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Aqua-mediated rapid and benign synthesis of 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one-appended novel 2-arylidene indanones of pharmacological interest at ambient temperature

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Abstract

In the present investigation, a green aqua-mediated protocol for the synthesis of novel 2-arylidene indanone derivatives from 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one was unveiled. The application of water in organic reactions as a solvent is one of the incredible tools of green chemistry as reactions can be carried out under benign conditions minimizing environmental hazard and chemical waste. A library of novel 2-arylidene indanone derivatives are synthesized in good to excellent yield by utilizing the green potential of water as a solvent. The structures of all novel 2-arylidene indanone derivatives reported herein are confirmed using Fourier-transform infrared spectroscopy (FTIR), ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, distortionless enhancement by polarization transfer (DEPT), and High Resolution Mass Spectrometry (HRMS) techniques.

KEYWORDS

1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one, ^{19}F NMR spectroscopy, green chemistry, HRMS, water

1 | INTRODUCTION

2,3-dihydro-1H-inden-1-one skeleton, i.e. 1-indanone, is a fused organic molecule in which benzene is fused with a cyclopentanone ring. It is one of the crucial compounds for the advancement of numerous biologically active carbocyclic and heterocyclic scaffolds.[1,2] Most of its notable derivatives have been utilized as synthetic intermediates in various organic transformations. One of its derivative, 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one, is considered as a privileged compound due to its involvement in Ramelteon drug synthesis.[3] Ramelteon is a drug that is being used to help individuals who have sleep-onset insomnia, a sleeping disorder, and is in the category of medicines called melatonin receptor agonists. [4] It works likewise to melatonin, a characteristic substance in the brain that is required for sleep. Typically, human body secretes more melatonin around evening time. Melatonin levels begin to go up at night once the sun sets and they drop toward the start of the day once the sun goes up. Ramelteon is a sleep operator that specifically ties to G-protein-coupled receptors (MT1 and MT2) in the suprachiasmatic nucleus. 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one is a promising tricyclic synthetic intermediate for the synthesis of compounds having value as human therapeutic agents. The 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one molecule has a structure similar to medicinal agents (Figure 1), which signifies the importance of the former in the medicinal field.

2-arylidene indanone derivatives have attracted plenty interest due to the significance of indanone moiety in diverse biological activities. The majority of the recent investigations with this skeleton are due to their extensive variety of pharmacological applications. It is structurally similar to chalcone but comparatively contains a more planar system.

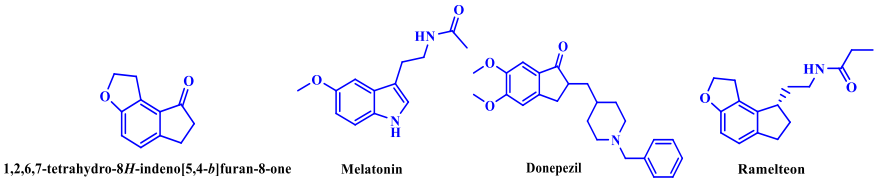


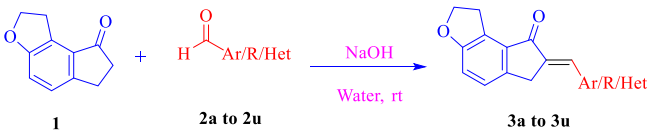
FIGURE 1 Some biologically important intermediates and medicinal agents

2-arylidene indanone derivatives are found to show an excellent profile of biological activities because of the presence of α, β-unsaturated framework-like chalcones. They have been investigated as inhibitors of acetyl cholinesterase toward the treatment of Alzheimer's disease, inhibitors of tubulin assembly, as inhibitors of breast cancer, lung cancer, and leukemia, inhibitors of dual specificity phosphatase, and as inhibitors of monoamine oxidase.[5] Furthermore, they are also explored as antioxidant, antimalarial, antimicrobial, anti-inflammatory, and analgesic agents.[6] An extraordinary medicine that contains an indanone moiety is Donepezil that is an oral acetylcholinesterase inhibitor utilized for treatment of Alzheimer's disease and it enhances neurocognitive function in patients.[7] The structural similarities of 2-arylidene indanone to chalcones make chemistry of the former even more exciting. Chalcones are a notable class of compounds, they act as vital intermediates in organic chemistry, and furthermore, they show potent and numerous biological properties. Noteworthy biological profiles of compounds containing chalcone moieties include activities like anticancer, anti HIV, anticonvulsant, antioxidant, antihypertensive, antiviral, antitubercular, anti-inflammatory, and antimicrobial.[8]

