChE enzymes linked to some global diseases including epilepsy, glaucoma, AD, PD, and leukemia.

2 | RESULTS AND DISCUSSION

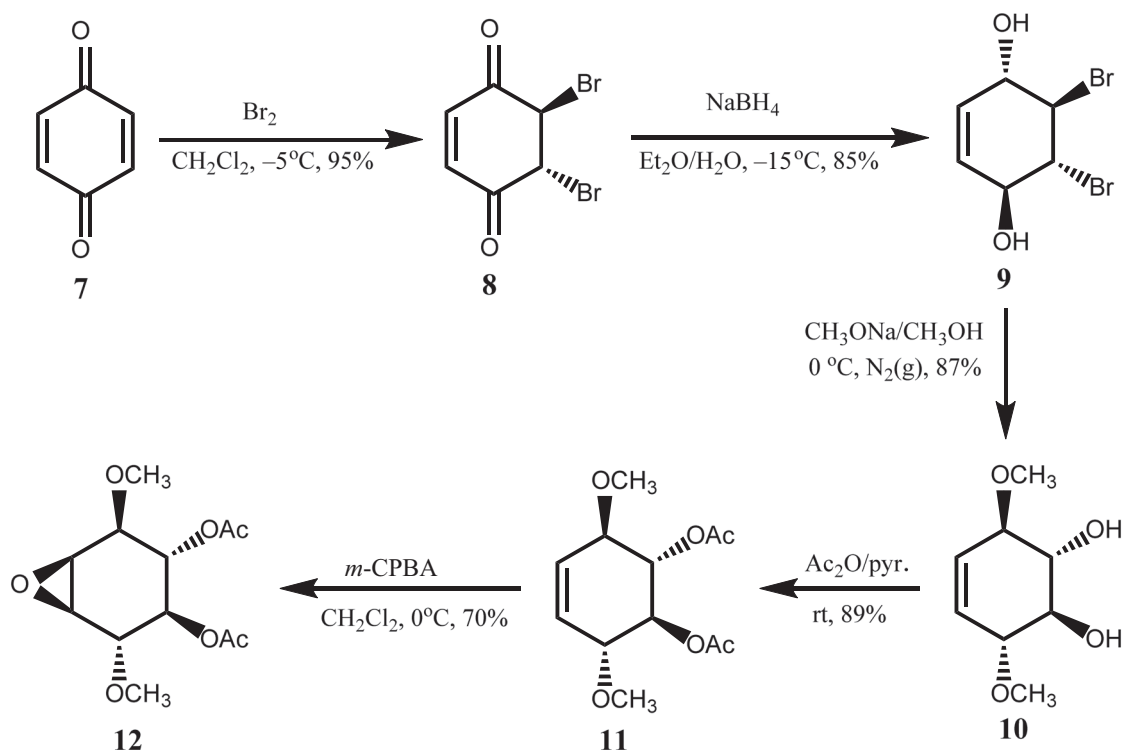
2.1 | Chemistry

p-Benzoquinone **7** was brominated at low temperature to give only the *trans*-dibromo compound **8** in a high yield. The required key intermediate, allylic *trans*-diol **9**, for the synthesis of the target compounds was obtained as the sole product by stereoselective reduction of the carbonyl groups with NaBH₄ in ether.^[54–56] Dimethoxydiol **10**, which is a conduritol-B derivative, was obtained from the reaction of dibromodiol **9** with sodium methoxide prepared by dissolving sodium metal in methanol under nitrogen atmosphere in high yields (87%).^[57,58] The stereochemical course of the transformation was mainly determined as the *trans* configuration to methoxy groups. Dimethoxydiacetate **11** was smoothly prepared from the dimethoxydiol **10**, as described previously (Scheme 1).^[57] The structures of both **10** and **11**, which possess C₂ symmetry, were unambiguously deduced from their ¹H and ¹³C NMR spectra. Thus, according to the NMR data of dimethoxydiacetate **11**, it was clear that the conduritol-B configuration was retained after the methoxylation and acetylation reactions of **9**, respectively.

