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Research paper

Synthesis and structure-activity relationship study of benzofuran-based chalconoids bearing benzylpyridinium moiety as potent acetylcholinesterase inhibitors

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ABSTRACT

A series of benzofuran-based chalconoids **6a**–**v** were designed and synthesized as new potential AChE inhibitors. The in vitro assay of synthesized compounds **6a**–**v** showed that most compounds had significant anti-AChE activity at micromolar or sub-micromolar levels. Among the tested compounds, 3-pyridinium derivative **6m** bearing *N*-(2-bromobenzyl) moiety and 7-methoxy substituent on the benzofuran ring exhibited superior activity. This compound with IC_{50} value of 0.027 μM was as potent as standard drug donepezil.

1. Introduction

Alzheimer's disease (AD) is a fatal and age-related neurodegenerative disease causes a progressive dementia in the elderly population and is characterized by progressive cognitive impairments including memory loss, decline in motor and language skills and learning problems [1,2]. The reported data by WHO demonstrated that more than 30 million people are afflicted with AD worldwide, and the number of patients is expected to increase up to 100 million by 2050 [3].

Although extensive efforts have been made to understand the complex pathophysiology of AD but its etiology is not completely known. However, several factors have been identified which involved in the onset and progression of AD. The main factors are oxidative stress, biometals dysfunctions, deposit of abnormal proteins such as amyloid beta-peptide (Aβ) and τ-protein, and degeneration of cholinergic neurons in the central nervous system [4,5]. Particularly, the impairment of the cholinergic neurotransmission in the brain, results in a substantial acetylcholine (ACh) deficiency which leads to cognitive and memory deficits associated in AD patients [6–8]. Accordingly, one approach to improve cholinergic neurotransmission in the AD patients is to break down the ACh metabolism. ACh can be mainly hydrolyzed by acetylcholinesterase (AChE) at the cholinergic synapses. Consequently, several AChE inhibitors such as donepezil, tacrine, rivastigmine, and galantamine have been developed and approved by FDA for AD treatment. These agents have some beneficial effects on cognitive and neuropsychiatric symptoms of AD [9,10].

The X-ray crystallographic study of AChE structure indicates that it consists of two distinct ligand binding sites, a catalytic anionic

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site (CAS) at the bottom, and a peripheral anionic site (PAS) at the entrance [11]. While the AChE inhibitors binding to either site can restrain the activity of AChE, but dual binding site inhibitors are more promising compounds for developing disease-modifying drugs for treating of AD [12]. Recently, a series of donepezil-tacrine, oxoisoaporphine-tacrine hybrids, and coumarin derivatives have been designed as potent AChE inhibitors. These compounds were able to bind simultaneously to both sites of the enzyme, exhibiting high AChE inhibitory activity [13–15].

In the search for finding new potent and selective AChE inhibitors as potential anti-Alzheimer drugs [16–18], we have previously reported coumaranone- or coumarin-based chalconoids bearing benzyl pyridinium scaffold as donepezil analogs (Fig. 1) [19–21]. The experiences on the binding mode of donepezil with AChE revealed that the benzyl piperidine moiety of the molecule which protonated at the physiologic pH can interact with the CAS, and the indanone part of donepezil binds to the PAS [22,23]. Similarly, the computational studies on the binding interactions of coumaranone- or coumarin-based chalconoids with AChE indicated that the *N*-benzylpyridinium part of the molecules interacts with the catalytic site of AChE, and the aromatic part of coumaranone or coumarin ring engages in π–π stacking with the peripheral anionic site of the enzyme [19–21]. In the present report, we describe synthesis, biological activity and docking study of new benzofuran-based AChE inhibitors containing *N*-benzylpyridinium motif (Fig. 1). Indeed, the coumaranone or coumarin part of the primary hits was replaced with benzofuran ring which recently has been considered in many designed multi-potent AD modifying agents [24].

2. Chemistry

The synthesis of designed compounds **6a**–**v** was outlined in Scheme 1. The intermediate compounds 2-acetylbenzofurans **3a**–**c** were prepared according to the literature method [25]. Thus, the reaction of salicylaldehyde derivatives **1a**–**c** with chloroacetone (**2**) in the presence of K_2CO_3 afforded 2-acetylbenzofurans **3a**–**c**. Condensation of 2-acetylbenzofurans **3a**–**c** with either pyridine-3-carboxaldehyde or pyridine-4-carboxaldehyde in *n*-butanol under microwave irradiation gave selectively (*E*)-isomers of α,β-unsaturated ketones **4a**–**c** or **5a,b**, respectively (Scheme 1). Compound **4a** was reported in the literature [26] and compounds **4b,c** and **5a,b** were new compounds. Finally, compounds **4a**–**c** or **5a,b** were reacted with appropriate benzyl halide in refluxing acetonitrile to give *N*-benzylpyridinium halide salts **6a**–**v** in good yields. The (*E*)-geometry of final compounds **6a**–**v** was assigned based on coupling constants of vinylic hydrogens ($J_{\alpha,\beta}$ > 15 Hz).

3. Results and discussion

3.1. Anti-AChE activity

The inhibitory activity of synthesized compounds **6a**–**v** was evaluated in vitro against AChE enzyme and presented as IC_{50} values in Table 1. Donepezil was used as standard drug.

As seen in Table 1, the obtained IC_{50} values for tested compounds were in the range of 0.027–31 μM, indicating the potential of compounds for anti-AChE activity. Unfortunately, fluorine-

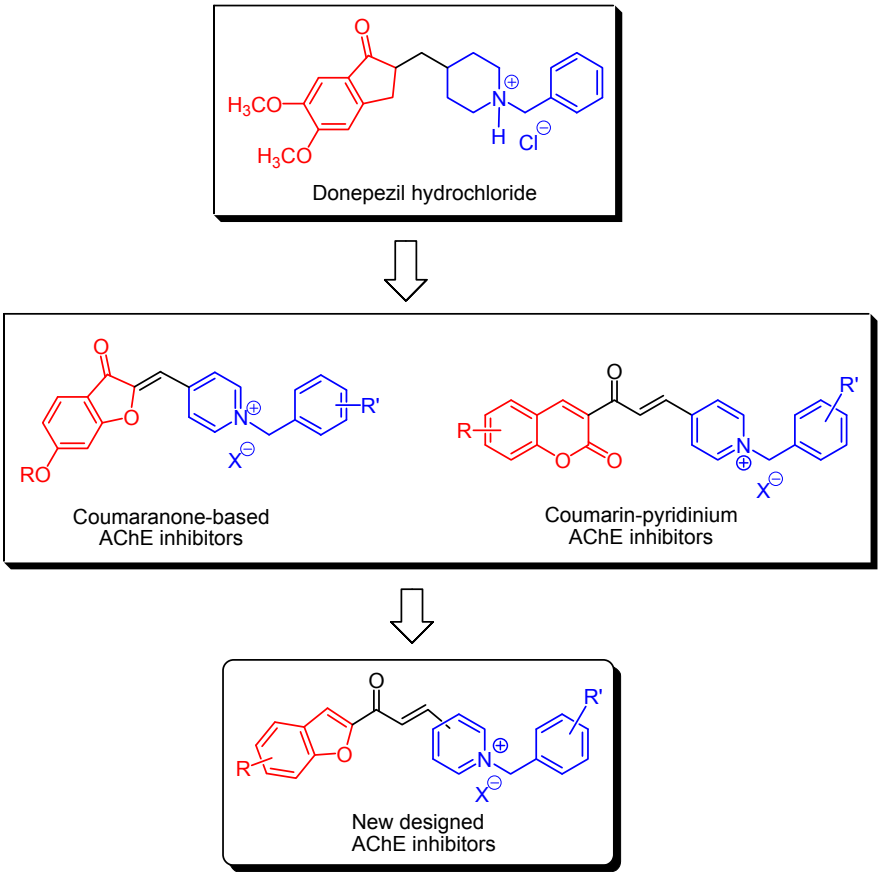
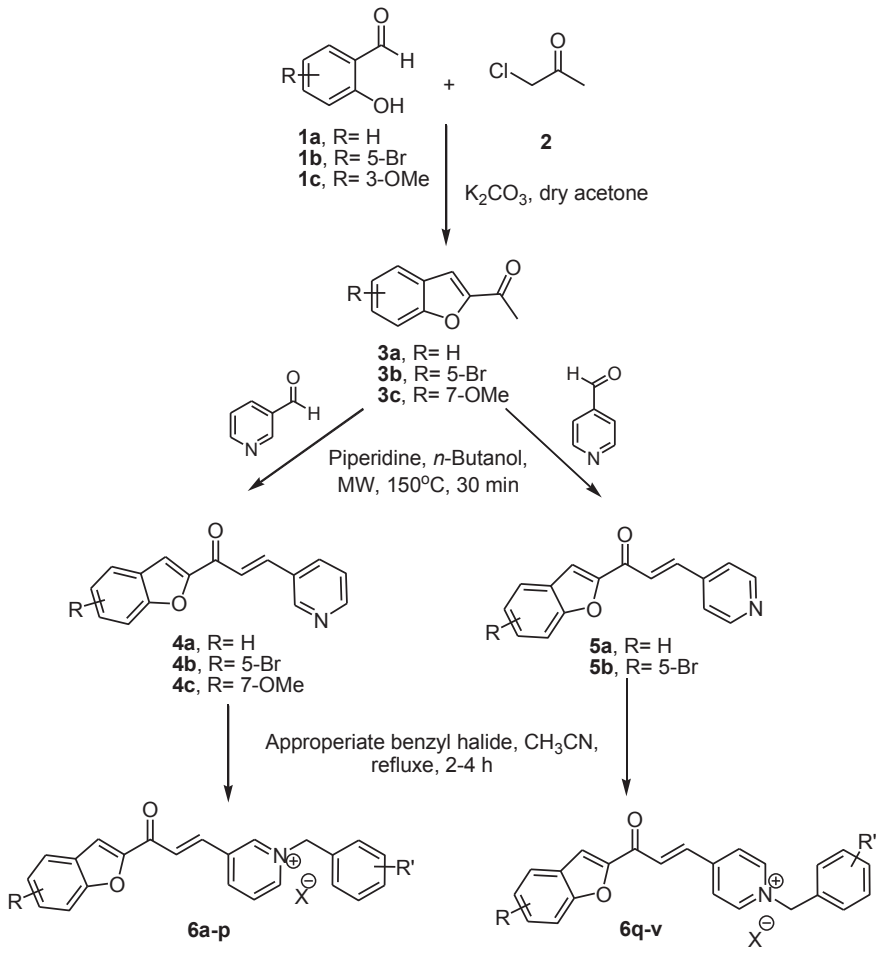


