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Wittig homologation of 2-(chloromethyl)-2*H*-chromen-2-ol derivatives: a new facile synthesis of substituted 2,3-dihydrobenzoxepine-4-carboxylates

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ABSTRACT

Wittig homologation of 2-(chloromethyl)-2*H*-chromen-2-ol derivatives **2a**–**t** with (ethoxycarbonylmethylene)triphenylphosphorane provided the 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylates **3a**–**t** with *Z* (*cis*) selectivity. Various basic catalysts were studied for the reaction of 2-(chloromethyl)-2*H*-chromen-2-ol **2a** with the combination of Wittig reagent to provide compound **3b**. The reaction of 2-(chloromethyl)-2*H*-chromen-2-ol **2a** with other Wittig reagents, such as methylene(triphenylene)phosphorane and (1-ethoxycarbonylethylidene)triphenylphosphorane provided ketone derivative **4a** rather 2-oxoethylidene derivative **3b**. The ketone derivative **4a** was reacted with Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane to give 2,3-dihydrobenzoxepine-4-carboxylate **3b**. The present approach is novel, straight forward and being reported for the first time.

1. Introduction

Benzoxepines and their derivatives are important benzo-fused heterocyclic compounds with various biological applications in drugs, pharmaceuticals, and agrochemicals.[1] Pterulones ((*E*/*Z*-**I**), 6-hydroxypterulone (**II**), pterulinic acid (*E*/*Z*-**III**)) and pterulone-**B** (*E*-**IV**) are novel monochlorinated 2,3-dihydrobenzoxepine natural products isolated from *Pterula* species (Fig. 1) and are effective inhibitors of eukaryotic respiratory chain at the NADH site of the ubiquinone oxidoreductase (complex **I**).[2] Pterulones displayed potent antifungal, and in vitro week cytotoxic activity toward mammalian cells and their synthesis are well reported in the literature.[3] 2,3-Dihydro-1-benzoxepine synthesis constitutes an important objective and RCM reaction of allyloxy biphenyl thioacetals with titanocene species,[4] and palladium catalyzed [5+2] annulation of 2-aroylmethoxyarylboronic acids with alkynes[5] are available methods in the literature. However, to the best of our knowledge there is no method available for the synthesis of substituted 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylates.

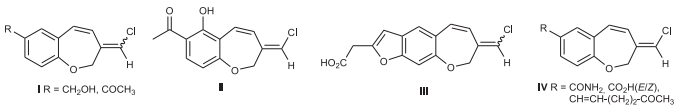

Fig. 1. Structures of pterulones.

2. Results and discussion

As a part of our research interest in design and synthesis of biologically active heterocyclic compounds[6] with potential activities, herein we report the synthesis of 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylate derivatives by the Wittig[7] homologation of 2,2,3-trisubstituted 2*H*-chromenes for the first time. β-Ketoester having chloro substituent at 4th position has an impact on their reactivity and therefore we studied the reactivity of salicylaldehyde **1a** with ethyl 4-chloro-3-oxobutanoate under basic conditions to provide 2-(chloromethyl)-2*H*-chromen-2-ol **2a**.[8a] Thus obtained 2-(chloromethyl)-2*H*-chromen-2-ol derivative **2a** (1 equiv) is initially taken up for the Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane[9] (2.5 equiv) in dichloromethane (DCM) at room temperature for 24 h (Scheme 1) and to provide (3*Z*,4*E*)-ethyl-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **3b** in 46% yield preferentially with *Z* (*cis*) configuration[10] (^{1}H NMR experiment) as colorless solid. The IR spectrum of **3b** has shown absorption bands at ν_{max}=1712, 1616 and 1554 cm^{-1} corresponding to two carbonyl group and an olefin double bond. The ^{1}H NMR spectrum showed two separate signals corresponds to ethoxy groups, one methylene singlet, and other characteristic singlet at δ=7.58 ppm corresponds to C-5 of benzoxepine, another singlet at δ=6.52 ppm of 2-oxoethylidene, and four protons corresponds to aromatic ring.

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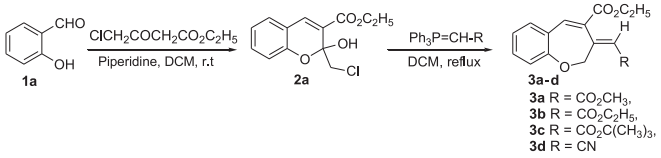
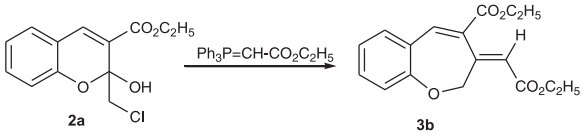
Compound **3b** was further analyzed by ^{13}C NMR spectroscopy, where the characteristic two quaternary signals at δ=160.9 and δ=131.1 ppm correspond to C-3 and C-4 of the oxepine part. The signal at δ=66.4 ppm corresponds to C-2 of the OCH_2 carbon. The signal at δ=165.9, 166.0 ppm corresponds to ester carbonyls and 122.2 to oxoethylidene carbon. Compound **3b** showed molecular ion MS (ESI) *m*/*z* 325 $[M+Na]^+$, and further confirmed by HRMS (*m*/*z* calcd for $C_{17}H_{18}O_5Na$ $[M+Na]^+$: 325.1046 and found: 325.1073).



Scheme 1. Synthesis of 2,3-dihydrobenzoxepinecarboxylate derivatives **3a**–**d**.