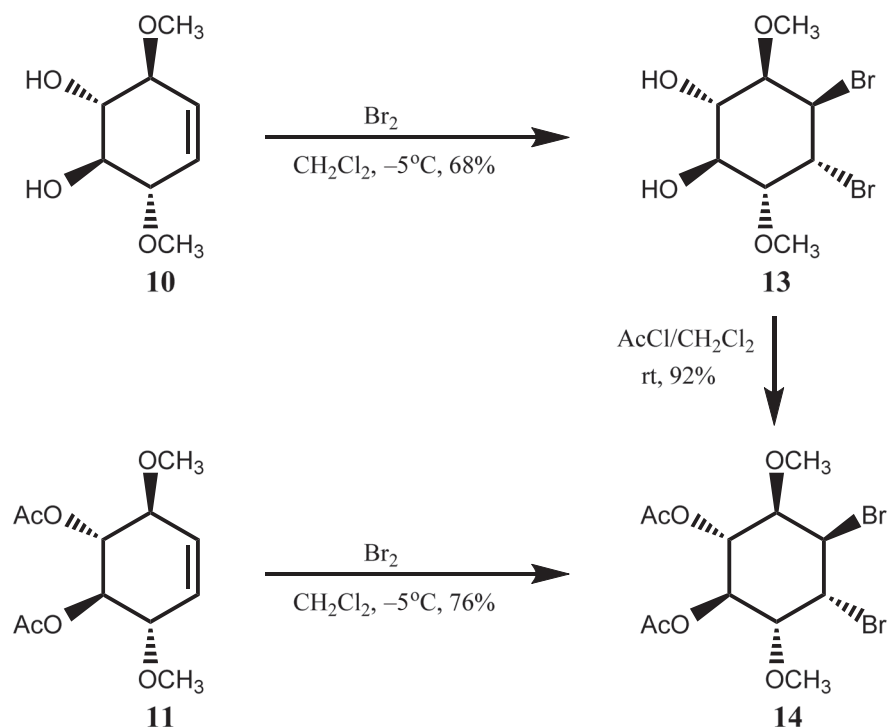
Epoxide **12** was obtained from the treatment of dimethoxydiacetate **11** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in methylene chloride at 0°C. Thus, epoxide **12** was smoothly accomplished as a single isomer in a 70% yield (Scheme 1). A twelve-line pattern in the ¹³C NMR spectrum of **12** confirms the proposed structure. These carbon atoms resonated at 170.0 ppm (–CO₂CH₃), 169.8 ppm (–CO₂CH₃), 78.4 ppm (–CHOMe), 78.0 ppm (–CHOMe), 72.7 ppm (–CHOAc), 68.5 ppm (–CHOAc), 58.5 ppm (–OCH₃), 57.3 ppm (–OCH₃), 54.10 ppm (–CHOCH), 52.6 ppm (–CHOCH), and 20.7 ppm (–CO₂CH₃ × 2).

Treatment of dimethoxydiol **10** with bromine in CH₂Cl₂ at low temperature for 2 days led to the formation of DL-1,6-dibromo-1,6-dideoxy-2,5-di-O-methyl-*chiro*-inositol **13**^[59] (naming by ChemDraw, DL-4,5-dibromo-4,5-dideoxy-3,6-O-methyl-*chiro*-inositol^[59]) as the sole product in 68% yield (Scheme 2). The stereochemical course of the bromination may be *syn* or *anti* with respect to the cyclohexane ring. The structure of compound **13** was unambiguously deduced from its ¹H and ¹³C NMR spectra. Especially, the ¹³C NMR spectrum of **13** consisted of four carbon resonances owing to the C₂ symmetry. These carbon atoms resonated at 77.7 ppm (C–OMe × 2), 73.2 ppm (C–OH × 2), 57.5 ppm (–OCH₃ × 2), and 50.0 ppm (C–Br × 2). However, the NMR spectroscopic studies did not allow the assignment of the exact configuration of the bromine groups. The absolute configuration of *chiro*-inositol derivative **13**^[59] was unambiguously established by X-ray crystallography.

However, to investigate the introduction of bromine into the double bond, bromination of dimethoxydiacetate **11** under the same condition led to the desired dibromodiacetate **14**, which is a