Numerous green chemistry-oriented organic synthesis methods have been developed to synthesize a broad range of compounds with no or less environmental hazard. One such a method that has pulled in the consideration of chemists is organic synthesis using nature's favorite solvent that is, water. With growing consideration toward greener methodologies for organic synthesis, modification of greener strategies is the need of the hour and in such a circumstance, water may be the solvent of higher preference because of its versatile characteristics. Water is the universal solvent and displays anomalously intense hydrogen bonding and a wide temperature range to remain in the liquid state. Low viscosity, high dielectric constant, high specific heat, high surface tension, and large cohesive energy density are some eye-catching properties of water, which make it superior over a large number of organic solvents in terms of safety and synthetic efficiency.[9–13] Water accelerates polar reactions of carbonyl compounds because of the formation of powerful hydrogen bonding, which endows electrophilic activation. Worthy reviews on green chemistry-directed organic synthesis using water have been reported, which explore the service of water as a solvent. Noticeable examples of water used as a solvent in organic synthesis are Diels-Alder Reactions,[14–19] Claisen rearrangement,[20] Mukaiyama aldol reaction,[21] Knoevenagel reaction,[22] chemoselective alkylation,[23] dehydrogenation cyclization,[24] coupling of amines,[25] and multicomponent reactions.[26,27] In continuation with our interest in the development of mild, operationally simple, and environmentally friendly protocols for the synthesis of pharmacologically important compounds, we envisaged to access novel 2-arylidene indanone derivatives (**3a**–**3u**) of biological importance. Aforementioned significances of water prompted us to explore its potential as a reaction medium in organic synthesis leading to bioactive compounds. In this context, herein, we report the synthesis of 2-arylidene indanone derivatives using water as a green solvent at room temperature. To the best of our knowledge, this is the first report on aqua-mediated synthesis of 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one-appended 2-arylidene indanone derivatives.

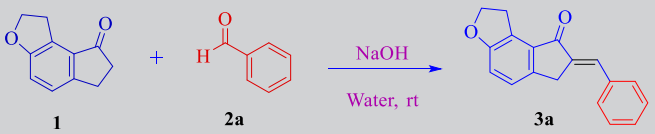
2 | RESULTS AND DISCUSSION

After the pioneer revelation of water as a solvent in 1980 by Breslow, there has been striking improvement with the view of utilizing water as a solvent in organic synthesis. Therefore, taking into account the significance of water and the 2-arylidene indanone moiety together, in this article we wish to report room temperature base-catalyzed aqua-mediated clean and rapid synthesis of (E)-7-(arylidene)-1,-2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one derivatives without using any catalyst and high temperature conditions. The present protocol has advantages like a short reaction time, benign reaction conditions, high product yield, easy work-up procedure, and more importantly purification using a simple crystallization method (nonchromatographic purification). Water has been found to exert a remarkable effect to force the reaction to completion without adding any kind of organic solvent. As a model reaction, when we performed the base-catalyzed aldol reaction of 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one with benzaldehyde in water, we obtained the desired product in a very short period of time and strikingly the yield was additionally high. This



SCHEME 1 Aqua-mediated synthesis of 2-arylidene indanones

TABLE 1 Optimization of base for the synthesis of **3a**[a]

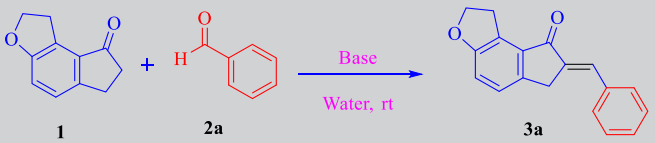


1 2a 3a

Entry	Base (mmol)	Time (min)	Solvent	Yield (%)[b]
1	1	320	Water	20
2	2	240	Water	50
3	3	100	Water	58
4	4	50	Water	75
5	5	30	Water	94
6	6	25	Water	90
7	7	25	Water	88
8	8	23	Water	87

[a]*Reaction conditions*: **1a** (0.8 mmol), **2a** (1 mmol), at room temperature.
[b]Isolated yield of pure product.

TABLE 2 Effect of various bases for the synthesis of **3a**[a]



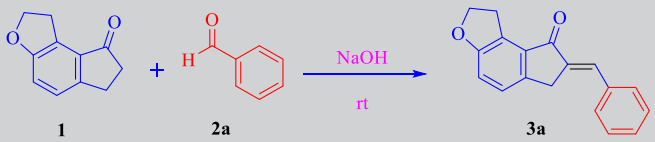
1 2a 3a

Entry	Base	Time (min)	Solvent	Yield (%)[b]
1	K_2CO_3	180	Water	35
2	Na_2CO_3	210	Water	40
3	$NaHCO_3$	240	Water	30
4	NaOMe	180	Water	49
5	Piperidine	200	Water	56
6	Pyrrolidine	210	Water	48
7	$Li(OH)_2.H_2O$	100	Water	74
8	NEt_3	300	Water	54
9	KOH	45	Water	89
10	Pyridine	420	Water	38
11	NaOH	30	Water	94

[a]*Reaction conditions*: **1a** (0.8 mmol), **2a** (1 mmol), and base (5 mmol) at room temperature.
[b]Isolated yield of pure product.

implausible outcome energized us to synthesize a variety of 2-arylidene derivatives (Scheme 1). To check the precise amount of NaOH, we varied the amount of NaOH from 1 to 8 mmol (Table 1). When the amount NaOH was increased from 1 to 5 mmol, surprisingly the yield of **3a** was found to increase with a reduction in completion time. However, dramatically, yield of **3a** diminished when the amount of NaOH was increased from 5 to 8 mmol. This without a doubt indicates the best result was obtained using 5 mmol NaOH. After this primary investigation, various bases (Table 2)