The result encouraged us to search for the optimization of reaction conditions for the formation of compound **3b**. We have examined the reaction of **2a** (1 equiv) with Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane (1.5 equiv) in DCM at room temperature, the product **3b** was isolated in 32% yield after 24 h, however under reflux conditions, the yield was improved to 65% with 2 equiv of Wittig reagent. The effect of solvents THF, MeCN, MeOH, EtOH, $CHCl_3$, benzene, toluene, and H_2O was studied with 3 equiv of Wittig reagent and found that DCM, and benzene were the solvent of choice in terms of yield (96%) and reaction time (Table 1, entries 1–11). One equivalent of Wittig reagent is utilized as a base to trap the HCl formed during the reaction and another equivalent utilized for the homologation to provide **3b**. Since the Wittig reagent used in excess (3 equiv), next we have modified the reaction conditions in combination of tertiary amines (1.2 equiv) and Wittig reagent (1.4 equiv) to minimize excess Wittig reagent to provide **3b** in good yield (96%). Accordingly, we have taken up study on the reaction of **2a** with the various bases in which

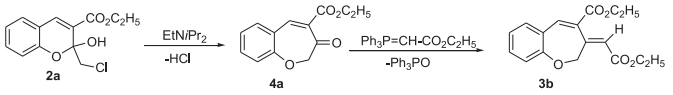
Table 1
Optimization of the reaction conditions for the synthesis of **3b**



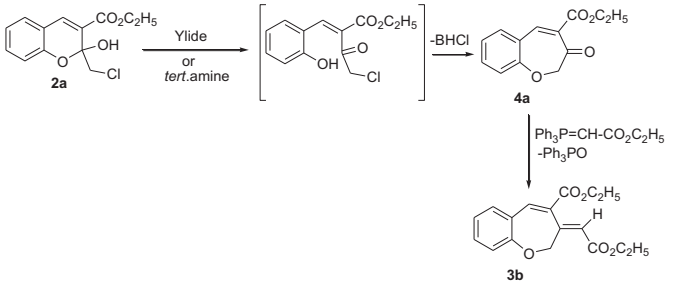
Entry	Ylide [equiv]	Base[a]	Solvent	Time [h]	Yield[d] [%]
1	1.5	—	DCM[b]	24	32
2	2.5	—	DCM[b]	24	46
3	3.0	—	DCM[c]	24	96
4	1.5	—	Benzene[b]	24	30
5	3.0	—	Benzene[c]	6	90
6	3.0	—	Toluene[c]	12	60
7	2.5	—	EtOH[b]	24	20
8	2.5	—	MeOH[b]	24	10
9	3.0	—	H_2O[c]	6	58
10	3.0	—	MeCN[b]	24	70
11	3.0	—	THF[c]	2	60
12	1.4	Pyridine	DCM[c]	24	26
13	1.4	Pyridine	Benzene[c]	24	20
14	1.4	DABCO	DCM[c]	12	60
15	1.4	DBU	DCM[c]	12	68
16	1.4	EtN^iPr_2	DCM[c]	12	96
17	1.4	EtN^iPr_2	Benzene[c]	8	90
18	1.4	DMAP	DCM[c]	12	84
19	1.4	DMAP	Benzene[c]	8	90
20	1.4	Et_3N	DCM[c]	12	70

[a] 1.2 equiv
[b] Room temperature.
[c] Reflux conditions.
[d] Isolated.

EtN^iPr_2 in DCM was found to be better when compared to other bases, such as pyridine, Et_3N, DABCO, DBU and DMAP (Scheme 2, Table 1, entries 12–20), where the primary and secondary amines were not effective under these conditions. A plausible mechanism is shown in Scheme 3, 2*H*-chromene **2a** upon Wittig reaction/basic conditions rearranging (S_N2) to (*E*)-ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **4a** (^1H NMR experiment) with the elimination of HCl. Thus formed (ketone derivative) **4a** readily undergoes in situ homologation with Wittig reagent afford **3b** with the elimination of Ph_3PO (see Supplementary data). Under similar conditions **3a** & **3c** were synthesized in very good yields. Compound **3d** is prepared by the reaction of **2a** with (cyanomethylene) triphenylphosphorane generated in situ with *t*-BuOK[11] under nitrogen atmosphere in benzene at 0 °C to room temperature (Scheme 1).



Scheme 2. Synthesis of benzoxepine derivative **3b**.

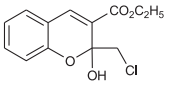
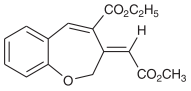
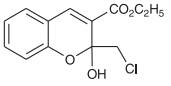
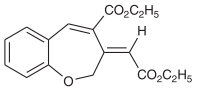
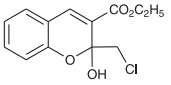
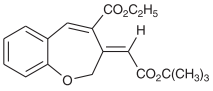
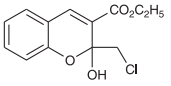
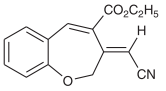
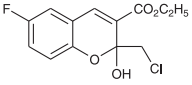
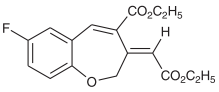
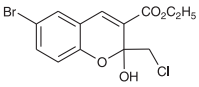
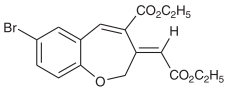
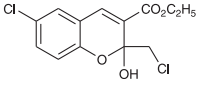
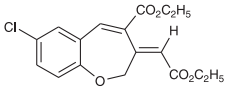
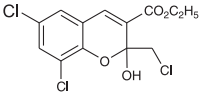
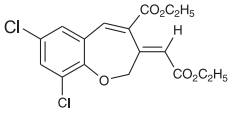
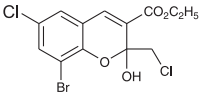
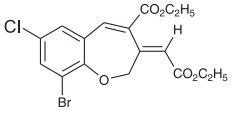
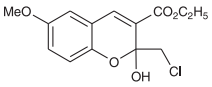
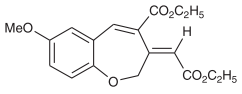
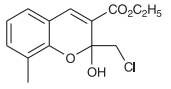
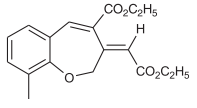
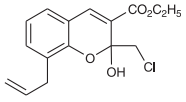
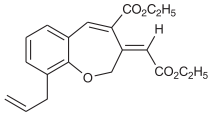
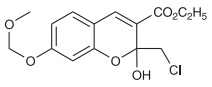
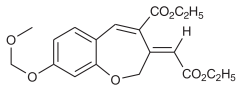
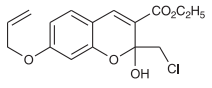
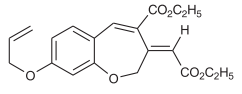
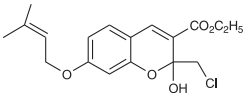
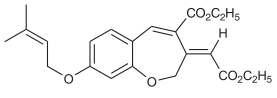