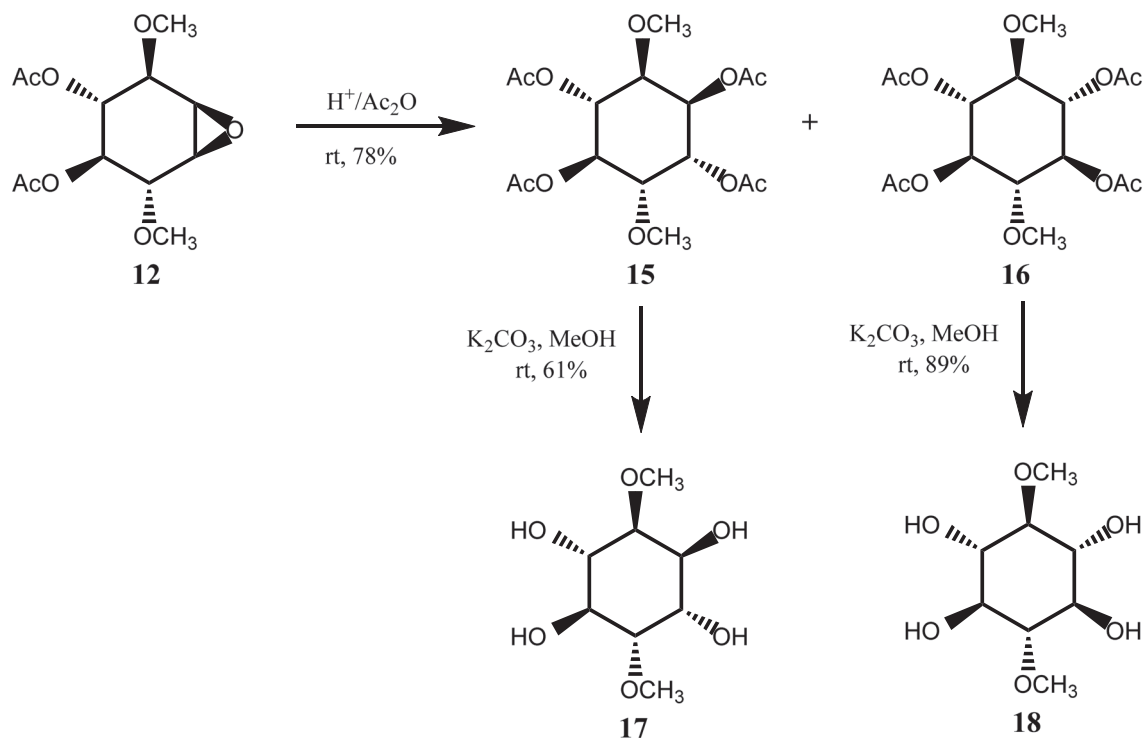


SCHEME 1 The synthesis of dimethoxy conduritol-B epoxide **12**. *m*-CPBA, *m*-chloroperoxybenzoic acid

SCHEME 2 Bromination of compounds **10** and **11**

chiro-inositol derivative, as the sole product in a 76% yield. A six-line pattern in the ^{13}C NMR spectrum of **14** confirms the proposed structure due to C_2 symmetry in the molecule. These carbon atoms resonated at 169.9 ppm ($\text{C}=\text{O} \times 2$), 76.3 ppm ($-\text{C}-\text{OAc} \times 2$), 72.3 ppm ($-\text{C}-\text{OMe} \times 2$), 58.1 ppm ($-\text{OCH}_3 \times 2$), 49.9 ppm ($-\text{C}-\text{Br} \times 2$), and

20.7 ppm ($-\text{CH}_3 \times 2$). Moreover, the potential of this approach was controlled via acetylation of the $-\text{OH}$ groups in **13** with CH_3COCl in methylene chloride at room temperature, resulting in dibromodiacetoxy **14**. After crystallization from AcOEt /hexane, compound **14** was obtained in 92% yield as the only isomer confirmed by

**SCHEME 3** Regio- and stereocontrolled opening of cyclitol epoxide **12**

NMR spectroscopy. Thus, the addition of excellent regio- and stereo-selective bromine to compounds **10** and **11** resulted in products **13** and **14**, a *chiro*-inositol derivative. Bromine may be added stereospecifically to form *trans*-adducts, which have served as valuable precursors in synthetic organic chemistry. The regiochemistry of the bromonium ion ring opening under these conditions was fully not corroborated by the simplification of the NMR pattern observed for this adduct due to the symmetry considerations. The formation mechanism of compounds **13** and **14** was examined in detail in our previous study.^[59]

Treatment of epoxide **12** with Ac₂O under acidic conditions yielded the desired regioisomers **15**, *chiro*-inositol derivative, and **16**, *scyllo*-inositol derivative, in 78% yield (Scheme 3). Ring opening of epoxide **12** led to the corresponding C2 regioadduct **15** as the major product and the corresponding C1 regioadduct **16** as the minor product. However, an eight-line pattern in the ¹³C NMR spectrum of **15** confirms the proposed structure due to C₂ symmetry in the molecule. These carbon atoms resonated at 170.2 ppm (–CO₂CH₃ × 2), 169.1 ppm (–CO₂CH₃ × 2), 77.4 ppm (–CHOME), 71.4 ppm (–CHOAc × 2), 65.8 ppm (–CHOAc × 2), 58.5 ppm (–OCH₃ × 2), 20.83 ppm (–CO₂CH₃ × 2), and 20.77 ppm (–CO₂CH₃ × 2). Regioadduct **16**, found in the lowest amount, has C_{2v} symmetry in contrast to **15** with C₂ symmetry and shows as a five-line pattern in the ¹³C NMR spectrum, which resonated at 169.8 ppm (–CO₂CH₃ × 4), 79.3 ppm (–CHOME × 2), 71.9 ppm (–CHOAc × 4), 60.6 ppm (–OCH₃ × 2), and 20.7 ppm (–CO₂CH₃ × 4), respectively. Thus, its NMR spectra support the proposed structure **16**. Therefore, adduct **16** should be the adduct C1 of epoxide.