TABLE 3 Comparison with solvent-free reaction[a]



Entry	Solvent	Time (min)	Yield (%)[b]
1	Solvent-free	230	35
2	Water	30	94

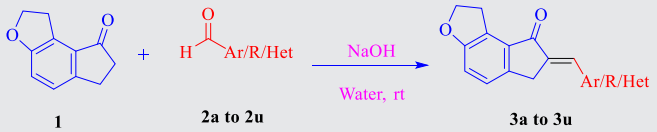
[a]*Reaction conditions*: **1a** (0.8 mmol), **2a** (1 mmol), and NaOH (5 mmol) at room temperature.
[b]Isolated yield of the pure product.

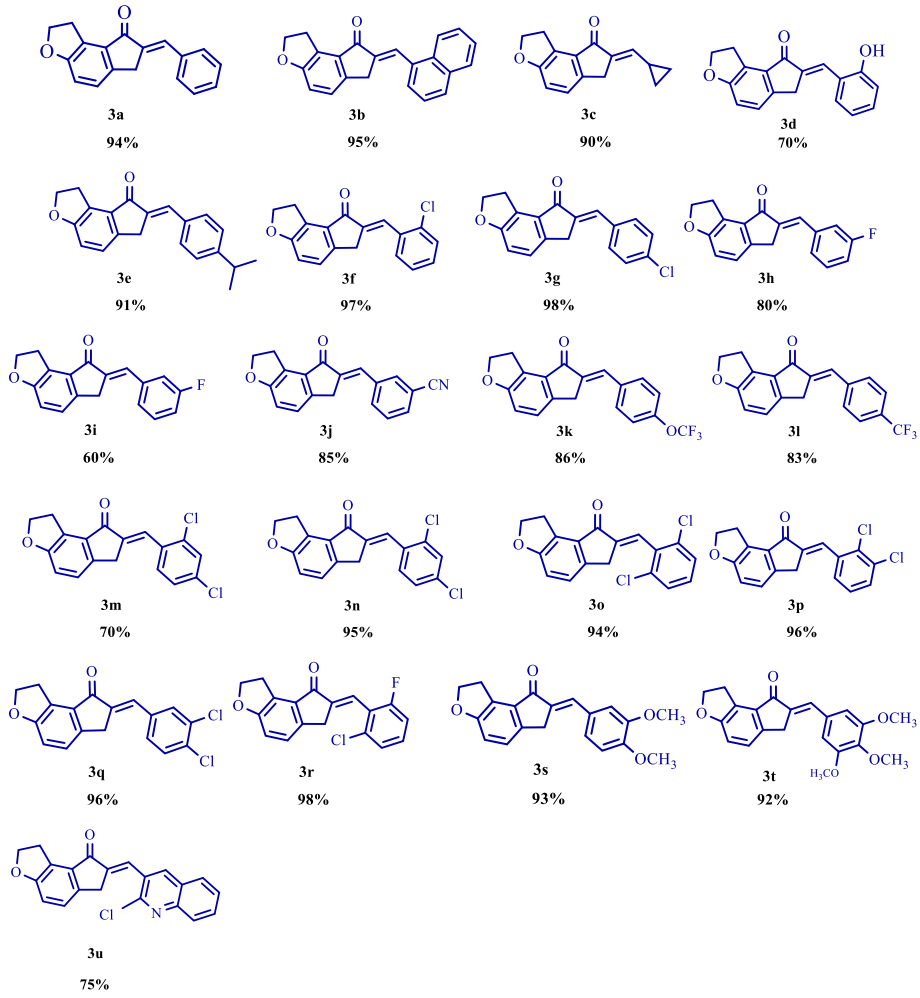
were tested to check if any of these could improve the yield of the product. The reaction in the presence of pyridine, K_2CO_3, Na_2CO_3, $NaHCO_3$, NEt_3, piperidine, pyrrolidine, and NaOMe afforded product **3a** in a less amount as compared to NaOH as a base. However, with $Li(OH)_2.H_2O$ and KOH, product formation was more satisfactory. Additionally, time taken for completion of the reaction by all these bases was also high as compared to NaOH as a base. Thus, by considering advantages of NaOH over these bases, it was chosen as a base of prime choice for the synthesis of 2-arylidene indanones.