Fig. 1. Structural similarity of donepezil hydrochloride as a FDA-approved AChE inhibitor and *N*-benzylpyridinium chalconoids derived from coumaranone, and coumarin as potent anti-AChE agents, and benzofuran-based chalconoids as newly designed AChE inhibitors.



Scheme 1. Synthesis of benzofuran-based chalconoids **6a**–**p** and **6q**–**v** bearing 3-pyridinium or 4-pyridinium moiety.

substituted compounds **6e**, **6g**, **6s**, and **6v** were not soluble in the test conditions and their inhibitory activity was not reported.

Structurally, the synthesized compounds **6a**–**p** and **6q**–**v** were 3-pyridinium and 4-pyridinium derivatives, respectively. The two parent 3- and 4-pyridinium compounds as represented by **6a** and **6q** were potent AChE inhibitors (IC_{50}s 0.058 and 0.064 μM, respectively). Substitution at the benzyl residue was largely controversial and depended on the other structural features of the molecule. For example, while the 2,3-dichloro substituent on the *N*-benzyl-3-pyridinium derivatives improved the activity (compare **6j** and **6p** to **6f** and **6l**), this substituent diminished the activity in the 4-pyridinium series. Exceptionally, the 2-Br substituent on the benzyl moiety offered a modest improvement over 2-H analog. The 2-bromobenzyl derivatives **6b**, **6h**, **6m**, and **6r** were more potent than their benzyl congeners **6a**, **6f**, **6l**, and **6q**. Displacement of bromo from 2- to 4-position on the benzyl group dramatically decreased the activity.

Substitution at the 5- or 7-position of the benzofuran ring was generally not tolerated. The only exception to this SAR was demonstrated by compound **6m** where the preferred 2-bromobenzyl substituent then led to the tolerance of the 7-methoxy substituent on the benzofuran ring, providing the most potent compound in the series (IC_{50} = 0.027 μM). The activity of 2-bromobenzyl derivative **6m** was comparable to that of standard drug donepezil.

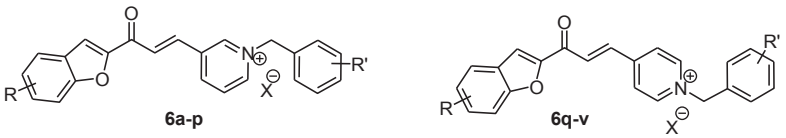
By comparing the IC_{50} values of related regioisomers in the 3-pyridinium and 4-pyridinium series (**6a** vs. **6q**, **6b** vs. **6r**, and **6f** vs. **6u**), it was revealed that they were equipotent.

3.2. Molecular docking study

In order to understanding the interactions of our new compounds in the active site of the AChE, the title compounds were investigated computationally to define their binding profile. For instance, the most active compound **6m** was subjected for further analysis. The best pose of docking was selected in terms of free energy of binding. The interaction of compound **6m** and residues in the gorge of enzyme was simply illustrated in Fig. 2. Particularly, three aromatic and hydrophobic patch of the active site namely CAS, AS (anionic site) or mid-gorge recognition site and PAS were involved in the interaction.

As shown in Fig. 2, compound **6m** exhibited gorge-binding mode, in which the compound spans the narrow hydrophobic gorge from the bottom to the rim. The main stabilizing forces were hydrophobic interactions including π–π stacking and halogen bonding. CAS amino acid residue Trp83 was found to have π–π stacking with benzofuran ring. Similarly, the pendant bromophenyl end of the molecule was involved in the π–π stacking with PAS amino acid residue Trp278. While the pendant phenyl ring was stacked with Trp278, 2-bromo substituent interacted with Arg288 through halogen bonding. Being locked the molecule in the gorge of the enzyme; the pyridinium ring was accommodated in the active site through π-cation interaction with Tyr333.

Table 1
Structures and anti-AChE activities (IC_{50}s, μM) of compounds **6a**–**v**.



Compound	R	R′	X	IC_{50} (μM)[a]
6a	H	H	Br	0.058 ± 0.003
6b	H	2-Br	Br	0.035 ± 0.002
6c	H	4-Br	Br	0.357 ± 0.021
6d	H	4-NO_2	Br	29.2 ± 1.69
6e	H	2,5-F_2	Br	ND[b]
6f	5-Br	H	Br	5.41 ± 0.43
6g	5-Br	2-F	Cl	ND
6h	5-Br	2-Br	Br	2.15 ± 0.21
6i	5-Br	4-Br	Br	31 ± 2.79
6j	5-Br	2,3-Cl_2	Cl	2.85 ± 0.19
6k	5-Br	3,4-Cl_2	Cl	0.786 ± 0.086
6l	7-OMe	H	Br	3.89 ± 0.32
6m	7-OMe	2-Br	Br	0.027 ± 0.003
6n	7-OMe	4-Br	Br	10.7 ± 1.11
6o	7-OMe	4-Cl	Cl	11.2 ± 1.45
6p	7-OMe	2,3-Cl_2	Cl	0.985 ± 0.08
6q	H	H	Br	0.064 ± 0.007
6r	H	2-Br	Br	0.041 ± 0.002
6s	H	4-F	Cl	ND
6t	H	2,3-Cl_2	Cl	3.12 ± 0.28
6u	5-Br	H	Br	5.96 ± 0.71
6v	5-Br	4-F	Cl	ND
Donepezil				0.023 ± 0.003

[a] Mean ± S.E.; values are means of three independent experiments.
[b] ND; Not Dissolved.

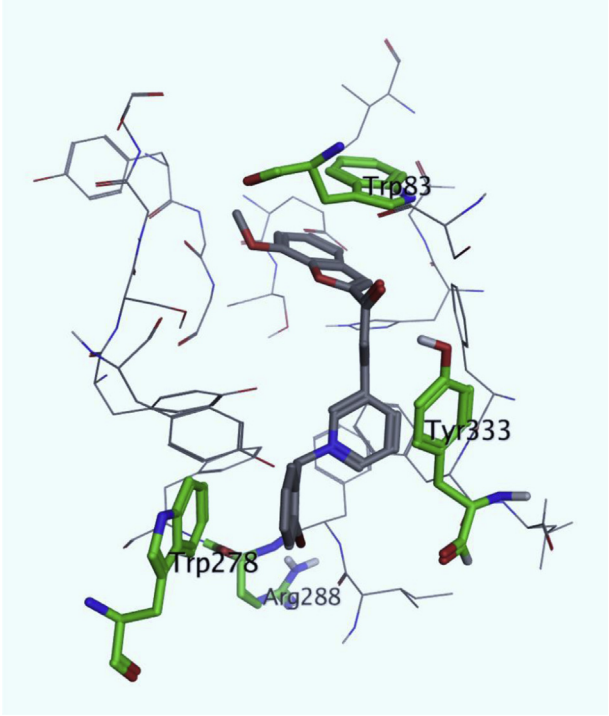


Fig. 2. Interaction of compound **6m** in the active site of AChE. Key residues are shown green. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Conclusion

We have designed and synthesized a series of benzofuran-based chalconoids as new potential AChE inhibitors. Most compounds showed significant anti-AChE activity at micromolar or sub-micromolar levels. Among the tested compounds, 3-pyridinium derivative **6m** bearing *N*-(2-bromobenzyl) moiety and 7-methoxy substituent on the benzofuran ring was the most active compound. Compound **6m** with IC_{50} value of 0.027 μM was as potent as standard drug donepezil. The SAR study revealed that the 3-pyridinium and 4-pyridinium regioisomers were equipotent and both of them could be considered as a parent scaffold for structural optimization on the benzofuran ring and benzyl residue.