Scheme 3. Plausible mechanism.

In order to evaluate the efficiency of the methodology, various substituted 2-(chloromethyl)-2*H*-chromen-2-ol derivatives having electron withdrawing and donating substituents at various positions on aromatic ring fluoro (entry **2e**), bromo (entry **2f**), chloro (entry **2g**), 6,8-dichloro (entry **2h**), 6-chloro-8-bromo (entry **2i**), methoxy (entry **2j**), methyl (entry **2k**), *C*-allyl (entry **2l**), *O*-alkyl derivatives (entry **2m**–**o**), phenyl (entry **2p**) and pyrimidinyl (entry **2q**), naphthyl (entry **2r**, **2s**) and pyran (entry **2t**) were studied with (ethoxycarbonylmethylene)triphenylphosphorane to form series of new (3*Z*,4*E*)-ethyl-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates **3a**–**t** in very good yields (Table 2). Electron withdrawing groups afforded high yields compared to electron donating groups. 2-(chloromethyl)-2*H*-chromen-2-ol **2e**, **2i**, **2k**, **2m**, **2r**, **2s** and **2t** are new, and prepared from the corresponding salicylaldehydes with ethyl 4-chloro-3-oxobutanoate in good yields.[8a] Compounds **2p** and **2q** are prepared by *Suzuki* coupling[8a] of 5-bromosalicylaldehyde with phenylboronic acid and pyrimidin-2-ylboronic acid in presence of $Pd(PPh_3)_4$.

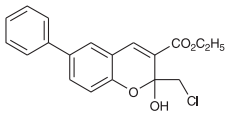
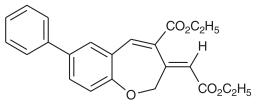
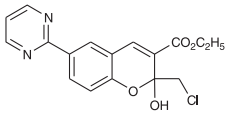
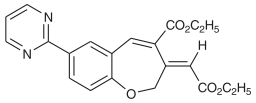
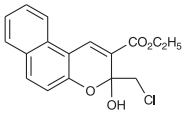
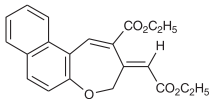
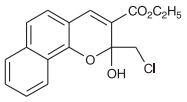
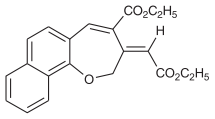
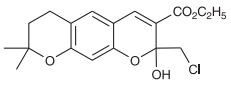
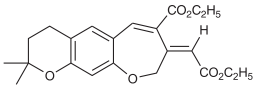
Having achieved the preparation of substituted 2,3-dihydrobenzo[*b*]oxepine-4-carboxylates **3a**–**t**; next we examined the reaction of 2-(chloromethyl)-2*H*-chromen-2-ol derivative **2a** with other Wittig reagent, such as methylene(triphenylene)phosphorane under optimized conditions (Scheme 4),[11] however the reaction could not provide the corresponding oxepine derivative **3**, but yielded (*E*)-Ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **4a** in 60% yield, this may be due to methylene(-triphenylene)phosphorane could presumably acting as a base on ketone **4a** rather than nucleophile. The reaction of **2a** with another Wittig reagent (1-ethoxycarbonylethylidene)triphenylphosphorane,[9f,12] in DCM at room temperature, and on reflux conditions

Table 2
Synthesis of 2,3-dihydrobenzoxepine-4-carboxylates

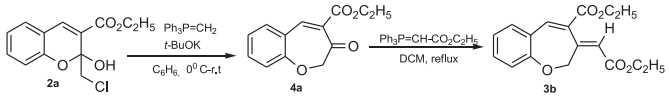
Entry	2*H*-Chromenes (**2**)	Oxepines (**3**)	Time (h)	Yield[a] (%)
a			12	94
b			12	96
c			14	82
d			14	60
e			8	93
f			10	92
g			10	88
h			8	88
i			8	90
j			14	82
k			14	80
l			16	90
m			16	88
n			14	92
o			14	89

(*continued on next page*)

Table 2 (*continued*)

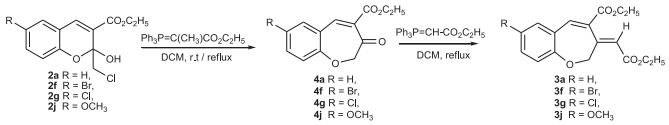
Entry	2*H*-Chromenes (**2**)	Oxepines (**3**)	Time (h)	Yield[a] (%)
p			16	78
q			16	72
r			18	88
s			18	63
t			18	60

[a] Isolated yields.