During the course of study, we also performed the synthesis of **3a** under solvent-free conditions to confirm the importance of water as a solvent. The solvent-free reaction afforded desired chalcone (**3a**) in low yield, and in contrast, the model reaction in water furnished the anticipated chalcone in excellent amount (Table 3). This outcome signifies the role of water in the present protocol. After the optimization of reaction conditions, the generality of the protocol was determined by reacting with a broad range of aryl aldehydes. The results summarized in Table 4 indicate that an array of functionality was tolerated under optimized reaction conditions. Aldehydes with a variety of functionality have been tested to present the versatile substrate scope of the protocol revealed in this. We commenced our investigations with chlorine bearing aromatic aldehydes that afforded the desired compounds **3f**, **3g**, **3n**, **3o**, **3p**, and **3q** in excellent yields (94–98%). Then, we switched our interest to fluorine-bearing benzaldehydes to afford compounds **3r**, **3h**, and **3i**. Here also, fantastic yields (80–98%) were obtained except for compound **3i** (60% yield). After this primary investigation, we performed the reaction with aromatic aldehydes containing alkoxy substituent/s. Initially, we thought substituents having a strong +R effect will diminish the yield. However, the result was exactly contrast giving products **3k**, **3s**, and **3t** (86–93% yield) similar to previous reactions. Furthermore, 2-hydroxy benzaldehyde, 4-[dimethylamino]benzaldehyde, and 2-chloroquinoline-3-carbaldehyde were also found to form compounds **3d**, **3m**, and **3u** in which the yield (70–75%) was comparatively less. The less yields can be attributed to the presence of a hydroxyl substituent in 2-Hydroxy benzaldehyde, a powerful electron-donating effect of the dimethylamino group in 4-[dimethylamino]benzaldehyde. The reaction of 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one with 4-formylbenzonitrile, 1-naphthaldehyde, 4-isopropyl benzaldehyde, and cyclopropanecarbaldehyde furnished compounds **3j**, **3b**, **3e**, and **3c**, respectively, with magnificent yield (83–91%). As such, to validate the generality of this protocol for the synthesis of 2-arylidene indanone derivatives, numerous substituted benzaldehydes were investigated under the same optimized reaction conditions. Thus, this benign strategy is found to be robust and could tolerate a variety of electron-donating, electron-withdrawing, and halogen substituents with fantastic yields. Because of the greener, high product yield, and benign focal points of water as a solvent, we did not switch our interest to toxic and expensive organic solvents. All the more significantly, in all instances no side products were detected (checked by TLC) permitting purification of products by more convenient simple crystallization method as compared to column chromatography. The synthesized compounds were characterized using various spectral techniques. All the more essentially, ^{19}F NMR and distortionless enhancement by polarization transfer (DEPT) spectroscopy strategies are intentionally utilized for characterization purpose. From ^{19}F NMR, the presence of fluorine atoms was effectively demonstrated while by utilizing DEPT, protonated and quaternary carbons are distinguished. The physicochemical data of 2-arylidene indanone derivatives is depicted in Table 5.

The plausible mechanism involved in the formation of 2-arylidene indanones is presented in Scheme 2. The reaction starts with the formation of an enolate anion of 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one, which attacks on the electrophilic carbon of aldehyde to form the intermediate **X**. The intermediate then picks up the proton from water to form ketol **Y**. In the last step, ketol Y undergoes

TABLE 4 Substrate scope and generality with various aldehydes[a]





[a]*Reaction conditions*: 1a (0.8 mmol), 2a (1 mmol), and NaOH (5 mmol) at room temperature.

spontaneous elimination of water molecules due to base-catalyzed dehydration (β-elimination) to furnish the product.

3 | EXPERIMENTAL

3.1 | Chemicals and instrumentation

1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one was purchased from Henan Tianfu Chemical Co., Ltd., Zhengzhou, China. Other chemicals (Make: Sigma-Aldrich, Merck, and Avra synthesis) with high purity were purchased from a local supplier. All the chemicals were used as received without any further purification. Melting points were determined in open capillaries and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker using $CDCl_3$ and DMSO-d_6 as solvents, Fourier-transform infrared spectroscopy (FTIR), spectra were obtained with potassium bromide pellets, and High Resolution Mass Spectrometry (HRMS) were recorded on Brucker with ESI as a source. Reactions were monitored by thin-layer chromatography using aluminum sheets with silica gel 60F254 (Merck).

TABLE 5 Physicochemical data of 2-arylidene indanone derivatives

Entry	Name of the products	Time (min)	M.P. (°C)	Yield (%)[a]
3a	(E)-7-benzylidene-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	30	119	94
3b	(E)-7-(naphthalen-1-ylmethylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	31	161	95
3c	(E)-7-(cyclopropylmethylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	25	174	90
3d	(E)-7-(2-hydroxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	35	202	70
3e	(E)-7-(4-isopropylbenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	30	157	91
3f	(E)-7-(2-chlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	20	160	97
3g	(E)-7-(4-chlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	22	197	98
3h	(E)-7-(3-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	26	180	80
3i	(E)-7-(4-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	32	178	60
3j	(E)-3-((8-oxo-1,2,6,8-tetrahydro-7H-indeno[5,4-b]furan-7-ylidene)methyl)benzonitrile	40	208	85
3k	(E)-7-(4-[trifluoromethoxy]benzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b] furan-8-one	20	172	86
3l	(E)-7-(4-[trifluoromethyl]benzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	23	155	83
3m	(E)-7-(4-(dimethylamino)benzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	50	240	70
3n	(E)-7-(2,4-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	35	228	95
3o	(E)-7-(2,6-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	35	168	94
3p	(E)-7-(2,3-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	29	194	96
3q	(E)-7-(3,4-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	36	190	96
3r	(E)-7-(2-chloro-6-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	10	111	98
3s	(E)-7-(3,4-dimethoxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	40	205	93
3t	(E)-7-(3,4,5-trimethoxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one	45	256	92
3u	(E)-7-([2-chloroquinolin-3-yl]methylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b] furan-8-one	18	264	75

[a]Isolated yield of the pure products.