5. Experimental

5.1. Chemistry

The commercially available reagents were purchased from Merk AG, Aldrich or Acros Organics and used without further purification. For the synthesis of compounds **4** and **5**, the experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for an organic synthesis and modified with a condenser and mechanical stirrer. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. The IR spectra were taken using Nicolet FT-IR Magna 550 spectrometer (KBr disks). Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector (in positive mode). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker 400 or 500 NMR instruments. The atom numbering of target compounds used for NMR data interpretation is depicted in Fig. 3. The chemical shifts (δ) and coupling constant

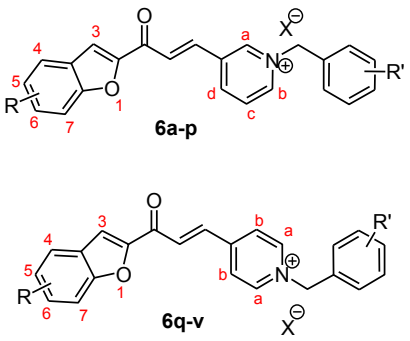


Fig. 3. Atom numbering of the target compounds **6a**–**v** used for ^{1}H NMR data.

(*J*) are expressed in parts per million (ppm) and Hertz (Hz), respectively.

*5.1.1. General procedure for the preparation of 2-acetylbenzofuran derivatives **3a**–**c** [25]*

A mixture of salicylaldehyde derivative **1a**–**c** (5 mmol) and anhydrous potassium carbonate (5.5 mmol) in dry acetone (30 ml) were refluxed for 2 h. Chloroacetone (**2**, 5.5 mmol) was added dropwise within 2–3 h and reflux was continued for another 5 h. Then, the potassium salts were filtered off and triturated with warm acetone. The solution was concentrated by evaporating part of the solvent and the obtained precipitate was filtered and washed with cold ethanol to give the pale yellow crystals of 2-acetylbenzofuran derivatives **3a**–**c**.

*5.1.1.1. 1-(Benzofuran-2-yl)ethan-1-one **(3a)**.* Yield 72%, pale yellow solid; mp 75–76 °C (lit [25]. mp 76 °C); IR (KBr, cm^{-1}) ν_{max}: 1673 (C=O); ^{1}H NMR (DMSO-d$_6$, 400 MHz), 2.50 (s, 3H, CH$_3$), 7.36 (td, 1H, H$_5$ benzofuran, J = 8.0 Hz, J = 1.2 Hz), 7.53 (td, 1H, H$_6$ benzofuran, J = 8.0 Hz, J = 1.2 Hz) 7.71 (dd, 1H, H$_7$ benzofuran, J = 8.0 Hz, J = 1.2 Hz), 7.83 (dd, 1H, H$_4$ benzofuran, J = 8.0 Hz, J = 1.2 Hz), 7.89 (s, 1H, H$_3$ benzofuran), ^{13}C NMR (DMSO-d$_6$, 100 MHz) δ: 26.8, 112.6, 114.7, 124.1, 124.4, 127.3, 128.8, 152.5, 155.4, 188.3.

*5.1.1.2. 1-(5-Bromobenzofuran-2-yl)ethan-1-one **(3b)**.* Yield 75%, yellow solid; mp 110–111 °C (lit [25]. mp 110 °C); IR (KBr, cm^{-1}) ν_{max}: 1661 (C=O); ^{1}H NMR (DMSO-d$_6$, 500 MHz), 2.50 (s, 3H, CH$_3$), 7.70 (m, 2H, H$_{6,7}$ benzofuran), 7.83 (s, 1H, H$_3$ benzofuran), 8.06 (s, 1H, H$_4$ benzofuran), ^{13}C NMR (DMSO-d$_6$, 125 MHz) δ: 26.3, 113.1, 114.2, 116.0, 125.8, 128.9, 130.8, 153.0, 153.6, 187.7.

*5.1.1.3. 1-(7-Methoxybenzofuran-2-yl)ethan-1-one **(3c)**.* Yield 78%, white solid; mp 91–93 °C (lit [25]. mp 91 °C); IR (KBr, cm^{-1}) ν_{max}: 1660 (C=O); ^{1}H NMR (DMSO-d$_6$, 500 MHz), 2.50 (s, 3H, CH$_3$), 3.97 (s, 3H, OCH$_3$), 7.12 (d, 1H, H$_6$ benzofuran, J = 8.0 Hz), 7.27 (t, 1H, H$_5$ benzofuran, J = 8.0 Hz), 7.36 (d, 1H, H$_4$ benzofuran, J = 8.0 Hz), 7.84 (s, 1H, H$_3$ benzofuran), ^{13}C NMR (DMSO-d$_6$, 125 MHz) δ: 26.3, 55.8, 109.8, 114.1, 115.0, 124.6, 128.3, 144.4, 145.4, 152.1, 187.6.

*5.1.2. General procedure for the preparation of (E)-1-(benzofuran-2-yl)-3-(pyridine-3-yl) prop-2-en-1-ones **(4a–c)** or (E)-1-(benzofuran-2-yl)-3-(pyridine-4-yl)prop-2-en-1-ones **(5a,b)***

To a mixture of 2-acetylbenzofuran derivative **3a**–**c** (6 mmol) and pyridine carbaldehyde (6 mmol) in *n*-butanol (10–15 ml), was added catalytic amount of piperidine (5–6 drops). Then, the mixture was heated under microwave irradiation at 160 °C for 30 min. After completion of the reaction (monitored by tlc), ether was added and extracted two times with 5% HCl. To the aqueous layer was added 5% aqueous KOH portion wise until it precipitated. The precipitated solid was isolated by filtration and crystallized from ethanol to afford corresponding compounds **4a**–**c** or **5a,b**.

*5.1.2.1. (E)-1-(Benzofuran-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one **(4a)**.* Yield 75%, light yellow solid; mp 155–157 °C (lit [26]. mp 154–156 °C), IR (KBr, cm^{-1}) ν_{max}: 1657 (C=O), ^{1}H NMR (CDCl$_3$, 500 MHz), 7.27 (s, 1H, H$_3$ benzofuran), 7.34 (m, 1H, H$_5$ benzofuran), 7.38 (dd, 1H, H$_7$ benzofuran, J = 8.0 Hz, J = 2.0 Hz), 7.51 (m, 1H, H$_6$ benzofuran), 7.63 (d, 1H, H$_\alpha$ vinylic, J = 15.5 Hz), 7.69 (dd, 1H, H$_4$ benzofuran, J = 8.0 Hz, J = 2.0 Hz), 7.92 (d, 1H, H$_\beta$ vinylic, J = 16.0 Hz), 8.13 (m, 1H, H$_c$-pyridine), 8.35 (d, 1H, H$_d$-pyridine, J = 7.0 Hz), 8.64 (d, 1H, H$_b$-pyridine, J = 5.5 Hz), 9.05 (s, 1H, H$_a$-pyridine),^{13}C NMR (CDCl$_3$, 125 MHz) δ: 112.4, 113.6, 123.1, 123.3, 123.8, 124.0, 127.2, 128.4, 130.5, 134.8, 140.7, 150.0, 151.2, 153.4, 155.8, 179.1. Anal. Calcd for C$_{16}$H$_{11}$NO$_2$: C, 77.10; H, 4.45; N, 5.62; Found C, 76.74; H, 4.67; N, 5.74.

*5.1.2.2. (E)-1-(5-Bromobenzofuran-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one **(4b)**.* Yield 70%, yellow solid; mp 191–193 °C; IR (KBr, cm^{-1}) ν_{max}: 1665 (C=O); ^{1}H NMR (DMSO-d$_6$, 500 MHz), 7.52 (s, 1H, H$_4$ benzofuran), 7.66–7.76 (m, 2H, H$_{6,7}$ benzofuran), 7.86 (d, 1H, H$_\alpha$ vinylic, J = 15.5 Hz), 8.00 (d, 1H, H$_\beta$ vinylic, J = 15.5 Hz), 8.13 (m, 1H, H$_c$-pyridine), 8.27 (s, 1H, H$_3$ benzofuran), 8.35 (d, 1H, H$_d$-pyridine, J = 7.5 Hz), 8.64 (d, 1H, H$_b$-pyridine, J = 5.5 Hz), 9.05 (s, 1H, H$_a$-pyridine), ^{13}C NMR (DMSO-d$_6$, 125 MHz) δ: 113.2, 114.4, 116.2, 123.4, 123.8, 125.8, 126.0, 129.0, 130.0, 131.2, 135.1, 140.4, 150.3, 151.1, 154.0, 178.1. Anal. Calcd for C$_{16}$H$_{10}$BrNO$_2$: C, 58.56; H, 3.07; N, 4.27; Found C, 58.65; H, 3.33; N, 4.03.