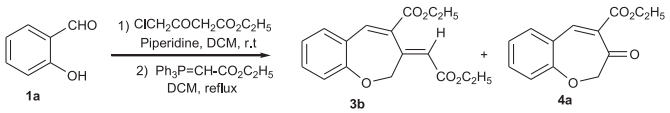
Scheme 4. Wittig homologation of **4a**.

(benzene/toluene were also studied), the reaction could not give the corresponding α-methyl derivative **3**, but **4a** was exclusively formed (Scheme 5) in very good yield (80%). This may be due to steric congestion between ketone derivative **4a** and Wittig reagent $Ph_3P{=}C(CH_3)COOC_2H_5$, the fact that the tetra substituted double bond would suffer from allylic strain. Synthesis of substituted benzo[*b*]oxepin-3(2*H*)-ones recently reported by Chan et al. by the gold catalyzed intramolecular heterocyclization/Petasis–Ferrier rearrangement of 2-(prop-2-ynyloxy) aromatic aldehydes.[13] Interestingly for the first time we observed the formation of **4a** by the reaction of **2a** with (1-ethoxycarbonylethylidene)triphenylphosphorane in DCM at room temperature in very good yield. The generality of this reaction was then tested with electron donating and withdrawing groups present on 2-(chloromethyl)-2*H*-chromen-2-ol. Electron donating substituent methoxy **2j** and the electron withdrawing substituents bromo (**2f**), chloro (**2g**) afforded ketone derivatives **4j**, **4f**, & **4g** (crude products ^{1}H NMR experiment). Thus obtained ketone derivatives **4a**, **4f**, **4g** & **4j** were subjected to Wittig homologation with (ethoxycarbonylmethylene) triphenylphosphorane in DCM solvent under reflux conditions to afford its corresponding 2,3-dihydrobenzo[*b*]oxepine-4-carboxylate derivatives **3b** (96%), **3f** (90%), **3g** (86%) & **3j** (80%, Scheme 5).



Scheme 5. Wittig reactions of **4a**, **4f**, **4g** & **4j**.

Further we attempted an effort for one-pot synthesis of **3b**, accordingly salicylaldehyde **1a** is reacted with ethyl 4-chloro-3-oxobutanoate under basic condition (30 mol % piperidine in DCM) provided 2-(chloromethyl)-2*H*-chromen-2-ol derivative **2a** (TLC). The Wittig reagent (ethoxycarbonylmethylene)triphenylphosphorane (3 equiv) is added to **2a** at room temperature and the contents were refluxed for 24 h, after usual work up and column chromatography the products obtained were **3b** (40%) and **4a** (20%, Scheme 6). The one-pot reaction is also carried out with EtN^iPr_2 (2.5 equiv), but the 2-(chloromethyl)-2*H*-chromen-2-ol derivative **2a** obtained in low yield. In general, we found that the piperidine (30 mol %) and Wittig reagent (3 equiv) is essential to provide 2,3-dihydrobenzoxepine derivatives **3a**–**t** in one-pot reaction. Under these conditions, the electron withdrawing groups were an advantage over donating present on salicylaldehydes to provide corresponding benzoxepines in good yields.



Scheme 6. One-pot synthesis of **3b**.

3. Conclusion

In conclusion, we have developed a new approach for the synthesis of substituted 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylates **3a**–**t** with *Z* (*cis*) selectivity by Wittig homologation of 2-(chloromethyl)-2*H*-chromen-2-ol derivatives **2a**–**t** using commercially available chemicals for the first time. Rearrangement of 2-(chloromethyl)-2*H*-chromen-2-ol to ketone derivatives upon Wittig/basic conditions and in situ Wittig homologation to provide 2,3-dihydrobenzoxepines is the new aspect. The results

summarized in Table 2 indicate the scope and generality of the reaction with respect to the examples described therein. All the compounds **3a**–**t** were characterized by spectral data (^{1}H NMR, ^{13}C NMR, IR and mass). The ketone derivatives **4** are important synthons and presently utilizing in our laboratory for the synthesis of heterocyclic compounds, biological applications and will be reported in due course.

4. Experimental section

4.1. General

The chemicals, salicylaldehydes (Sigma–Aldrich), piperidine, and all the solvents were obtained commercially. Wittig reagents were prepared as per the literature procedures. The 2-(chloromethyl)-2*H*-chromen-2-ol derivatives were synthesized according to our earlier reported method.[8a] All the melting points were determined on a *Mettler-Temp* apparatus and are uncorrected. IR was recorded with a *Thermo Nicolet Nexus* 670 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a *Gemini* 200 MHz, *Bruker Avance* 300 MHz spectrometers. Chemical shifts (δ) are quoted in parts per million and are referenced to tetramethylsilane (TMS) as internal standard. EIMS obtained on 7070*H spectrometers* operating at 70 eV using a direct inlet system. HRMS were carried out on Agilent 6510 Q-TOF LC/MS instrument. All reactions were monitored by thin layer chromatography (TLC) on pre-coated silica gel 60 F_{254} (mesh); spots were visualized under UV light. Column chromatographic separations were carried out on silica gel (60–120 mesh).