To conclude the synthesis of our target compound **17**, approaches to convert the acetate groups into free alcohols using NH₃(g) in methanol were unsuccessful. Hydrolysis of tetraacetate groups in **15** was performed with K₂CO₃ in MeOH under very mild conditions to give DL-2,5-di-O-methyl-*chiro*-inositol **17** in 61% yield. The structure of **17** was established on the basis of ¹H and ¹³C NMR data, which was further verified by the infrared (IR) and high-resolution mass spectroscopy

(HRMS) data as spectroscopic evidence. In addition, hydrolysis of the mixture of **15** and **16** using K₂CO₃ in MeOH under basic conditions gave DL-2,5-di-O-methyl-*chiro*-inositol **17** and DL-1,4-di-O-methyl-*scyllo*-inositol **18**, and their ratio (9:1) was determined on the basis of ¹H and ¹³C NMR data. In accordance with the Fürst-Plattner rule^[60,61] the epoxide ring under acidic conditions opens selectively to form the *trans*-diaxial product (major product), the *chiro*-isomer **15**, and bromination of **10** (its acetate **11**) provides selectivity to form the *trans*-diaxial product, the *chiro*-isomer **13** (its acetate **14**).

2.2 | Enzyme inhibition results

The enzyme inhibition results of hCA I and hCA II isoenzymes and AChE enzymes (IC₅₀ and K_i values) are presented in Table 1. AD is a deadly neurodegenerative discomfort that increases gradually, and it has become a significant health difficulty, especially in industrialized countries with high living controls. The AD pathogenesis is not fully clarified; therefore, there is no therapy for the disease, except for symptomatic curation against mild-to-moderate AD kinds. As AD is recognized with acetylcholine (ACh) deficit in the brain of patients with AD, AChE inhibitors have become the most prescribed medication class in the curation of AD.^[62, 63] Indeed, it is recorded that AD is related to metal agglomeration in senile plaques formed in oxidative stress and patients. Then, it is fundamental that any potential medication that can be used for the duration of AD has both cholinesterases inhibitory as well as antioxidant effects. Inhibition of AChEIs can give rise to the recovery of cognitive impairment and they are the most extensively utilized effective clinical drugs for AD.^[64] Several pieces of evidence over the years have recorded that interplay could exist among AD and epilepsy. Patients with AD have a remarkably higher risk of developing epilepsy than AD and non-AD patients are associated with an increment occurrence of possessions

TABLE 1 The summarized inhibition parameters of novel inositol derivatives (**11–17**) against enzymes including carbonic anhydrases I and II isoenzymes and acetylcholinesterase

Compounds	hCA I			hCA II			AChE		
	IC ₅₀ (μM)	R ²	K _i (μM)	IC ₅₀ (μM)	R ²	K _i (μM)	IC ₅₀ (μM)	R ²	K _i (μM)
11	440.1	.9378	238 ± 18	379.3	.9727	539 ± 61	423.6	.8731	553 ± 181
12	585.3	.9781	226 ± 49	431.0	.9081	226 ± 78	425.9	.9018	682 ± 47
13	333.0	.8677	169 ± 19	440.0	.9503	143 ± 53	423.9	.8698	619 ± 190
14	325.2	.9470	160 ± 58	309.1	.9258	142 ± 35	203.1	.8686	193 ± 43
15	380.8	.9654	152 ± 10	263.6	.9967	65 ± 13	344.8	.9230	221 ± 20
16	371.6	.9892	171 ± 31	265.2	.9754	169 ± 54	215.3	.9743	244 ± 43
17	261.8	.9385	88 ± 7	321.7	.9446	122 ± 1	738.8	.8376	765 ± 210
AZA ^a	0.89	.9672	0.21 ± 1	1.0	.9822	0.27 ± 1	–	–	–
TAC ^a							0.54	.9618	0.21 ± 1

^aAcetazolamide (AZA) and tacrine (TAC) were used as standard inhibitors for all carbonic anhydrases (CAs) and acetylcholinesterases (AChEs), respectively.

in patients with early-onset forms of the disease. Recently, AChEI has also been considered as a promising approach for pharmacological intervention in epilepsy.^[65,66]

It is clear from the results presented in Table 1 that these compounds effectively inhibited AChE, with K_i values in the range of 193 ± 43 to $765 \pm 210 \mu\text{M}$. However, all of these compounds had micromolar inhibition profiles. The most active (\pm)-(1SR,2SR,3RS,4RS,5RS,6RS)-4,5-dibromo-3,6-dimethoxycyclohexane-1,2-diyl diacetate (**14**) showed a K_i value of $193 \pm 43 \mu\text{M}$. However, tacrine showed a K_i value of $0.214 \pm 0.02 \mu\text{M}$ against the cholinergic enzyme of AChE. The results recorded that all these derivatives demonstrated efficient AChE inhibitory effects; however, these inhibition abilities were lower than that of tacrine (K_i : $0.21 \pm 1 \mu\text{M}$) as the standard cholinergic enzyme inhibitor. All novel inositol derivatives (**11–17**) demonstrated a competitive inhibition type against the cholinergic AChE enzyme which is the primary cholinesterase in the body and serves to terminate synaptic transmission.^[67]