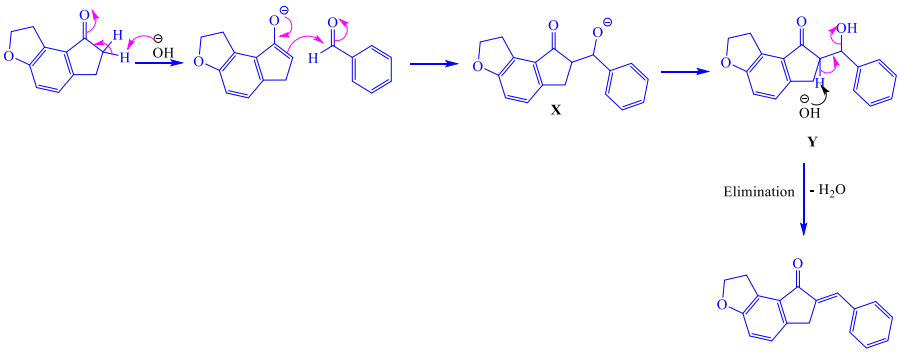
3.2 | Experimental procedure

1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one (0.8 mmol) and aldehyde (1 mmol) were added to an appropriate amount of distilled water taken in a 50 mL conical flask. To this, NaOH (5 mmol) was added and the resulting basic mixture was warmed and then stirred for 10–50 min to get the desired products. The completion of reaction was continuously monitored using thin layer chromatography (n-hexane/EtOAc [8:2]). The crude products were obtained simply by filtration without adding any acid. The obtained crude products were dried under IR lamp and recrystallized using hot ethanol. The synthesized products were characterized using FTIR, ^{1}HNMR, ^{13}C NMR, DEPT, ^{19}F NMR, and HRMS spectral techniques.

3.3 | Physical and spectral data for synthesized compounds

3.3.1 | (E)-7-benzylidene-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-94%; Yellow crystals; m.p. 119°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.58 (t, J = 8.9 Hz, 2H), 4.00



SCHEME 2 Plausible reaction mechanism

(s, 2H), 4.70 (t, J = 8.9 Hz, 2H), 7.04 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.53–7.41 (m, 3H), 7.61 (d, J = 2.3 Hz, 1H), and 7.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.55, 32.08, 72.46, 115.55, 124.75, 125.17, 128.92, 129.60, 130.73, 133.45, 134.57, 135.47, 135.79, 141.60, 160.54, and 194.67; HRMS: Calculated: 263.1072 [M + H], Observed: 263.1069[M + H].

3.3.2 | (E)-7-(naphthalen-1-ylmethylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-95%; Yellow solid; m.p. 161°C; IR (KBr, cm^{-1}): 3,051.39, 2,999.31, 2,958.80, 2,900.94, 1,680.00, 1,614.42, 1,469.76, 1,217.08, and 769.60; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.61 (t, J = 8.9 Hz, 2H), 3.92 (d, J = 2.1 Hz, 2H), 4.71 (t, J = 8.9 Hz, 2H), 7.03 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.61–7.50 (m, 3H), 7.77 (d, J = 7.2 Hz, 1H), 7.92–7.87 (m, 2H), 8.22 (d, J = 8.2 Hz, 1H), and 8.38 (d, J = 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.59, 31.64, 72.46, 115.62, 124.05, 124.84, 125.20, 125.25, 126.30, 126.80, 126.99, 128.77, 129.85, 130.40, 132.33, 133.70, 134.79, 138.18, 141.99, 160.51, and 194.30; HRMS: Calculated: 313.1228 [M + H], Observed: 313.1227[M + H].

3.3.3 | (E)-7-(cyclopropylmethylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-90%; Pink solid; m.p. 174°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.81–0.73 (m, 2H), 1.12–1.01 (m, 2H), 1.69–1.59 (m, 1H), 3.53 (t, J = 8.9 Hz, 2H), 3.79 (s, 2H), 4.66 (t, J = 8.9 Hz, 2H), 6.22 (dt, J = 10.8, 2.1 Hz, 1H), 7.17–7.35 (m, 1H), and 7.00 (d, J = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 9.20, 12.97, 28.50, 29.68, 72.37, 115.09, 124.57, 125.19, 135.29, 135.52, 141.24, 143.00, 160.30, and 193.01; HRMS: Calculated: 227.1072 [M + H], Observed: 227.1068 [M + H].

3.3.4 | (E)-7-(2-hydroxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-65%; Yellow solid; m.p. 202°C; IR (KBr, cm^{-1}): 3,082.25, 2,972.31, 2,897.08, 1,670.35, 1,589.34, 1,454.33, and 1,240.23; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.99 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.39–6.98 (m, 4H), 6.89 (d, J = 8.2 Hz, 1H), 5.51 (s, 1H), 4.70 (t, J = 8.9 Hz, 2H), 3.95 (s, 2H), and 3.58 (t, J = 8.8 Hz, 2H); HRMS: Calculated: 279.1021 [M + H], Observed: 279.1017 [M + H].