4.2. Typical procedure for the synthesis of substituted 2-(chloromethyl)-2*H*-chromen-2-ol (2e, 2h, 2i, 2k, 2m, 2r, 2s, 2t)

Ethyl 4-chloro-3-oxobutanoate (164 mg, 1 mmol) was added to the mixture of a stirred solution of 5-fluoro-2-hydroxybenzaldehyde (140 mg, 1 mmol) and piperidine (30 mol %) in DCM (2 mL) at room temperature over a period of 15 min. The mixture was stirred for another 8 h at the same temperature. After completion of the reaction (TLC), the crude product was subjected to column chromatography purification (hexane/ethyl acetate 95:5) to give **2e** (183 mg, 64% yield) as yellow liquid.

*4.2.1. Ethyl 2-(chloromethyl)-6-fluoro-2-hydroxy-2H-chromene-3-carboxylate (**2e**).* Yellow liquid; R_f (20% EtOAc/hexane) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.0 Hz, 3H, OCH_2CH_3), 4.06 (d, J=11.3 Hz, 1H, CH_2Cl), 4.28 (d, J=11.3 Hz, 1H, CH_2Cl), 4.32 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.94 (d, J=8.9 Hz, 1H, Ar), 7.24–7.32 (m, 2H, Ar), 7.64 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 49.1, 61.7, 98.2, 117.9, 119.2, 123.1, 127.0, 128.1, 132.4, 135.3, 150.8, 164.7 ppm. IR (KBr) 3404, 2981, 2927, 1710, 1633, 1478, 1272, 1210, 1019 cm^{-1}. MS (ESI): 285, 287 $[M+H]^+$.

*4.2.2. Ethyl 6,8-dichloro-2-(chloromethyl)-2-hydroxy-2H-chromene-3-carboxylate (**2h**).* Yield 220 mg (66%); yellow liquid; R_f (20% EtOAc/hexane) 0.36; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J=6.8 Hz, 3H, OCH_2CH_3), 4.16 (d, J=11.3 Hz, 1H, CH_2Cl), 4.32 (d, J=11.3 Hz, 1H, CH_2Cl), 4.35 (q, J=6.8 Hz, 2H, OCH_2CH_3), 7.19 (d, J=2.26 Hz, 1H, Ar), 7.41 (d, J=2.26 Hz, 1H, Ar), 7.64 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 48.7, 61.7, 98.9, 120.1, 123.9, 126.5, 128.9, 130.6, 132.1, 134.7, 164.1, 167.0 ppm. IR (KBr) 3417, 2923, 1712, 1634, 1457, 1375, 1281, 1221, 1019 cm^{-1}. MS (ESI): 319, 321 $[M-OH]^+$.

*4.2.3. Ethyl,8-bromo-6-chloro-2-(chloromethyl)-2-hydroxy-2H-chromene-3-carboxylate (**2i**).* Yield 242 mg (64%); yellow liquid; R_f (20% EtOAc/hexane) 0.38; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=6.8 Hz, 3H, OCH_2CH_3), 4.18 (d, J=11.3 Hz, 1H, CH_2Cl), 4.32 (d, J=11.3 Hz, 1H, CH_2Cl), 4.34 (q, J=6.8 Hz, 2H, OCH_2CH_3), 7.22 (d, J=2.26 Hz, 1H, Ar), 7.56 (d, J=2.26 Hz, 1H, Ar), 7.62 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 49.0, 61.8, 98.9, 111.1, 120.1, 123.9, 127.2, 127.3, 134.8, 135.0, 147.8, 164.1 ppm. IR (KBr) 3413, 2981, 1712, 1662, 1632, 1448, 1278, 1210, 1017 cm^{-1}. MS (ESI): 363, 365 $[M-OH]^+$.

*4.2.4. Ethyl 2-(chloromethyl)-2-hydroxy-8-methyl-2H-chromene-3-carboxylate (**2k**).* Yield 174 mg (62%); yellow liquid; R_f (20% EtOAc/hexane) 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.0 Hz, 3H, OCH_2CH_3), 2.28 (s, 3H, CH_3), 4.06 (d, J=11.3 Hz, 1H, CH_2Cl), 4.18 (d, J=11.3 Hz, 1H, CH_2Cl), 4.29 (q, J=7.0 Hz, 2H, OCH_2CH_3), 6.86 (t, J=7.2 Hz, 1H, Ar), 7.04 (d, J=7.5 Hz, 1H, Ar), 7.16 (d, J=7.3 Hz, 1H, Ar) 7.64 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 15.3, 49.2, 61.3, 97.6, 117.5, 121.3, 121.5, 125.9, 126.5, 134.2, 137.1, 150.3, 165.1 ppm. IR (KBr) 3446, 2923, 1705, 1635, 1467, 1375, 1288, 1248, 1209, 1066, 1025 cm^{-1}. MS (ESI): 305, 307 $[M+Na]^+$.

*4.2.5. Ethyl 2-(chloromethyl)-2-hydroxy-7-(methoxymethoxy)-2H-chromene-3-carboxylate (**2m**).* Yield 183 mg (56%); yellow liquid; R_f (20% EtOAc/hexane) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 3.46 (s, 3H, CH_3), 4.02 (d, J=11.1 Hz, 1H, CH_2Cl), 4.22 (d, J=11.1 Hz, 1H, CH_2Cl), 4.29 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.15 (s, 2H, OCH_2), 6.60–6.69 (m, 2H, Ar), 7.12 (d, J=8.3 Hz, 1H, Ar), 7.62 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 49.1, 56.2, 61.2, 94.1, 98.3, 103.8, 110.6, 112.3, 119.0, 129.9, 136.6, 153.7, 161.1, 165.2 ppm. IR (KBr) 3423, 2975, 1705, 1614, 1501, 1375, 1281, 1212, 1157, 1076, 1003 cm^{-1}. MS (ESI): 351, 353 $[M+Na]^+$.