*5.1.2.3. (E)-1-(7-Methoxybenzofuran-2-yl)-3-(pyridin-3-yl)prop-2-en-1-one **(4c)**.* Yield 72%, yellow solid; mp 135–137 °C; IR (KBr, cm^{-1}) ν_{max}: 1663 (C=O); ^{1}H NMR (CDCl$_3$, 500 MHz), 4.06 (s, 3H, OCH$_3$), 6.98 (dd, 1H, H$_6$ benzofuran, J = 8.0 Hz, J = 1.0 Hz), 7.25 (t, 1H, H$_5$ benzofuran, J = 8.0 Hz), 7.31 (dd, 1H, H$_4$ benzofuran, J = 8.0 Hz, J = 1.0 Hz), 7.43 (m, 1H, H$_c$-pyridine), 7.67 (s, 1H, H$_3$ benzofuran), 7.73 (d, 1H, H$_\alpha$ vinylic, J = 16.0 Hz), 7.92 (d, 1H, H$_\beta$ vinylic, J = 16.0 Hz), 8.05 (d, 1H, H$_d$-pyridine, J = 8.0 Hz), 8.13 (dd, 1H, H$_c$-pyridine, J = 7.5 Hz, J = 5.0 Hz), 8.69 (d, 1H, H$_b$-pyridine, J = 5.0 Hz), 8.96 (s, 1H, H$_a$-pyridine), ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 56.1, 109.6, 113.6, 115.1, 123.4, 124.7, 128.9, 135.2, 140.5, 146.1, 148.2, 149.7, 150.7, 153.6, 168.6, 176.8, 179.1. Anal. Calcd for C$_{16}$H$_{10}$BrNO$_2$: C, 73.11; H, 4.69; N, 5.02; Found C, 72.94; H, 4.84; N, 4.79.

*5.1.2.4. (E)-1-(Benzofuran-2-yl)-3-(pyridin-4-yl)prop-2-en-1-one **(5a)**.* Yield 77%, cream solid; mp 143–145 °C; IR (KBr, cm^{-1}) ν_{max}: 1658 (C=O); ^{1}H NMR (CDCl$_3$, 500 MHz), 7.27 (s, 1H, H$_3$ benzofuran), 7.34 (t, 1H, H$_5$ benzofuran, J = 8.0 Hz), 7.52 (d, 1H, H$_\alpha$ vinylic, J = 15.5 Hz), 7.53 (d, 2H, H$_b$-pyridine, J = 4.0 Hz), 7.63 (d, 1H, H$_7$ benzofuran, J = 8.5 Hz), 7.70 (m, 1H, H$_6$ benzofuran), 7.74 (d, 1H, H$_4$ benzofuran, J = 8.5 Hz), 7.83 (d, 1H, H$_\beta$ vinylic, J = 15.5 Hz), 8.71 (d, 2H, H$_a$-pyridine, J = 4.0 Hz), ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 112.4, 113.9, 122.1, 123.4, 124.1, 125.3, 127.1, 128.6, 141.3, 141.9, 150.5, 153.2, 155.9, 179.0. Anal. Calcd for C$_{16}$H$_{10}$BrNO$_2$: C, 77.10; H, 4.45; N, 5.62; Found C, 76.84; H, 4.67; N, 5.74.

*5.1.2.5. (E)-1-(5-Bromobenzofuran-2-yl)-3-(pyridin-4-yl)prop-2-en-1-one **(5b)**.* Yield 70%, light yellow solid, mp 189–191 °C, IR (KBr, cm^{-1}) ν_{max}: 1658 (C=O), ^{1}H NMR (CDCl$_3$, 500 MHz), 7.27 (s, 1H, H$_3$ benzofuran),7.50 (d, 1H, H$_7$ benzofuran, J = 8.0 Hz), 7.54 (d, 1H, H$_4$ benzofuran, J = 2.0 Hz), 7.60 (dd, 1H, H$_6$ benzofuran, J = 8.0 Hz, J = 2.0 Hz), 7.69 (d, 1H, H$_\alpha$ vinylic, J = 15.5 Hz), 7.83 (d, 1H, H$_\beta$ vinylic, J = 15.5 Hz), 7.87 (d, 2H, H$_b$-pyridine, J = 5.0 Hz), 8.72 (d, 2H, H$_a$-pyridine, J = 5.0 Hz), ^{13}C NMR (CDCl$_3$, 125 MHz) δ: 112.7, 113.9, 117.2, 122.3, 123.1, 125.2, 125.8, 129.0, 131.6, 141.5, 142.2, 149.1, 150.0, 154.0, 154.4, 178.7. Anal. Calcd for C$_{16}$H$_{10}$BrNO$_2$: C, 58.56; H, 3.07; N, 4.27; Found C, 58.39; H, 3.22; N, 4.04.

*5.1.3. General procedure for the synthesis of pyridinium halide derivatives **6a–v***

Compounds **4a–c** or **5a,b** (1 mmol) and potassium iodide (0.3 g) were dissolved in freshly distilled dry acetonitrile (7 ml) in a 25 ml flask by heating under reflux. Then, appropriate benzyl halide (1.8 mmol) was added dropwise. After heating under reflux for 2–4 h, it was left to cool to room temperature. The precipitated solid was separated by filtration, washed with diethyl ether and dried to afford corresponding compounds **6a-p** and **6q–v** respectively.

*5.1.3.1. (E)-3-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-benzylpyridinium bromide (**6a**).* From compound **4a** (R = H, 1 mmol, 0.249 g) and benzyl bromide (1.2 mmol, 0.205 g), for 3 h, product **6a** was obtained, yield 72%, cream solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2922, 2854 (CH_2), 1741, 1663 (C=O), 1609 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 5.99 (s, 2H, $-CH_2N^+$), 7.45–7.38 (m, 4H, 3H phenyl and H_5 benzofuran), 7.59 (t, 1H, H_6 benzofuran, J = 7.6 Hz), 7.69 (d, 2H, 2H phenyl, J = 7.6 Hz), 7.75 (d, 1H, H_7 benzofuran, J = 7.6 Hz), 7.90 (d, 1H, Hα vinylic, J = 15.6 Hz), 7.88 (d, 1H, H_4 benzofuran, J = 7.6 Hz), 8.28 (m, 1H, H_c-pyridine), 8.42 (d, 1H, Hβ vinylic, J = 15.6 Hz), 8.61 (s, 1H, H_3 benzofuran), 9.16 (d, 1H, H_d-pyridine, J = 7.0 Hz), 9.28 (d, 1H, H_b-pyridine, J = 5.2 Hz), 10.16 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 63.7, 112.8, 117.6, 124.5, 124.8, 127.2, 128.5, 128.9, 129.4, 129.6, 129.7, 129.9, 134.5, 135.4, 136.2, 144.6, 145.2, 145.3, 153.1, 156.0, 178.0. Anal. Calcd for $C_{23}H_{18}BrNO_2$: C, 65.73; H, 4.32; N, 3.33. Found: C, 65.94; H, 4.08; N, 3.62.

*5.1.3.2. (E)-3-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2-bromobenzyl)pyridinium bromide (**6b**).* From compound **4a** (R = H, 1.0 mmol, 0.249 g) and 2-bromobenzyl bromide (1.2 mmol, 0.205 g), for 2 h, product **6b** was obtained, yield 78%, cream solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2919, 2850 (CH_2), 1720, 1661 (C=O), 1609 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 6.09 (s, 2H, $-CH_2N^+$), 7.45–7.40 (m, 3H, 2H phenyl and H_5 benzofuran), 7.49 (d, 1H, H_7 benzofuran, J = 7.8 Hz), 7.60 (t, 1H, H_6 benzofuran, J = 7.8 Hz), 7.77 (m, 2H, 2H phenyl), 7.92 (d, 1H, H_4 benzofuran, J = 7.8 Hz), 7.94 (d, 1H, H_α vinylic, J = 16.0 Hz), 8.32 (m, 1H, H_c-pyridine), 8.39 (d, 1H, H_β vinylic, J = 16.0 Hz), 8.56 (s, 1H, H_3 benzofuran), 9.11 (d, 1H, H_d-pyridine, J = 6.8 Hz), 9.28 (d, 1H, H_b-pyridine, J = 5.5 Hz), 9.93 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 63.9, 112.8, 117.5, 123.8, 124.5, 124.8, 127.2, 128.6, 128.8, 129.1, 129.7, 131.8, 131.9, 133.2, 133.7, 135.4, 136.1, 144.9, 145.8, 146.0, 153.1, 156.0, 178.1. Anal. Calcd for $C_{23}H_{17}Br_2NO_2$: C, 55.34; H, 3.43; N, 2.81. Found: C, 55.43; H, 3.69; N, 3.14.