It is worth mentioning that the synthesized inositol derivatives (**11–17**) had an effective inhibition profile against the slow hCA I isoform, as seen in Table 1. The hCA I isoform was inhibited by these compounds in micromolar levels, with the K_i values varying between 88 ± 7 and $238 \pm 18 \mu\text{M}$. However, acetazolamide (AZA), which is considered a broad-specificity CA inhibitor owing to its widespread inhibition of CAs, showed a K_i value of $0.21 \pm 0 \mu\text{M}$ against hCA I isoenzyme. Among the inhibitors, DL-2,5-di-O-methyl-chiro-inositol (**17**) was obtained to be the excellent hCA I inhibitor with a K_i value of $88 \pm 7 \mu\text{M}$, respectively. All novel inositol derivatives, **11–17**, demonstrated a competitive inhibition type against the slow hCA I isoform that maintains acid–base balance and helps CO_2 transport in the human body.^[68,69]

The hCA I inhibition effects of all novel inositol derivatives (**11–17**) were found to be weaker than that of AZA, which was a clinically strong and standard CA inhibitor. Against the physiologically dominant isoform hCA II, novel inositol derivatives (**11–17**) demonstrated K_i values varying from 65 ± 13 to $539 \pm 61 \mu\text{M}$ (Table 1). These compounds had effective inhibition effects toward hCA II, whereas standard compound AZA showed a K_i value of $0.27 \pm 1 \mu\text{M}$ against hCA II. Thus, (1SR,2SR,3SR,4SR,5SR,6SR)-3,6-dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate (**15**) is shown as the most effective hCA II inhibition, with a K_i value of $65 \pm 13 \mu\text{M}$. All novel inositol derivatives (**11–17**) demonstrated a competitive inhibition type against the physiologically dominant hCA II isoform, which is one of 16 isoforms of the human α -CA family.^[70,71]

3 | CONCLUSION

We report the regio- and stereospecific synthesis of dimethoxy *chiro*- and *scyllo*-inositol derivatives having a *chiro*- and *scyllo*-inositol stereochemistry. Bromination of dimethoxydiol **10** and acid-catalyzed ring opening of dimethoxydiacetate conduritol-B epoxide **12** synthesized the target compounds as stereocontrolled. Also, the inhibition effects of all novel inositol derivatives (**11–17**) against hCA I and

hCA II isoenzymes and AChE enzyme were evaluated together. The novel inositol derivatives (**11–17**) showed inhibition effects against the hCA I and II isoenzymes and AChE enzyme activities at micromolar concentration. The results may be beneficial for designing and synthesizing new metabolic enzyme inhibitors and in the development of drugs to treat some metabolic and common diseases including epilepsy, leukemia, glaucoma, and AD in the future.

4 | EXPERIMENTAL

4.1 | Chemistry

4.1.1 | General

A capillary melting apparatus (Electrothermal) was used for determining melting points without further correction. IR spectra (see Supporting Information) were obtained from KBr (solution in 0.1-mm cells) or film with a Shimadzu spectrophotometer. The ^1H NMR, ^{13}C NMR, and ^{13}C attached proton test (APT) NMR spectra (see Supporting Information) were recorded on a 400 (100) MHz Bruker spectrometer (Avance III) and are reported in δ units with SiMe_4 as the internal standard. The structures were assigned, whenever necessary, with the help of 2D correlation experiments (correlation spectroscopy [COSY] and nuclear Overhauser effect spectroscopy [NOESY]). TLC was performed on E. Merck Silica Gel 60 F₂₅₄ plate (0.2 mm). Flash-column chromatography was performed on Merck silica gel (60 mesh). MgSO_4 was used for drying all organic extracts before filtration and the extracts were concentrated on a rotary evaporator. The solvents were distilled for all synthetic procedures. HRMS were recorded by liquid chromatography–mass spectrometry (LC–MS) time-of-flight (TOF) electrospray ionization technique (6230; Agilent).

The InChI codes of the investigated compounds, together with some biological activity data, are provided as Supporting Information.

(\pm)-(1SR,2SR,3SR,6SR)-3,6-Dimethoxycyclohex-4-ene-1,2-diol (**10**)

The title compound was prepared in 87% yield (recrystallized from AcOEt /hexane), as described in the literature.^[54–57]

(\pm)-(1RS,2RS,3SR,6SR)-3,6-Dimethoxycyclohex-4-ene-1,2-diyl diacetate (**11**)

3,6-Dimethoxycyclohex-4-ene-1,2-diol **10** (1.2 g, 6.89 mmol) was dissolved in pyridine (8 ml). To the magnetically stirred solution, Ac_2O (11 ml) was added, which was stirred at room temperature overnight. The mixture was poured into ice water (20 ml) and 4 M HCl solution (20 ml) was added, and the mixture was extracted with ether (3×100 ml). The combined organic extracts were washed with the saturated aqueous NaHCO_3 solution (100 ml) and water (50 ml), then dried over Na_2SO_4 , and concentrated in vacuo. The crude material was recrystallized from $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to give (\pm)-(1RS,2RS,3SR,6SR)-3,6-dimethoxycyclohex-4-ene-1,2-diyl diacetate **11**^[30] (1.58 g, 89%) as colorless crystals.