*4.2.6. Ethyl 2-(chloromethyl)-3-hydroxy-3H-benzo[f]chromene-2-carboxylate (**2r**).* Yield 196 mg (62%); yellow liquid; R_f (20% EtOAc/hexane) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.42 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.06 (d, J=11.3 Hz, 1H, CH_2Cl), 4.32 (d, J=11.3 Hz, 1H, CH_2Cl), 4.34 (q, J=7.2 Hz, 2H, OCH_2CH_3), 7.2 (d, J=9.1 Hz, 1H, Ar), 7.34–7.40 (m, 1H, Ar) 7.48–7.56 (m, 1H, Ar), 7.72 (d, J=8.1 Hz, 1H, Ar), 7.78 (d, J=8.9 Hz, 1H, Ar), 8.05 (d, J=8.3 Hz, 1H, Ar), 8.39 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 48.8, 61.3, 98.3, 110.8, 117.5, 119.6, 120.8, 124.5, 127.7, 128.7, 129.2, 130.0, 132.3, 133.5, 151.5, 165.2 ppm. IR (KBr) 3401, 2982, 1707, 1636, 1465, 1398, 1262, 1220, 1054 cm^{-1}. MS (ESI): 301 $[M-OH]^+$.

*4.2.7. Ethyl 2-(chloromethyl)-2-hydroxy-2H-benzo[h]chromene-3-carboxylate (**2s**).* Yield 134 mg (42%); yellow liquid; R_f (20% EtOAc/hexane) 0.28; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.30 (d, J=11.3 Hz, 1H, CH_2Cl), 4.34 (d, J=11.1 Hz, 1H, CH_2Cl), 4.36 (q, J=7.5 Hz, 2H, OCH_2CH_3), 7.30 (d, J=8.3 Hz, 1H, Ar), 7.46 (d, J=8.3, 1H, Ar), 7.52–7.62 (m, 2H, Ar), 7.76–7.82 (m, 1H, Ar), 7.87 (s, 1H, CHAr), 8.32–8.38 (m, 1H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 49.4, 61.3, 98.6, 112.4, 119.9, 121.7, 122.7, 123.9, 124.8, 126.3, 127.7, 128.3, 136.1, 137.3, 149.1, 165.1 ppm. IR (KBr) 3410, 3049, 2980, 1690, 1630, 1570, 1374, 1341, 1297, 1218, 1056, 1017 cm^{-1}. MS (ESI): 319 $[M+H]^+$.

*4.2.8. Ethyl 2-(chloromethyl)-2-hydroxy-8,8-dimethyl-7,8-dihydro-2H,6H-pyrano[3,2-g]chromene-3-carboxylate (**2t**).* Yield 133 mg (38%); yellow liquid; R_f (20% EtOAc/hexane) 0.30; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (s, 6H, $2CH_3$), 1.36 (t, J=6.8 Hz, 3H, OCH_2CH_3), 1.80 (t, J=6.8 Hz, 2H, CH_2), 2.71 (t, J=6.8 Hz, 2H, CH_2), 4.00 (d, J=10.6 Hz, 1H, CH_2Cl), 4.22 (d, J=10.6 Hz, 1H, CH_2Cl), 4.30 (q, J=6.8 Hz, 2H, OCH_2CH_3), 6.42 (s, 1H, Ar), 6.95 (s, 1H, Ar), 7.65 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 21.6, 26.8, 32.5, 49.2, 61.1, 75.4, 98.1, 104.6, 111.2, 115.4, 118.2, 129.8, 136.9, 152.2, 158.6, 165.6 ppm. IR (KBr) 3441, 2927, 1711, 1617, 1394, 1271, 1200, 1093 cm^{-1}. MS (ESI): 335, 337 $[M-OH]^+$.

HRMS-ESI calcd for $C_{18}H_{21}ClO_5Na$ $[M+Na]^+$ 375.09697; found 375.09655.

4.3. Method-A: typical procedure for the synthesis of substituted 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylates (3a–c & 3e–t)

A mixture of ethyl 2-(chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylate **2a** (268 mg, 1.0 mmol) and [(ethoxycarbonylmethylene) triphenylphosphorane (1.04 g, 3 mmol) in DCM (4 mL) were stirred under reflux conditions for 24 h. After completion of the reaction (TLC), solvent was removed under reduced pressure, and crude product was purified by column chromatography (hexane/ethyl acetate 9.5:0.5) provide (3*Z*,4*E*)-ethyl-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **3b** (290 mg, 96% yield) as colorless solid.

4.4. Method-B: typical procedure for the synthesis of substituted 2-oxoethylidene-2,3-dihydrobenzoxepine-4-carboxylates (3a–c & 3e–t)

Phosphonium ylide [(ethoxycarbonylmethylene)triphenylphosphorane, (487 mg, 1.4 mmol) was added to a stirred solution of ethyl 2-(chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylate **2a** (268 mg, 1.0 mmol) and EtN^iPr_2 (154 mg, 1.2 mmol) in DCM (4 mL) and the contents were refluxed for 12 h. After completion of the reaction (TLC), the solvent was removed under reduced pressure, and crude product was purified by column chromatography (hexane/ethyl acetate 9.5:0.5) provide (3*Z*,4*E*)-ethyl-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **3b** (290 mg, 96% yield) as colorless solid.