*5.1.3.3. (E)-3-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(4-bromobenzyl)pyridinium bromide (**6c**).* From compound **4a** (R = H, 1.0 mmol, 0.249 g) and 4-bromobenzyl bromide (1.2 mmol, 0.300 g), for 2 h, product **6c** was obtained, yield 75%, cream solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2925, 2852 (CH_2), 1739, 1662 (C=O), 1610 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 5.94 (s, 2H, −CH2N$^+$), 7.47–7.41 (m, 3H, 2H phenyl and H_5 benzofuran), 7.64–7.59 (m, 3H, 2H phenyl and H_6 benzofuran), 7.77 (d, 1H, H_7 benzofuran, J = 8.4 Hz), 7.91 (d, 1H, H_4 benzofuran, J = 8.4 Hz), 7.92 (d, 1H, H_α vinylic, J = 16.0 Hz), 8.29 (m, 1H, H_c-pyridine), 8.33 (d, 1H, Hβ vinylic, d, J = 16.0 Hz), 8.47 (s, 1H, H_3 benzofuran), 9.16 (d, 1H, H_d-pyridine, J = 7.0 Hz), 9.24 (d, 1H, H_b-pyridine, J = 5.6 Hz), 9.96 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 64.0, 112.8, 117.3, 124.5, 124.8, 127.2, 128.5, 128.9, 129.3, 129.6, 129.7, 129.9, 134.4, 135.5, 136.2, 144.4, 145.3, 145.4, 153.2, 156.0, 178.1. Anal. Calcd for $C_{23}H_{17}Br_2NO_2$: C, 55.34; H, 3.43; N, 2.81. Found: C, 55.08; H, 3.51; N, 3.07.

*5.1.3.4. (E)-3-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(4-nitrobenzyl)pyridinium bromide (**6d**).* From compound **4a** (R = H, 1.0 mmol, 0.249 g) and 4-nitrobenzyl bromide (1.2 mmol, 0.259 g), for 2 h, product **6d** was obtained, yield 85%, white solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2923, 2851 (CH_2), 1741 (C=O), 1616 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 6.24 (s, 2H, $-CH_2N^+$), 7.41 (d, 2H, 2H phenyl, J = 8.8 Hz), 7.60 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.76 (t, 1H, H_6 benzofuran, J = 7.6 Hz), 7.90 (d, 2H, 2H phenyl, J = 8.8 Hz), 7.99 (m, 2H, $H_{4,7}$ benzofuran), 8.29 (dd, 1H, H_c-pyridine, J = 7.4 Hz, J = 4.8 Hz), 8.30 (d, 1H, H_α vinylic, J = 16.4 Hz), 8.50 (d, 1H, Hβ vinylic, J = 16.4 Hz), 8.73 (s, 1H, H_3 benzofuran), 9.24 (d, 1H, H_d-pyridine, J = 7.4 Hz), 9.37 (d, 1H, H_b-pyridine, J = 4.8 Hz), 10.34 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.9, 100.9, 106.3, 119.4, 120.1, 124.1, 127.3, 129.8, 130.5, 131.2, 131.5, 133.4, 133.6, 137.9, 141.8, 143.6, 146.2, 150.2, 155.2, 164.8, 171.5. Anal. Calcd for $C_{23}H_{17}BrN_2O_4$: C, 59.37; H, 3.68; N, 6.02. Found: C, 59.24; H, 3.57; N, 6.24.

*5.1.3.5. (E)-3-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2,5-difluorobenzyl)pyridinium bromide (**6e**).* From compound **4a** (R = H, 1.0 mmol, 0.249 g) and 2,5-difluorobenzyl bromide (1.2 mmol, 0.248 g), for 2 h, product **6e** was obtained, yield 85%, white solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2923, 2854 (CH_2), 1739 (C=O), 1638 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 5.95 (s, 2H, $-CH_2N^+$), 7.78–7.70 (m, 3H, phenyl), 7.90 (d, 1H, H_α vinylic, J = 16.0 Hz), 7.50 (t, 1H, H_5 benzofuran, J = 7.4 Hz), 7.60 (t, 1H, H_6 benzofuran, J = 7.4 Hz), 7.78 (m, 2H, $H_{4,7}$ benzofuran), 7.95 (d, 1H, Hα vinylic, J = 16.0 Hz), 8.29 (m, 1H, H_c-pyridine), 8.44 (d, 1H, Hβ vinylic, J = 16.0 Hz), 8.55 (s, 1H, H_3 benzofuran), 9.12 (d, 1H, H_d-pyridine, J = 7.0 Hz), 9.24 (d, 1H, H_b-pyridine, J = 5.4 Hz), 9.76 (s, 1H, H_a-pyridine), ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 89.1, 109.2, 114.1, 116.6, 117.0, 120.9, 123.3, 124.7, 126.3, 127.3, 127.8, 129.8, 137.0, 143.0, 143.6, 145.1, 150.2, 155.2, 157.4, 163.5, 169.2, 177.8. Anal. Calcd for $C_{23}H_{16}BrF_2NO_2$: C, 60.54; H, 3.53; N, 3.07. Found: C, 60.18; H, 3.87; N, 2.83.

*5.1.3.6. (E)-1-Benzyl-3-(3-(5-bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium bromide (**6f**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and benzyl bromide (1.2 mmol, 0.205 g), for 3 h, product **6f** was obtained, yield 73%, orange solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2928, 2855 (CH_2), 1740, 1661 (C=O), 1608 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 5.90 (s, 2H, $-CH_2N^+$), 7.50–7.44 (m, 3H, 3H phenyl), 7.61 (d, 2H, 2H phenyl, J = 8.0 Hz), 7.72 (d, 1H, H_7 benzofuran, J = 7.8 Hz), 7.78–7.74 (dd, 1H, H_6 benzofuran, J = 7.8 Hz and J = 2.0 Hz), 7.92 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.19 (d, 1H, H_4 benzofuran, J = 2.0 Hz), 8.24 (d, 1H, Hβ vinylic, J = 15.6 Hz), 8.31 (m, 1H, H_c-pyridine), 8.31 (s, 1H, H_3 benzofuran), 9.16 (d, 1H, H_d-pyridine, J = 7.4 Hz), 9.23 (d, 1H, H_b-pyridine, J = 5.4 Hz), 9.80 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 64.1, 114.9, 116.1, 117.0, 126.7, 128.1, 128.9, 129.3, 129.4, 129.7, 129.9, 132.2, 134.3, 135.4, 136.5, 144.3, 145.5, 154.0, 154.7, 178.0. Anal. Calcd for $C_{23}H_{17}Br_2NO_2$: C, 55.34; H, 3.43; N, 2.81. Found: C, 55.57; H, 3.37; N, 3.06.

*5.1.3.7. (E)-3-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2-fluorobenzyl)pyridinium chloride (**6g**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and 2-fluorobenzyl chloride (1.2 mmol, 0.173 g), for 3 h, product **6g** was obtained, yield 84%, white solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2922, 2851 (CH_2), 1749 (C=O), 1637 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 6.03 (s, 2H, $-CH_2$-N$^+$), 7.37–7.31 (m, 2H, $H_{6,7}$ benzofuran), 7.53 (m, 1H, 1H Phenyl), 7.72 (m, 1H, 1H Phenyl), 7.78 (m, 1H, 1H phenyl), 7.95 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.19 (d, 1H, H_4 benzofuran, J = 1.2 Hz), 8.30 (m, 1H, 1H phenyl), 8.38 (d, 1H, Hβ vinylic, J = 15.6 Hz), 8.46 (s, 1H, H_3 benzofuran), 9.18 (d, 1H, H_d-pyridine,

J = 7.4 Hz), 9.21 (d, 1H, H_b-pyridine, J = 5.5 Hz), 9.95 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 53.3, 110.1, 114.1, 115.6, 118.5, 121.3, 124.2, 124.7, 127.3, 129.8, 130.5, 130.6, 136.3137.0, 143.0, 143.6, 145.1, 150.2, 155.2, 159.5, 172.4, 178.5. Anal. Calcd for $C_{23}H_{16}BrClFNO_2$: C, 58.44; H, 3.41; N, 2.96. Found: C, 58.27; H, 3.69; N, 3.09.