(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2,5-Dimethoxy-7-oxabicyclo[4.1.0]-heptane-3,4-diyl diacetate (**12**)

(±)-(1*RS*,2*RS*,3*SR*,6*SR*)-3,6-Dimethoxycyclohex-4-ene-1,2-diyl diacetate **11** (4.25 g, 16.46 mmol) was dissolved in CH₂Cl₂ (50 ml) and this solution was cooled to 0°C. To the solution, *m*-CPBA (2.98 g, 17.28 mmol) was added in small portions. Then the reaction mixture was warmed to room temperature. To this solution, which was stirred at room temperature for 24 hr, *m*-CPBA (2.98 g, 17.28 mmol) was added and then refluxed for 48 hr. The reaction mixture was evaporated under reduced pressure, dissolved in ethyl acetate (100 ml), and washed with 2 M NaOH (3 × 50 ml) and brine (50 ml). The organic layer was dried over Na₂SO₄ and evaporated. The residue was recrystallized from ethyl acetate/hexane (1:3) to give (1*RS*,2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2,5-dimethoxy-7-oxabicyclo[4.1.0]heptane-3,4-diyl diacetate **12** (3.16 g, 70%) as a white solid. Mp, 78–80°C; ¹H NMR (400 MHz CDCl₃): δ 5.13 (dd, 1H, A part of AB system, *J* = 10.9, 8.9 Hz, –CHOAc), 4.99 (dd, 1H, B part of AB system, *J* = 10.9, 8.2 Hz, –CHOAc), 3.86 (dd, 1H, *J* = 8.9, 1.7 Hz, –CHOMe), 3.68 (d, 1H, *J* = 8.1 Hz, –CHOMe), 3.52 (m, 1H, –CHOCH), 3.51 (s, 3H, –OCH₃), 3.50 (s, 3H, –OCH₃), 3.28 (d, 1H, *J* = 3.8 Hz, –CHOCH), 2.07 (s, 3H, –CO₂CH₃), 2.06 (s, 3H, –CO₂CH₃); ¹³C NMR (100 MHz CDCl₃): δ 170.0 (–CO₂CH₃), 169.8 (–CO₂CH₃), 78.4 (–CHOMe), 78.0 (–CHOMe), 72.7 (–CHOAc), 68.5 (–CHOAc), 58.5 (–OCH₃), 57.3 (–OCH₃), 54.10 (–CHOCH), 52.6 (–CHOCH), 20.7 (–CO₂CH₃ × 2); IR (KBr, cm^{–1}): 2,994, 2,932, 2,820, 1,740, 1,458, 1,436, 1,370, 1,219, 1,157, 1,092, 1,042, 1,022, 949, 841, 806, 718, 613; HRMS: *m/z* calculated for C₁₂H₁₈NaO₇ [M+Na]⁺, 297.094; found: 297.085.

(±)-(1*SR*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-4,5-Dibromo-3,6-dimethoxycyclohexane-1,2-diol: DL-1,6-dibromo-1,6-dideoxy-2,5-di-O-methyl-chiro-inositol (**13**)

A solution of Br₂ (1.11 g, 6.95 mmol) in CH₂Cl₂ (10 ml) was added dropwise to a solution of **10** (1.21 g, 6.95 mmol) in CH₂Cl₂ (40 ml) at –5°C and the mixture were stirred for 2 days. The reaction mixture was warmed to room temperature and the solvent of the mixture was removed under pressure. The crude material was recrystallized from AcOEt/hexane to give DL-1,6-dibromo-1,6-dideoxy-2,5-di-O-methyl-chiro-inositol **13** (1.57 g, 68%) as colorless crystals. Mp, 147–150°C; ¹H NMR (400 MHz, CDCl₃) δ 4.83 (d, 2H, *J* = 2.5 Hz, –CHOH), 3.94 (dd, 2H, *J* = 2.4, 6.7 Hz, –CHBr), 3.73 (td, 2H, *J* = 2.5, 6.6 Hz, –CHOMe), 3.50 (s, 6H, –OCH₃), 3.33 (bs, 2H, –OH); ¹³C NMR (100 MHz, CDCl₃) δ 77.7 (C–OMe × 2), 73.2 (C–OH × 2), 57.5 (–OCH₃ × 2), 50.0 (C–Br × 2); IR (KBr, cm^{–1}): 3,410, 3,368, 2,994, 2,924, 2,839, 1,377, 1,346, 1,265, 1,188, 1,126, 1,107, 1,053, 980, 964, 625; HRMS: *m/z* calculated for C₈H₁₄Br₂NaO₄ [M+Na]⁺, 356.991; found: 356.910.