*4.4.1. (3Z,4E)-Ethyl 3-(2-methoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3a**).* Yellow solid; R_f (20% EtOAc/hexane) 0.52; mp 68–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (t, J=7.2 Hz, 3H, OCH_2CH_3), 3.77 (s, 3H, OCH_3), 4.32 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.24 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.96–7.06 (m, 2H, Ar), 7.24–7.38 (m, 2H, Ar), 7.60 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 51.4, 61.3, 66.3, 119.8, 121.7, 122.3, 123.3, 131.0, 132.2, 135.7, 141.0, 144.2, 160.9, 165.9, 166.4 ppm. IR (KBr) 2986, 2928, 1710, 1615, 1556, 1480, 1439, 1386, 1338, 1290, 1257, 1217, 1150, 1113, 1058, 1006 cm^{-1}. MS (ESI): 289 $[M+H]^+$, 311 $[M+Na]^+$. HRMS-ESI calcd for $C_{16}H_{17}O_5$ $[M+H]^+$ 289.10705; found 289.10649.

*4.4.2. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo [b]oxepine-4-carboxylate (**3b**).* Colorless solid; R_f (20% EtOAc/hexane) 0.62; mp 63–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.24 (s, 2H, OCH_2), 6.53 (s, 1H, C=CH), 6.96–7.06 (m, 2H, Ar), 7.24–7.38 (m, 2H, Ar), 7.59 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 14.5, 60.3, 61.3, 66.4, 119.8, 122.2, 123.3, 131.1, 132.2, 135.7, 140.9, 144.0, 160.9, 165.9, 166.0 ppm. IR (KBr) 2981, 2927, 1712, 1616, 1554, 1479, 1446, 1286, 1255, 1220, 1192, 1153, 1112, 1059, 1000 cm^{-1}. MS (ESI): 325 $[M+Na]^+$; HRMS-ESI calcd for $C_{17}H_{18}O_5Na$ $[M+Na]^+$ 325.1046; found 325.1073.

*4.4.3. (3Z,4E)-Ethyl 3-(2-tert-butoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3c**).* Yellow liquid; R_f (20% EtOAc/hexane) 0.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.52 (s, 9H, 3× CH_3), 4.32 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.19 (s, 2H, OCH_2), 6.44 (s, 1H, C=CH), 6.96–7.06 (m, 2H, Ar), 7.24–7.34 (m, 2H, Ar), 7.54 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.6, 28.4, 61.2, 66.4, 80.6, 119.8, 122.3, 123.3, 124.1, 131.3, 131.9, 135.7, 140.4, 143.0, 160.9, 165.4, 166.1 ppm. IR (KBr) 2978, 2931, 1709, 1603, 1449, 1371, 1285, 1252, 1223, 1146, 1057, 1009 cm^{-1}. MS (ESI): 331 $[M+H]^+$, 353 $[M+Na]^+$. HRMS-ESI calcd for $C_{19}H_{22}O_5$ Na $[M+Na]^+$ 353.13594; found 353.13514.

*4.4.4. Typical procedure for the synthesis of (3Z,4E)-ethyl 3-(cyanomethylene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3d**).* In an oven dried round bottom flask, the triphenyl(cyanomethyl)phosphonium bromide (840 mg, 2.2 mmol) in dry benzene (1 mL) is transferred under nitrogen atmosphere. The reaction flask is cooled to 0 °C, the potassium *tert*-butoxide (246 mg, 2.2 mmol) was added at a time and the contents were stirred for 1 h. After the mixture becomes light yellow color, the ethyl 2-(chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylate **2a** (268 mg, 1 mmol) in benzene (1 mL) was added slowly at the same temperature. The contents were slowly brought to room temperature (6 h), after completion of the reaction (TLC), the reaction mixture was quenched with aqueous NH_4Cl solution, and extracted with ether (3×10 mL). The organic layer was dried over Na_2SO_4, solvent removed under reduced pressure and crude product was purified by column chromatography (hexane/ethyl acetate 9:1) to give **3d** (150 mg, 60% yield) as colorless solid; mp 43–44 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.0 Hz, 3H, OCH_2CH_3), 4.32 (q, J=7.0 Hz, 2H, OCH_2CH_3), 4.89 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 7.04–7.10 (m, 2H, Ar), 7.33–7.42 (m, 2H, Ar), 7.74 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 61.6, 70.4, 102.7, 116.3, 119.8, 123.0, 123.3, 127.2, 133.2, 136.3, 142.8, 148.7, 160.8, 165.4 ppm. IR (KBr) 3091, 2923, 2853, 2208, 1707, 1602, 1483, 1290, 1255, 1226, 1170, 1010 cm^{-1}. MS (ESI): 255 $[M\ ]^+$.

*4.4.5. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-7-fluoro-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3e**).* Yellow solid; R_f (20% EtOAc/hexane) 0.50; mp 84–85 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.22 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.99 (d, J=8.6 Hz, 1H, Ar), 7.20–7.26 (m, 1H, Ar), 7.36 (d, J=2.3 Hz, 1H, Ar), 7.48 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 14.2, 60.6, 61.6, 66.6, 121.1, 122.8, 124.4, 127.1, 131.7, 132.3, 134.3, 139.1, 143.3, 159.1, 166.1, 166.9 ppm. IR (KBr) 2983, 2922, 1709, 1619, 1589, 1478, 1385, 1279, 1247, 1160 cm^{-1}. MS (ESI): 359 $[M+K]^+$.