*5.1.3.8. (E)-3-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2-bromobenzyl)pyridinium bromide (**6h**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and 2-bromobenzyl bromide (1.2 mmol, 0.300 g), for 2 h, product **6h** was obtained, yield 77%, yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2905, 2850 (CH_2), 1740, 1663 (C=O), 1609 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 6.03 (s, 2H, $-CH_2N^+$), 7.39 (d, 1H, 1H phenyl, J = 7.6 Hz), 7.64–7.42 (m, 1H phenyl), 7.53–7.49 (m, 1H phenyl), 7.73 (d, 1H, H_7 benzofuran, J = 7.6 Hz), 7.75 (d, 1H, H_6 benzofuran, J = 7.6 Hz), 7.80–7.77 (m,1H, 1H phenyl), 7.95 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.19 (s, 1H, H_4 benzofuran), 8.28 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.32 (dd, 1H, H_c-pyridine, J = 7.0 Hz, J = 5.4 Hz), 8.35 (s, 1H, H_3 benzofuran), 9.11 (d, 1H, H_d-pyridine, J = 7.0 Hz), 9.24 (d, 1H, H_b-pyridine, J = 5.4 Hz), 9.75 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 64.1, 115.0, 116.1, 117.0, 123.8, 126.7, 128.3, 128.8, 129.1, 129.3, 131.7, 131.9, 132.2, 133.2, 133.8, 135.4, 136.5, 144.7, 146.0, 146.1, 154.0, 154.7, 178.1. Anal. Calcd for $C_{23}H_{16}Br_3NO_2$: C, 47.79; H, 2.79; N, 2.42. Found: C, 48.04; H, 2.94; N, 2.64.

*5.1.3.9. (E)-3-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(4-bromobenzyl)pyridinium bromide (**6i**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and 4-bromobenzyl bromide (1.2 mmol, 0.300 g), for 2 h, product **6i** was obtained, yield 80%, yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2905, 2851 (CH_2), 1731, 1663 (C=O), 1609 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 5.99 (s, 2H, $-CH_2N^+$), 7.67 (m, 4H, 2H phenyl and $H_{6,7}$ benzofuran), 7.78–7.72 (m, 2H, 2H Phenyl), 7.90 (d, 1H, Hα vinylic, J = 15.6 Hz), 8.15 (s, 1H, H_4 benzofuran), 8.29 (m, 1H, H_c-pyridine), 8.41 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.56 (s, 1H, H_3 benzofuran), 9.18 (d, 1H, H_d-pyridine, J = 7.2 Hz), 9.31 (d, 1H, H_b-Pyridine, J = 5.2 Hz), 10.16 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.3, 113.7, 116.4, 116.6, 120.1, 124.1, 127.3, 129.8, 130.5, 131.2, 131.5, 133.4, 133.6, 137.0, 143.0, 143.6, 145.1, 150.2, 155.2, 159.5, 177.8. Anal. Calcd for $C_{23}H_{16}Br_3NO_2$: C, 47.79; H, 2.79; N, 2.42. Found: C, 48.01; H, 2.90; N, 2.21.

*5.1.3.10. (E)-3-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2,3-dichlorobenzyl) pyridinium chloride (**6j**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and 2,3-dichlorobenzyl chloride (1.2 mmol, 0.234 g), for 4 h, product **6j** was obtained, yield 75%, light yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2914 (CH_2), 1740, 1661 (C=O), 1609 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 6.12 (s, 2H, $-CH_2N^+$), 7.47 (d, 1H, H_7 benzofuran, J = 7.2 Hz),7.51–7.46 (m,1H, 1H phenyl) 7.80–7.75 (m, 3H, 2H phenyl and H_6 benzofuran), 7.95 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.19 (d, 1H, H_4 benzofuran, J = 1.2 Hz), 8.32 (dd, 1H, H_c-pyridine, J = 7.0 Hz, J = 4.8 Hz), 8.36 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.44 (s, 1H, H_3 benzofuran), 9.16 (d, 1H, H_d-pyridine, J = 7.0 Hz), 9.26 (d, 1H, H_b-pyridine, J = 4.8 Hz), 9.85 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.6, 115.0, 116.2, 117.0, 126.4, 126.7, 128.4, 128.8, 129.3, 129.5130.4, 131.4, 131.8, 132.0, 132.2, 133.0, 134.1, 135.4, 136.5, 144.8, 146.0, 154.0, 154.7, 178.1. Anal. Calcd for $C_{23}H_{15}BrCl_3NO_2$: C, 52.76; H, 2.89; N, 2.67. Found: C, 52.98; H, 3.11; N, 2.53.

*5.1.3.11. (E)-3-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(3,4-dichlorobenzyl) pyridinium chloride (**6k**).* From compound **4b** (R = 5-Br, 1.0 mmol, 0.328 g) and 3,4-dichlorobenzyl chloride (1.2 mmol, 0.234 g), for 4 h, product **6k** was obtained, yield 79%, light yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2917, 2854 (CH_2), 1738, 1660 (C=O), 1612 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 5.95 (s, 2H, $-CH_2N^+$), 7.78–7.70 (m, 4H, 2H phenyl and $H_{6,7}$ benzofuran), 7.91 (d, 1H, H_α vinylic, J = 16.0 Hz), 8.07 (d, 1H phenyl, J = 7.6 Hz), 8.17 (d, 1H, H_4 benzofuran, J = 1.2 Hz), 8.29 (m, 1H, H_c-pyridine), 8.39 (d, 1H, H_β vinylic, J = 16.0 Hz), 8.48 (s, 1H, H_3 benzofuran), 9.16 (d, 1H, H_d-pyridine, J = 8.0 Hz), 9.28 (d, 1H, H_b-pyridine, J = 5.5 Hz), 10.07 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.3, 115.0, 116.3, 117.0, 126.7, 128.3, 128.9, 129.4, 130.1, 131.7, 132.0.132.1, 132.2, 132.8, 135.0, 135.5, 136.6, 144.5, 145.5, 145.8, 154.1, 154.7, 178.1. EI-MS *m/z* (%) 493 (M^++6, 1), 491 (M^++4, 4), 489 (M^++2, 9), 487 (M^+, 7), 327 (83), 300 (44), 262 (12), 250 (26), 238 (12), 225 (27), 159 (100), 77 (22). Anal. Calcd for $C_{23}H_{15}BrCl_3NO_2$: C, 52.76; H, 2.89; N, 2.67. Found: C, 52.49, H, 3.04, N, 2.39.

*5.1.3.12. (E)-1-Benzyl-3-(3-(7-methoxybenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium bromide (**6l**).* From compound **4c** (R = 7-OMe, 1.0 mmol, 0.279 g) and benzyl bromide (1.2 mmol, 0.234 g), for 3 h, product **6l** was obtained, yield 70%, light yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2923, 2854 (CH_2), 1752, 1665 (C=O), 1613 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 3.97 (s, 3H, -OCH_3), 6.05 (s, 2H, $-CH_2N^+$), 7.19 (d, 1H, H_6 benzofuran, J = 8.0 Hz), 7.32 (t, 1H, H_5 benzofuran, J = 8.0 Hz), 7.44–7.41 (m, 4H, 3H phenyl and H_4 benzofuran), 7.73 (dd, 2H, 2H phenyl, J = 7.0 Hz, J = 2.0 Hz), 7.90 (d, 1H, H_α vinylic, J = 16.0 Hz), 8.28 (dd, 1H, H_c-pyridine, J = 8.0 Hz, J = 5.5 Hz), 8.49 (d, 1H, H_β vinylic, J = 16.0 Hz), 8.73 (s, 1H, H_3 benzofuran). 9.19 (d, 1H, H_d-pyridine, J = 8.0 Hz), 9.34 (d, 1H, H_b-pyridine, J = 5.5 Hz), 10.34, (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 56.2, 62.3, 107.4, 111.7, 114.3, 116.2, 117.8, 125.7, 127.3, 128.5, 129.0, 129.6, 134.5, 135.7, 143.0, 143.6, 145.3, 145.8, 150.2, 151.5, 158.1, 175.9. Anal. Cald for $C_{24}H_{20}BrNO_3$: C, 64.01; H, 4.48; N, 3.11. Found: C, 63.80; H, 4.71; N, 3.30.

*5.1.3.13. (E)-1-(2-Bromobenzyl)-3-(3-(7-methoxybenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium bromide (**6m**).* From compound **4c** (R = 7-OMe, 1.0 mmol, 0.279 g) and 2-bromobenzyl bromide (1.2 mmol, 0.234 g), for 2 h, product **6m** was obtained, yield 78%, light yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2933 (CH_2), 1757, 1662 (C=O), 1611 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 3.36 (s, 3H, -OCH_3), 6.06 (s, 2H, $-CH_2N^+$), 7.20 (d, 1H, H_6 benzofuran, J = 8.0 Hz), 7.33 (t, 1H, H_5 benzofuran, J = 8.0 Hz), 7.46–7.41 (m, 3H, 3H Phenyl), 7.52–7.48 (m, 1H, 1H Phenyl), 7.78 (d, 1H, H_4 benzofuran, J = 8.0 Hz), 7.94 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.31 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.33 (dd, 1H, H_c-pyridine, J = 8.0 Hz, J = 5.5 Hz), 8.47 (s, 1H, H_3 benzofuran), 9.10 (d, 1H, H_d-pyridine, J = 8.0 Hz), 9.25 (d, 1H, H_b-pyridine, J = 5.5 Hz), 9.83 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 56.4, 46.0, 111.1, 115.9, 117.6, 123.8, 125.6, 128.5, 128.7, 128.8, 129.1, 131.8, 131.9, 133.2, 133.8, 135.4, 136.2, 144.8, 145.6, 145.8, 145.9, 146.0, 153.2, 177.9. Anal. Calcd for $C_{24}H_{19}Br_2NO_3$: C, 54.47; H, 3.62; N, 2.65. Found: C, 54.30; H, 3.38; N, 2.97.