(±)-(1*SR*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-4,5-Dibromo-3,6-dimethoxycyclohexane-1,2-diyl diacetate (**14**)

A solution of Br₂ (0.62 g, 3.87 mmol) in CH₂Cl₂ (10 ml) was added dropwise to a solution of **11** (1.0 g, 3.87 mmol) in CH₂Cl₂ (40 ml) at –5°C and the mixture were stirred for 2 days. The reaction mixture was warmed to room temperature and the solvent of the mixture was

removed under pressure. The crude material was recrystallized from AcOEt/hexane to give (±)-(1*SR*,2*SR*,3*RS*,4*RS*,5*RS*,6*RS*)-4,5-dibromo-3,6-dimethoxycyclohexane-1,2-diyl diacetate **14** (1.23 g, 76%) as colorless crystals. Mp, 185–187°C; ¹H NMR (400 MHz, CDCl₃) δ 5.42 (dd, 2H, *J* = 2.8, 6.9 Hz, –CHOAc), 4.83 (d, 2H, *J* = 2.7 Hz, –CHBr), 3.95 (td, 2H, *J* = 2.7, 6.8 Hz, –CHOMe), 3.44 (s, 6H, –OCH₃), 2.08 (s, 6H, –CH₃); ¹³C NMR (100 MHz, CDCl₃) δ 169.9 (C=O × 2), 76.3 (C–OAc × 2), 72.3 (C–OMe × 2), 58.1 (–OCH₃ × 2), 49.9 (C–Br × 2), 20.7 (–CH₃ × 2); IR (KBr, cm^{–1}): 3,001, 2,964, 2,939, 2,833, 1,747, 1,366, 1,250, 1,221, 1,209, 1,132, 1,109, 1,051, 1,042, 912, 826; HRMS: *m/z* calculated for C₁₂H₁₈Br₂NaO₆ [M+Na]⁺, 441.064; found: 440.924.

Acetylation of **13**

To a solution of 4,5-dibromo-3,6-dimethoxycyclohexane-1,2-diol **13** (0.31 g, 0.92 mmol) in CH₂Cl₂ (5 ml), acetyl chloride (10 ml) was added and the mixture was stirred at room temperature for 6 hr. The solvent of the mixture was removed under pressure. The crude material was recrystallized from AcOEt/hexane to give dibromide **14** (0.35 g, 92%).

(1*SR*,2*SR*,3*SR*,4*SR*,5*SR*,6*SR*)-3,6-Dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate (**15**) and (1*SR*,2*SR*,3*SR*,4*SR*,5*SR*,6*SR*)-3,6-dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate (**16**)

(1*RS*,2*RS*,3*SR*,4*SR*,5*RS*,6*SR*)-2,5-Dimethoxy-7-oxabicyclo[4.1.0]heptane-3,4-diyl diacetate **12** (1.03 g, 3.76 mmol) and acetic anhydride (20 ml) were placed in a 50-ml flask. To this solution, a catalytic amount (five drops) of conc. H₂SO₄ was added at 0°C. The reaction mixture was stirred at room temperature for 12 hr. This mixture was acidified with 1 N HCl and stirred in an ice bath for 1 hr. The reaction mixture was extracted with chloroform (3 × 50 ml). Organic layers were combined and washed with saturated NaHCO₃ (3 × 50 ml) and brine (50 ml). The organic layer was dried over Na₂SO₄ and evaporated. The ratio of the two isomers to each other (**15**:**16**, 9:1) was determined by NMR spectroscopy. The overall yield was 78% (1.1 g, 2.92 mmol) and the isolated yields were as follows: (1*SR*,2*SR*,3*SR*,4*SR*,5*SR*,6*SR*)-3,6-dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate **15**: 35% (0.49 g, 1.30 mmol) and (1*RS*,2*RS*,3*SR*,4*SR*,5*SR*,6*SR*)-3,6-dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate **16**: 6% (85.00 mg, 0.23 mmol).

Tetraacetate 15: mp, 136–138°C; IR (KBr, cm^{–1}): 2,940, 2,828, 1,740, 1,505, 1,485, 1,435, 1,370, 1,211, 1,161, 1,107, 1,045, 1,011, 934, 725, 675, 614; ¹H NMR (400 MHz CDCl₃) δ 5.47 (d, 2H, *J* = 2.3 Hz, –CHOAc × 2), 5.25 (dd, 2H, *J* = 7.2, 2.8 Hz, –CHOAc × 2), 3.58 (dt, 2H, *J* = 6.8, 2.5 Hz, –CHOMe × 2), 3.38 (s, 6H, –OCH₃ × 2), 2.17 (s, 6H, CO₂CH₃ × 2), 2.08 (s, 6H, CO₂CH₃ × 2); ¹³C NMR (100 MHz CDCl₃) δ 170.2 (–CO₂CH₃ × 2), 169.1 (–CO₂CH₃ × 2), 77.4 (–CHOMe), 71.4 (–CHOAc × 2), 65.8 (–CHOAc × 2), 58.5 (–OCH₃ × 2), 20.83 (–CO₂CH₃ × 2), 20.77 (–CO₂CH₃ × 2); HRMS: *m/z* calculated for C₁₆H₂₄NaO₁₀ [M+Na]⁺, 399.126; found: 399.115.