3.3.5 | (E)-7-(4-isopropylbenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-91%; Pale yellow crystals; m.p. 157°C; IR (KBr, cm^{-1}): 2,958.80, 2,895.15, 1,693.50, 1,624.06, 1,465.90, 1,269.16, and 819.75; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.68 (t, J = 8.8 Hz, 2H), 3.97 (d, J = 2.1 Hz, 2H), 3.56 (t, J = 8.8 Hz, 2H), 2.95 (sept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 6H), 7.02 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.32 (d, J = 8.0 Hz, 2H), and 7.62–7.57 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 23.80, 28.55, 32.11, 34.11, 72.44, 115.38, 124.66, 125.13, 127.07, 130.94, 133.09, 133.50, 134.69, 134.91, 141.56, 150.93, 160.48, and 194.73; HRMS: Calculated: 305.1541 [M + H], Observed: 305.1538 [M + H].

3.3.6 | (E)-7-(2-chlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-97%; Pale yellow crystals; m.p. 160°C; IR (KBr, cm-^{1}): 2,964.59, 2,899.01, 1,685.79, 1,624.06, 1,473.62, 1,195.87, and 773.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.58 (t, J = 8.9 Hz, 2H), 3.92 (dd, J = 2.4, 0.9 Hz, 2H), 4.70 (t, J = 8.9 Hz, 2H), 7.04 (d, J = 8.01 Hz, 1H), 7.24 (m, 1H), 7.33 (m, 2H), 7.48 (m, 1H), 7.70 (m, 1H), and 7.99 (t, J = 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.68, 31.65, 72.62, 115.87, 125.31, 125.04, 126.93, 129.58, 130.00, 130.40, 133.79, 134.63, 136.36, 138.09, 141.72, 160.72, and 194.27; HRMS: Calculated: 297.0682[M + H], Observed: 297.0680[M + H].

3.3.7 | (E)-7-(4-chlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-98%; Yellow solid; m.p. 197°C; IR (KBr, cm^{-1}): 2,966.52, 2,895.15, 1,683.86, 1,618.28, 1,587.42, 1,467.83, 1,238.30, and 812.03; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 4.69 (t, J = 8.9 Hz, 2H), 3.95 (d, J = 2.2 Hz, 2H), 3.56 (t, J = 8.9 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 8.3 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), and 7.04 (d, J = 8.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.54, 31.98, 72.47, 115.70, 124.82, 125.19, 129.20, 131.80, 131.97, 133.93, 134.44, 135.58, 136.22, 141.35, 160.62, and 194.41; HRMS: Calculated: 297.0682[M + H], Observed: 297.0680[M + H].

3.3.8 | (E)-7-(3-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-80%; Yellow solid; m.p. 180°C; IR (KBr, cm-1)—2,964.59, 2,895.15, 1,689.64, 1,624.06, 1,475.54, 1,273.02, and 781.17;; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t,

J = 8.9 Hz, 2H), 3.93 (d, dd, J = 2.2, 1.0 Hz, 2H), 4.69 (t, J = 8.9 Hz, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.10 (m, 1H), 7.29 (m, 1H), 7.41–7.32 (m, 1H), 7.38–7.48 (m, 2H), and 7.55 (t, J = 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.68, 32.08, 72.60, 115.93, 116.48, 116.69, 116.72, 116.94, 124.98, 125.36, 126.84, 126.87, 130.48, 130.56, 132.07, 132.10, 134.51, 137.06, 137.70, 137.77, 141.54, 160.77, 161.85, 164.30, and 194.50; HRMS: Calculated: 281.0977 [M + H], Observed: 281.0976 [M + H].

3.3.9 | (E)-7-(4-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-60%; Yellow solid; m.p. 178°C; IR (KBr, cm^{-1}): 3,053.32, 2,970.38, 2,900.94, 1,689.64, 1,625.99, 1,591.27, 1,498.69, 1,205.51, and 810.10; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.55 (d, J = 8 Hz, 2H), 3.93 (s, 2H), 4.68 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 1H), 7.12 (s, 2H), 7.24 (s, 1H), 7.54 (s, 1H), and 7.63 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.54, 31.94, 72.46, 115.59, 116.02, 116.19, 124.78, 125.17, 131.71, 131.74, 132.16, 132.56, 132.63, 134.50, 135.32, 135.34, 141.40, 160.59, 162.30, 164.30, and 194.50; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm): -109.91; HRMS: Calculated: 281.0977 [M + H], Observed: 281.0976 [M + H].

3.3.10 | (E)-3-((8-oxo-1,2,6,8-tetrahydro-7H-indeno[5,4-b]furan-7-ylidene)methyl) benzonitrile

Yield-85%; Yellow solid; m.p. 208°C; IR (KBr, cm^{-1}): 3,043.67, 2,964.59, 2,906.73, 1,685.79, 1,620.21, 1,469.76, 1,234.44, and 827.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.55 (t, J = 8.9 Hz, 2H), 3.97 (s, 2H), 4.68 (t, J = 8.9 Hz, 2H), 7.05(d, J = 8 Hz, 1H), 7.29 (d, J = 8 Hz, 1H), 7.54 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), and 7.91(s, 1H); HRMS: Calculated: 288.1024 [M + H], Observed: 288.1022 [M + H].