*5.1.3.14. (E)-1-(4-Bromobenzyl)-3-(3-(7-methoxybenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium bromide (**6n**).* From compound **4c** (R = 7-OMe, 1.0 mmol, 0.279 g) and 4-bromobenzyl bromide (1.2 mmol, 0.234 g), for 2 h, product **6n** was obtained, yield 75%, orange solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2929, 2847 (CH_2), 1720, 1665 (C=O), 1613 (C=C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 3.97 (s, 3H, -OCH_3), 6.03 (s, 2H, $-CH_2N^+$), 7.19 (d, 1H, H_6 benzofuran, J = 7.6 Hz), 7.32 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.42 (d, 1H, H_4 benzofuran, J = 7.6 Hz), 7.65 (d, 2H, 2H Phenyl, J = 8.4 Hz), 7.71 (d, 2H, 2H Phenyl, J = 8.4 Hz), 7.89 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.28 (m, 1H, H_c-pyridine), 8.46 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.69 (s, 1H, H_3 benzofuran), 9.18 (d, 1H, H_d-pyridine, J = 8.0 Hz), 9.31 (d, 1H, H_b-pyridine, J = 5.5 Hz), 10.27 (s, 1H, H_a-

pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 58.5, 62.6, 111.2, 115.8, 118.0, 123.4, 125.6, 128.5, 128.7, 128.9, 131.9, 132.5, 133.8, 135.4, 136.2, 144.9, 145.2, 145.6, 145.9, 153.2, 177.9. EI-MS *m/z* (%) 450 (M +2, 10), 448 (M^+, 11), 434 (9), 417 (16), 369 (42), 353 (10), 339 (23), 313 (32), 279 (100), 264 (49), 250 (51), 236 (42). Anal. Calcd for $C_{24}H_{19}Br_2NO_3$: C, 54.47; H, 3.62; N, 2.65. Found: C, 54.36; H, 3.44; N, 2.83.

*5.1.3.15. (E)-1-(4-Chlorobenzyl)-3-(3-(7-methoxybenzofuran-2-yl)-3-oxoprop-1-en-1- yl)pyridinium chloride (**6o**).* From compound **4c** (R = 7-OMe, 1.0 mmol, 0.279 g) and 4-chlorobenzyl chloride (1.2 mmol, 0.234 g), for 3 h, product **6o** was obtained, yield 70%, light yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2924, 2856 (CH_2), 1731, 1661 (C═O), 1624 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 3.34 (s, 3H, -OCH_3), 5.95 (s, 2H, $-CH_2N^+$), 7.21 (d, 1H, H_6 benzofuran, J = 7.6 Hz), 7.34 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.45 (d, 1H, H_4 benzofuran, J = 7.6 Hz), 7.54 (d, 2H, 2H Phenyl, J = 8.4 Hz), 7.74 (d, 2H, 2H Phenyl, J = 8.4 Hz), 7.91 (d, 1H, H_α vinylic, J = 16.0 Hz), 8.30 (dd, 1H, H_c-pyridine, J = 8 Hz, J = 5.5 Hz), 8.44 (d, 1H, H_β vinylic, J = 16.0 Hz), 8.59 (s, 1H, H_3 benzofuran), 9.14 (d, 1H, H_d-pyridine, J = 8 Hz), 9.26 (d, 1H, H_b-pyridine, J = 5.5 Hz),10.19 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 53, 56.1, 108.9, 113.2, 125.4, 127.3, 128.4, 129.0, 132.4, 133.6, 135.9, 137.0, 141.5, 142.4, 143.0, 144.9, 145.1, 151.5, 155.2, 157.5, 177.8. Anal. Calcd for $C_{24}H_{19}Cl_2NO_3$: C, 65.47; H, 4.35; N, 3.18. Found: C, 65.74; H, 4.24; N, 3.39.

*5.1.3.16. (E)-1-(2,3-Dichlorobenzyl)-3-(3-(7-methoxybenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium chloride (**6p**).* From compound **4c** (R = 7-OMe, 1.0 mmol, 0.279 g) and 2,3-dichlorobenzyl chloride (1.2 mmol, 0.234 g), for 4 h, product **6p** was obtained, yield 75%, yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2924, 2852 (CH_2), 1745, 1664 (C═O), 1613 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 3.98 (s, 3H, -OCH_3), 6.12 (s, 2H, $-CH_2N^+$), 7.20 (d, 1H, H_6 benzofuran, J = 7.8 Hz), 7.34 (t, 1H, H_5 benzofuran, J = 7.8 Hz), 7.52–7.44 (m, 3H, 2H phenyl and H_4 benzofuran), 7.79 (m, 1H, Ph), 7.94 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.32 (dd, H_c-pyridine, J = 8.0 Hz, J = 5.5 Hz), 8.37 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.51 (s, 1H, H_3 benzofuran), 9.15 (d, 1H, H_d-pyridine, J = 7.5 Hz), 9.25 (d, 1H, H_b-pyridine, J = 5.5 Hz), 9.89 (s, 1H, H_a-pyridine); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 56.4, 62.1, 111.1, 115.9, 117.6, 125.6, 128.3, 128.6, 128.7, 128.8, 129.5, 130.4, 131.7, 132.0, 133.0, 134.2, 135.5, 136.2, 144.8, 145.6, 145.9, 146.1, 153.2, 178.0. EI-MS *m/z* (%) 444 (M +4, 1), 442 (M +2, 3), 440 (M^+, 4), 308 (22), 279 (100), 236 (11), 175 (14), 159 (99), 148 (3). Anal. Calcd for $C_{24}H_{18}Cl_3NO_3$: C, 60.72; H, 3.82; N, 2.95. Found: C, 60.41; H, 3.91; N, 2.62.

*5.1.3.17. (E)-4-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-benzylpyridinium bromide (**6q**).* From compound **5a** (R = H, 1.0 mmol, 0.249 g) and benzyl bromide (1.2 mmol, 0.205 g), for 3 h, product **6q** was obtained, yield 70%, orange solid, mp > 300 °C, IR (KBr, cm^{-1}) ν_{max}: 2922, 2853 (CH_2), 1743, 1664 (C═O), 1635 (C═C alkene), ^{1}H NMR (DMSO-d_6, 400 MHz), 5.92 (s, 2H, $-CH_2N^+$), 7.44 (m, 3H, 3H phenyl), 7.61 (d, 2H, 2H phenyl, J = 7.2 Hz), 7.79–7.73 (m, 2H, $H_{5,6}$ benzofuran), 7.92 (d, 1H, H_α vinylic, J = 15.6 Hz), 7.94 (d, 1H, H_7 benzofuran, J = 7 Hz), 8.20 (d, 1H, H_4 benzofuran, J = 7.2 Hz), 8.43 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.51 (s, 1H, H_3 benzofuran), 8.68 (d, 2H, H_b-pyridine, J = 5.5 Hz), 9.41 (d, 2H, H_a-pyridine, J = 5.5 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 63.2, 115.0, 117.0, 120.9, 123.3, 124.7, 124.8, 125.7, 127.3, 127.8, 129.3, 129.6, 131.9, 137.6, 145.5, 155.2, 157.0, 160.5, 177.8. Anal. Calcd for $C_{23}H_{18}BrNO_2$: C, 65.73; H, 4.32; N, 3.33. Found: C, 66.03; H, 4.66; N, 3.65.

*5.1.3.18. (E)-4-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2-bromobenzyl)pyridinium bromide (**6r**).* From compound **5a** (R = H, 1.0 mmol, 0.249 g) and 2-bromobenzyl bromide (1.2 mmol, 0.300 g), for 2 h, product **6r** was obtained, yield 75%, dark yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2940, 2858 (CH_2), 1723, 1663 (C═O), 1634 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 6.00 (s, 2H, $-CH_2N^+$), 7.38 (d, 1H, 1H phenyl, J = 7.6 Hz), 7.42 (t, 2H, 2H phenyl, J = 7.6 Hz), 7.50 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.61 (t, 1H, H_6 benzofuran, J = 7.4 Hz), 7.78 (m, 2H, 1H phenyl and H_7 benzofuran), 7.94 (d, 1H, H_α vinylic, J = 15.6 Hz), 7.94 (d, 1H, H_4 benzofuran, J = 8.0 Hz), 8.44 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.54 (s, 1H, H_3 benzofuran), 8.68 (d, 2H, H_b-pyridine, J = 5.8 Hz), 9.21 (d, 2H, H_a-pyridine, J = 5.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 63.4, 112.8, 118.0, 123.7, 124.6, 124.9, 127.1, 127.2, 129.1, 130.0, 131.6, 131.9, 132.6, 133.6, 133.8, 137.0, 146.1, 151.2, 153.1, 156.1, 177.9. EI-MS *m/z* (%) 420 (M +2, 4), 418 (M^+, 6), 169 (41), 152 (100), 118 (59), 89 (51), 63 (32), 43 (38). Anal. Calcd for $C_{23}H_{17}Br_2NO_2$: C, 55.34; H, 3.43; N, 2.81. Found: C, 55.21; H, 3.72; N, 2.98.