Tetraacetate 16: mp, 204–207°C; IR (KBr, cm^{–1}): 1,732, 1,377, 1,223, 1,165, 1,123, 1,030, 968, 934, 698, 606, 579, 417; ¹H NMR (400 MHz CDCl₃) δ 5.08 (dd, 4H, *J* = 6.9, 2.8 Hz, –CHOAc × 4), 3.43 (m, 8H, –CHOMe × 2, –OCH₃ × 2), 2.08 (s, 12H, CO₂CH₃ × 4); ¹³C NMR (100 MHz CDCl₃) δ 169.8 (–CO₂CH₃ × 4), 79.3 (–CHOMe × 2),

71.9 ($-\text{CHOAc} \times 4$), 60.6 ($-\text{OCH}_3 \times 2$), 20.7 ($-\text{CO}_2\text{CH}_3 \times 4$); HRMS: m/z calculated for $\text{C}_{16}\text{H}_{24}\text{NaO}_{10} [\text{M}+\text{Na}]^+$, 399.126; found: 399.124.

DL-2,5-Di-O-methyl-chiro-inositol (17)

(1SR,2SR,3SR,4SR,5SR,6SR)-3,6-Dimethoxycyclohexane-1,2,4,5-tetraol tetraacetate **15** (0.20 g, 0.53 mmol) was dissolved in absolute MeOH (10 ml). To the magnetically stirred solution, K_2CO_3 (0.29 g, 2.13 mmol) was added, and the mixture was stirred at room temperature for 12 hr. The reaction mixture was filtered and the solvent was removed in the evaporator. The crude material was purified by column chromatography on silica gel by using EtOAc/petroleum ether (1:1) to give DL-2,5-di-O-methyl-chiro-inositol **17** (61%, 67.00 mg, 0.32 mmol). Mp, 162–164°C; IR (KBr, cm^{-1}): 3,360, 2,990, 2,920, 2,824, 2,496, 1,458, 1,400, 1,334, 1,192, 1,142, 1,103, 1,049, 976, 910, 853, 799, 764, 625; ^1H NMR (400 MHz D_2O): δ 4.23 (bs, 2H, $-\text{CHOH} \times 2$), 3.55 (m, 2H, $-\text{CHOH} \times 2$), 3.38 (bs, 6H, $-\text{OCH}_3 \times 2$), 3.33 (m, 2H, $-\text{CHOMe}$); ^{13}C NMR (100 MHz, D_2O): δ 80.0 ($-\text{CHOH} \times 2$), 72.0 ($-\text{CHOH} \times 2$), 66.8 ($-\text{CHOMe} \times 2$), 56.9 ($-\text{OCH}_3 \times 2$); HRMS: m/z calculated for $\text{C}_8\text{H}_{16}\text{NaO}_6 [\text{M}+\text{Na}]^+$, 231.083; found: 231.083.

4.2 | Enzyme inhibition assays

Both hCA isoenzymes were purified using Sepharose-4B-L-tyrosine-sulfanilamide affinity column chromatography.^[72–74] CA isoenzymes' activity of novel inositol derivatives (**11–17**) was spectrophotometrically determined at 348 nm according to the method of Verpoorte et al.,^[75] with its detailed efficiency being provided in previous studies.^[76] In this enzymatic hydrolysis reaction, *p*-nitrophenylacetate was utilized as a substrate.^[77] One enzyme unit of CA is accepted as the amount of CA that gives absorbance difference at 348 nm for 3 min at 25°C.^[78] Bradford's technique^[79] was used for the determination of protein quantity during the purification studies. As a standard protein, bovine serum albumin was used.^[80] Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was used for screening of both CA isoenzymes purity.^[81]

The AChE inhibitory effects of novel inositol derivatives (**11–17**) were spectrophotometrically measured at 412 nm according to Ellman et al.'s method,^[82] as previously described.^[83] The measurements were determined using acetylthiocholine iodide and 5,5'-dithio-bis(2-nitro-benzoic) acid as substrates.^[84]

To determine the inhibition kinetics of novel inositol derivatives (**11–17**), the activity (%) and [inositols] graph was drawn and half-maximal inhibitor concentrations (IC_{50}) for the novel inositol derivatives (**11–17**) were calculated.^[85] Finally, K_i values of the novel inositol derivatives (**11–17**) were obtained from Lineweaver–Burk graphs,^[86] as previously described in detail.^[87]

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CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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