3.3.11 | (E)-7-(4-[trifluoromethoxy] benzylidene)-1,2,6,7-tetrahydro-8H-indeno [5,4-b]furan-8-one

Yield-86%; Pale yellow crystals; m.p. 172°C; IR (KBr, cm^{-1}): 3,066.82, 2,985.81, 2,906.73, 1,689.64, 1,622.13, 1,471.69, 1,313.52, and 823.60; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t, J = 8.9 Hz, 2H), 4.00 (d, J = 2.1 Hz, 2H), 4.70 (t, J = 8.9 Hz, 2H), 7.06 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 2.3 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), and 7.76 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.67, 32.08, 72.62, 116.09, 125.09, 125.40, 125.90, 125.94, 130.75, 131.58, 134.40, 138.09, 141.52, 146.97, 147.13, 160.82, and 194.40; DEPT: 28.67, 32.08, and 72.62 (all down), 116.09, 125.40, 125.90, 130.75, and 131.58 (all up), and 125.09, 125.94, 134.40, 138.09, 141.52, 146.97, 147.13, 160.82, and 194.40 (all absent); HRMS—Calculated: 331.0945[M + H], Observed: 331.0941[M + H]; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm): -62.79.

3.3.12 | (E)-7-(4-[trifluoromethyl] benzylidene)-1,2,6,7-tetrahydro-8H-indeno [5,4-b]furan-8-one

Yield-83%; Pale yellow crystals; m.p. 155°C; IR (KBr, cm^{-1}): 3,072.60, 2,908.65, 2,854.65, 1,687.71, 1,616.35, 1,473.62, 1,273.02, and 821.68; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t, J = 8.9 Hz, 2H), 3.97 (m, 2H), 4.70 (t, J = 8.9 Hz, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.29 (m, 3H), 7.57 (t, J = 2.2 Hz, 1H), and 7.71–7.67 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.68, 32.04, 72.61, 115.90, 121.27, 125.00, 125.35, 131.77, 132.19, 134.20, 134.54, 136.59, 141.51, 146.97, 147.13, 160.78, and 194.52; ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm): -57.68; HRMS—Calculated: 331.0945[M + H], Observed: 331.0941[M + H].

3.3.13 | (E)-7-(4-(dimethylamino)benzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-70%; Bright yellow crystals; m.p. 240°C; IR (KBr, cm^{-1}): 2,966.52, 2,900.94, 1,685.79, 1,624.06, 1,473.62, 1,234.44, and 808.17; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.04 (s, 6H), 4.66 (t, J = 8.9 Hz, 2H), 3.92 (s, 2H), 3.56 (t, J = 8.9, 2H), 6.73 (d, Hz, 2H), 6.98 (d, 1H), 7.24 (s, 2H), and 7.56 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.55, 32.33, 40.12, 72.42, 111.95, 114.69, 123.31, 124.35, 124.93, 131.07, 132.75, 134.44, 135.28, 141.36, 151.14, 160.34, and 194.67; HRMS: Calculated: 306.1494[M + H], Observed: 297.1490[M + H].

3.3.14 | (E)-7-(2,4-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-95%; Pale yellow crystals; m.p. 228°C; IR (KBr, cm^{-1}): 3,076.46, 2,970.38, 2,899.01, 1,689.64, 1,622.13, 1,587.42, 1,475.54, 1,273.02, 825.53, and 779.24; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t, J = 8.9 Hz, 2H), 3.88 (s, 2H), 4.69 (t, J = 8.9 Hz, 2H), 7.04 (d, J = 8 Hz, 1H), 7.24 (m, 1H), 7.32 (m, 1H), 7.49 (d, J = 2.2 Hz, 1H), 7.63 (d, J = 8 Hz, 1H), and 7.90 (t, J = 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.66, 31.64, 72.62, 116.00, 125.11, 125.33, 127.38, 128.30, 130.28, 130.61, 132.33, 134.49, 135.69, 137.02, 138.44, 141.47, 160.80, and 194.03; HRMS: Calculated: 331.0282[M + H], Observed: 331.0292[M + H].

3.3.15 | (E)-7-(2,6-dichlorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-94%; Pale yellow crystals; m.p. 168°C; IR (KBr, cm^{-1}): 3,055.24, 2,968.45, 2,900.94, 1,697.36, 1,645.28, 1,473.62, 1,238.30, and 773.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.61–3.54 (m, 4H), 4.69 (t, J = 8.9 Hz, 2H), 7.02 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.24 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 8.1 Hz, 2H), and 7.53 (t, J = 2.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.56, 30.54, 72.46, 116.04, 124.99, 125.29, 128.15, 128.32, 129.66, 134.04, 134.24, 134.68, 141.51, 141.81, 160.49, and 193.29; HRMS: Calculated: 331.0292 [M + H], Observed: 331.0287 [M + H].