*5.1.3.19. (E)-4-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(4-fluorobenzyl)pyridinium chloride (**6s**).* From compound **5a** (R = H, 1.0 mmol, 0.249 g) and 4-fluorobenzyl chloride (1.2 mmol, 0.173 g), for 3 h, product **6s** was obtained, yield 82%, white solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2954, 2918 (CH_2), 1738, 1684 (C═O), 1643 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 5.94 (s, 2H, $-CH_2N^+$), 7.21 (d, 2H, 2H phenyl, J = 7.6 Hz), 7.23 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.39 (t,1H, H_6 benzofuran, J = 7.6 Hz), 7.59–7.64 (m, 2H, $H_{4,7}$ benzofuran), 7.69 (d, 2H, 2H phenyl, J = 7.6 Hz), 7.80 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.10 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.50 (s, 1H, H_3 benzofuran), 8.66 (d, 2H, H_b-pyridine, J = 5.8 Hz), 9.01 (d, 2H, H_a-pyridine, J = 5.8 Hz), ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 65.4, 111.5, 114.0, 116.6, 120.9, 122.6, 124.7, 124.8, 127.3, 127.8, 130.0, 130.6, 145.1, 146.3, 153.6, 157.0, 159.9, 160.5, 177.8. Anal. Calcd for $C_{23}H_{17}ClFNO_2$: C, 70.14; H, 4.35; N, 3.56. Found: C, 69.96; H, 4.57; N, 3.23.

*5.1.3.20. (E)-4-(3-(Benzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(2,3-dichlorobenzyl)pyridinium chloride (**6t**).* From compound **5a** (R = H, 1.0 mmol, 0.249 g) and 2,3-dichlorobenzyl chloride (1.2 mmol, 0.234 g), for 4 h, product **6t** was obtained, yield 73%, orange solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2964 (CH_2), 1708, 1658 (C═O), 1633 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 6.07 (s, 2H, $-CH_2N^+$), 7.43–7.38 (m, 2H phenyl), 7.48 (t, 1H, H_5 benzofuran, J = 7.6 Hz), 7.62 (t, 1H, H_6 benzofuran, J = 7.6 Hz), 7.78 (d, 2H, 1H phenyl and H_7 benzofuran, J = 7.6 Hz), 7.95 (d, 1H, H_4 benzofuran, J = 7.6 Hz), 7.95 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.48 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.57 (s, 1H, H_3 benzofuran), 8.69 (d, 2H, H_b pyridine, J = 5.5 Hz), 9.24 (d, 2H, H_a pyridine, J = 5.5 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 61.6, 112.8, 118.1, 124.6, 124.9, 127.2, 129.5, 130.0, 130.1, 131.6, 131.9, 132.7, 133.0, 134.6, 137.0, 146.1, 151.3, 153.1, 156.1, 178.0. Anal. Calcd for $C_{23}H_{16}Cl_3NO_2$: C, 62.12; H, 3.63; N, 3.15. Found: C, 62.33; H, 3.39; N, 3.44.

*5.1.3.21. (E)-1-Benzyl-4-(3-(5-bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)pyridinium bromide (**6u**).* From compound **5b** (R = 5-Br, 1.0 mmol, 0.328 g) and benzyl bromide (1.2 mmol, 0.205 g), for 3 h, product **6u** was obtained, yield 71%, yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2924, 2858 (CH_2), 1740, 1657 (C═O), 1636 (C═C alkene); ^{1}H NMR (DMSO-d_6, 400 MHz), 5.87 (s, 2H, $-CH_2N^+$), 7.43 (t, 1H, 1H phenyl, J = 7.6 Hz), 7.57 (d, 2H, 2H phenyl, J = 8.4 Hz), 7.62 (t, 1H, 1H phenyl, J = 7.6 Hz), 7.67 (m, 2H, 1H phenyl and H_6 benzofuran), 7.77 (d, 1H, H_7 benzofuran, J = 8.4 Hz), 7.91 (d, 1H, H_α vinylic, J = 16.0 Hz), 7.94 (s, 1H, H_4 benzofuran), 8.42 (d, 1H, H_β vinylic, J = 16.0 Hz), 8.54 (s, 1H, H_3 benzofuran), 8.66 (d, 2H, H_b-pyridine, J = 5.2 Hz), 9.34 (d, 2H, H_a-pyridine, J = 5.2 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.53, 112.8, 118.0, 123.3, 124.6, 124.9, 127.2, 130.0, 131.5, 132.4, 132.5, 137.0, 145.6, 150.9, 156.1, 159.9, 177.9. Anal.

Calcd for $C_{23}H_{17}Br_2NO_2$: C, 55.34; H, 3.43; N, 2.81. Found: C, 55.43, H, 3.69, N, 3.14.

*5.1.3.22. (E)-4-(3-(5-Bromobenzofuran-2-yl)-3-oxoprop-1-en-1-yl)-1-(4-fluorobenzyl)pyridinium chloride (**6v**).* From compound **5b** (R = 5-Br, 1.0 mmol, 0.328 g) and 4-fluorobenzyl chloride (1.2 mmol, 0.173 g), for 3 h, product **6v** was obtained, yield 82%, dark yellow solid, mp > 300 °C; IR (KBr, cm^{-1}) ν_{max}: 2924, 2847 (CH_2), 1751, 1663 (C=O), 1637 (C=C alkene); ^1H NMR (DMSO-d_6, 400 MHz), 5.87 (s, 2H, $-CH_2N^+$), 7.31 (m, 2H, 2H Phenyl),7.70 (m, 2H, 2H phenyl), 7.80–7.76 (m, 2H, $H_{6,7}$ benzofuran), 7.92 (d, 1H, H_α vinylic, J = 15.6 Hz), 8.21 (d, 1H, H_4 benzofuran, J = 1.6 Hz), 8.43 (d, 1H, H_β vinylic, J = 15.6 Hz), 8.47 (s, 1H, H_3 benzofuran), 8.65 (d, 2H, H_b-pyridine, J = 5.5 Hz), 9.36 (d, 2H, H_a-pyridine, J = 5.5 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 62.5, 115.0, 116.4, 116.7, 116.8, 117.0, 126.9, 127.3, 129.3, 131.8, 131.9, 132.2, 132.4, 137.4, 145.5, 150.7, 154.0, 154.8, 178.0. Anal. Calcd for $C_{23}H_{16}BrClFNO_2$: C, 58.44; H, 3.41; N, 2.96. Found: C, 58.18; H, 3.49; N, 3.22.

5.2. Cholinesterase inhibition assay

Electric-eel (*Torpedo californica*) AChE (type VI-S), acetylthiocholine iodide, 5,5′-dithiobis [2-nitrobenzoic acid] (DTNB), and donepezil were obtained from Sigma–Aldrich (Steinheim, Germany). To measure AChE inhibiting activities the slightly modified Ellman method was used [21]. All the compounds with the exception of **6e**, **6g**, **6s**, and **6v** were dissolved in the mixture of methanol/DMSO (4/1) and then diluted in the phosphate buffer (0.1 M, pH = 8) to obtain desired assay concentrations. Compounds **6e**, **6g**, **6s**, and **6v** were not soluble in the assay conditions and not tested. The assay concentrations were prepared in such a way that produced the inhibition in the range of 20–80%. The reaction mixture contained 3 ml of potassium phosphate buffer, 100 μL of DTNB, 50 μl of compound solution and 50 μl of enzyme which were mixed and incubated for 15 min at 25 °C. The reaction was then started by the addition of 10 μl acetylthiocholine. The hydrolysis rate of acetylthiocholine was determined at 412 nm through measuring the yellow 5-thio-2-nitrobenzoate anion resulting from enzyme catalysis. To compare the potency of the compounds, donepezil hydrochloride was used as the positive control. The obtained data was then further analyzed by GraphPad Prism version 6 for Windows (GraphPad Software, San Diego California USA, www.graphpad.com) to achieve IC_{50} values (mean ± S.E.).

5.3. Docking study

The three-dimensional structures of compound**s** was constructed and optimized using the HyperChem7 (Hypercube, Inc.). Energy minimization was performed with a distance gradient algorithm with convergence criterion of 0.05 kcal/(mol.Å) and a maximum of 1000 interactions, respectively. The Autodock 4.0 [27] was applied to dock compounds in the aromatic gorge of AChE co-crystallized with *N*-saccharinohexyl-galantamine (PDB id; 3I6Z). The geometric center of the ligand was used to define the active site interactions points. The docking result was analyzed by Accelrys Discovery Studio Visualizer 3.0 (AccelrysSoftware Inc., San Diego).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.08.061.

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