3.3.16 | (E)-7-(2-chloro-6-fluorobenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-98%; Yellow solid; m.p. 111°C; IR (KBr, cm^{-1}): 3,091.89, 2,978.09, 2,910.58, 1,703.14, 1,637.56, 1,469.76, 1,238.30, and 773.46; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t, J = 8.9 Hz, 2H), 3.67 (d, J = 4 Hz, 2H), 4.69 (t, J = 8.9 Hz, 2H), 7.03 (d, J = 8 Hz, 1H), 7.08 (ddd, J = 9.7, 7.4, 2.1 Hz, 1H), 7.20–7.17 (m, 1H), 7.34–7.27 (m, 2H), and 7.58–7.56 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.55, 31.14, 72.44, 114.45, 114.63, 116.01, 122.98, 123.14, 124.37, 124.91, 125.18, 125.52, 125.55, 130.30, 130.38, 134.51, 135.61, 135.66, 141.68, 141.69, 141.91, 158.86, 160.46, 160.87, and 193.53; 19F NMR (471 MHz, CDCl3) δ (ppm)—106.91; HRMS: Calculated: 315.0588 [M + H], Observed: 315.0588 [M + H].

3.3.17 | (E)-7-(3,4-dimethoxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-93%; Pale yellow crystals; m.p. 205°C; IR (KBr, cm^{-1}): 2,914.44, 2,845.00, 1,674.21, 1,587.42, 1,510.26, 1,469.76, 1,244.09, and 786.96; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.56 (t, J = 8.8 Hz, 2H), 3.94 (s, 3H), 3.95 (d, J = 2.0 Hz, 2H), 3.97 (s, 3H), 4.68 (t, J = 8.8 Hz, 2H), 6.94 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.38–7.22 (m, 2H), and 7.54 (t, J = 2.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.55, 32.00, 55.77, 56.00, 72.45, 111.27, 113.42, 115.27, 121.67, 124.66, 125.09, 128.49, 133.58, 133.73, 134.77, 141.32, 149.08, 150.55, 160.51, and 194.57; HRMS: Calculated: 323.1283 [M + H], Observed: 323.1280 [M + H].

3.3.18 | (E)-7-(3,4,5-trimethoxybenzylidene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one

Yield-60%; Yellow crystals; m.p. 256°C; IR (KBr, cm^{-1}): 2,993.52, 2,931.80, 2,833.43, 1,687.71, 1,622.13, 1,581.63, 1,500.62, 1,247.94, and 815.89; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.57 (t, J = 8.9 Hz, 2H), 3.92 (s, 3H), 3.94 (s, 6H), 3.98 (s, 2H), 4.69 (t, J = 8.8 Hz, 2H), 6.90 (s, 2H), 7.04 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), and 7.52 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.56, 31.85, 56.27, 61.03, 72.46, 108.13, 115.48, 124.76, 125.14, 130.96, 133.62, 134.62, 134.86, 139.75, 141.25, 153.39, 160.59, and 194.45; HRMS: Calculated: 353.1389[M + H], Observed: 353.1391 [M + H].

3.3.19 | (E)-7-([2-chloroquinolin-3-yl] methylene)-1,2,6,7-tetrahydro-8H-indeno[5,4-b] furan-8-one

Yield-75%; Dark yellow solid; m.p. 264°C; IR (KBr, cm^{-1}): 2,904.80, 2,850.79, 1,695.43, 1,658.78, 1,620.21, 1,473.62, 1,253.73, and 771.53; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 3.60 (t, J = 8.9 Hz, 2H), 4.01 (d, J = 2.4 Hz, 2H), 4.72 (t, J = 8.9 Hz, 2H), 7.07 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.79 (t, J = 7.6 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 8.42 (s, 1H), and 8.11–7.98 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ (ppm): 28.55, 31.46, 72.53, 116.03, 125.16, 125.27, 126.87, 127.68, 127.86, 127.99, 128.24, 128.54, 131.48, 134.36, 134.80, 138.03, 139.68, 141.23, 147.17, 160.78, and 193.55; HRMS: Calculated: 348.0791 [M + H], Observed: 348.0786 [M + H].

4 | CONCLUSIONS

In summary, the room temperature aqua-mediated protocol revealed in this article has advantages of a short reaction run, an operationally simple method, effortlessness of work up, and purification by a simple strategy, and consequently a really green methodology for the synthesis of novel 2-arylidene indanone derivatives. The hydrogen bond forming ability and high dielectric constant drive the reaction to completion within a short period of time. Essentially, all the synthesized 2-arylidene indanones (except **3a**) are novel with promising therapeutic applications. In addition, the strategy is adequate in terms of purity and product yield. Further examination is underway to explore the biological activities of newly synthesized compounds.

The supporting information comprises of copies of the ^{1}H NMR, ^{13}CNMR, ^{19}F NMR DEPT, and HRMS spectra of the respective compounds. Besides, it will expound on the experimental procedures pursued for achieving the exploration and in this way empower the researchers to more profoundly understand the research work conveyed.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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