*4.4.6. (3Z,4E)-Ethyl 7-bromo-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3f**).* Colorless solid; R_f (20% EtOAc/hexane) 0.48; mp 101–102 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.21 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.94 (d, J=8.7 Hz, 1H, Ar) 7.37 (dd, J=2.5, 8.7 Hz, 1H, Ar), 7.48 (s, 1H, CHAr), 7.51 (d, J=2.3 Hz, 1H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.6, 61.6, 66.7, 114.4, 121.8, 122.9, 124.9, 132.3, 134.7, 137.4, 139.1, 143.3, 159.6, 166.1, 166.2 ppm. IR (KBr) 2984, 1707, 1620, 1587, 1551, 1477, 1384, 1278, 1248, 1210, 1160, 1127 cm^{-1}. MS (ESI): 381, 383 $[M+H]^+$, 403, 405 $[M+Na]^+$. HRMS-ESI calcd for $C_{17}H_{17}BrO_5Na$ $[M+Na]^+$ 403.01516; found 403.01468.

*4.4.7. (3Z,4E)-Ethyl-7-chloro-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3g**).* Colorless solid; R_f (20% EtOAc/hexane) 0.46; mp 92–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.39 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.22 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.99 (d, J=8.7 Hz, 1H, Ar), 7.20–7.26 (m, 1H, Ar), 7.36 (d, J=2.3 Hz, 1H, Ar), 7.48 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 14.2, 60.5, 61.6, 66.6, 121.2, 122.8, 124.4, 127.1, 131.7, 132.3, 134.3, 139.1, 143.3, 159.1, 166.0, 166.1 ppm. IR (KBr) 2983, 2920, 1708, 1619, 1589, 1478, 1385, 1279, 1246, 1209, 1159, 1125 cm^{-1}. MS (ESI): 337 $[M+H]^+$, 359, 361

$[M+Na]^+$; HRMS-ESI calcd for $C_{17}H_{17}ClO_5Na$ $[M+Na]^+$ 359.0675; found 359.0678.

*4.4.8. (3Z,4E)-Ethyl-7,9-dichloro-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3h**).* Colorless solid; R_f (20% EtOAc/hexane) 0.40; mp 121–122 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.40 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.24 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.32 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 7.26 (d, J=2.6 Hz, 1H, Ar), 7.39 (d, J=2.2 Hz, 1H, Ar), 7.42 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.6, 61.7, 67.9, 123.4, 126.0, 126.1, 127.1, 131.6, 132.6, 133.5, 137.9, 143.1, 154.9, 165.7, 165.8 ppm. IR (KBr) 2985, 1709, 1627, 1589, 1467, 1384, 1334, 1276, 1225, 1156, 1059 cm^{-1}. MS (ESI): 388 $[M+NH_4]^+$. HRMS-ESI calcd for $C_{17}H_{16}Cl_2O_5Na$ $[M+Na]^+$ 393.02670; found 393.02694.

*4.4.9. (3Z,4E)-Ethyl 9-bromo-7-chloro-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3i**).* Colorless solid; R_f (20% EtOAc/hexane) 0.42; mp 129–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.40 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.24 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.32 (s, 2H, OCH_2), 6.53 (s, 1H, C=CH), 7.31 (d, J=2.3 Hz, 1H, Ar), 7.40 (s, 1H, CHAr), 7.55 (d, J=2.3 Hz, 1H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.3, 60.6, 61.7, 68.0, 115.1, 123. 3, 125.9, 127.6, 133.3, 133.5, 134.6, 137.9, 143.1, 155.8, 165.7, 165.8 ppm. IR (KBr) 2984, 2929, 1715, 1626, 1459, 1382, 1286, 1234, 1157, 1055 cm^{-1}. MS (ESI): 432, 434 $[M+NH_4]^+$.

*4.4.10. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-7-methoxy-2,3-dihydrobeno[b]oxepine-4-carboxylate (**3j**).* Yellow solid; R_f (20% EtOAc/hexane) 0.52; mp 65–66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.40 (t, J=6.9 Hz, 3H, OCH_2CH_3), 3.82 (s, 3H, OCH_3), 4.21 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.19 (s, 2H, OCH_2), 6.47 (s, 1H, C=CH), 6.80 (d, J=3.2 Hz, 1H, Ar), 6.84–6.88 (dd, J=2.7, 8.7 Hz, 1H, Ar), 6.96 (d, J=8.7 Hz, 2H, Ar), 7.49 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 55.6, 60.4, 61.4, 67.7, 118.1, 119.0, 120.6, 121.8, 123.8, 131.5, 140.4, 144.6, 154.5, 154.9, 166.1, 166.5 ppm. IR (KBr) 2982, 2920, 1706, 1620, 1560, 1493, 1457, 1390, 1346, 1251, 1215, 1160, 1036 cm^{-1}. MS (ESI): 333 $[M+H]^+$, 355 $[M+Na]^+$. HRMS-ESI calcd for $C_{18}H_{21}O_6$ $[M+H]^+$ 333.1333; found 333.1358.

*4.4.11. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-9-methyl-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3k**).* Pale yellow solid; R_f (20% EtOAc/hexane) 0.72; mp 71–72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=6.8 Hz, 3H, OCH_2CH_3), 1.39 (t, J=7.7 Hz, 3H, OCH_2CH_3), 2.35 (s, 3H, CH_3), 4.22 (q, J=7.7 Hz, 2H, OCH_2CH_3), 4.31 (q, J=6.8 Hz, 2H, OCH_2CH_3), 5.28 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.90 (t, J=7.7 Hz, 1H, Ar), 7.16 (d, J=6.8 Hz, 1H, Ar), 7.19 (d, J=7.7 Hz, 1H, Ar), 7.56 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.4, 16.5, 60.3, 61.3, 66.9, 121.4, 122.0, 123.4, 128.8, 130.6, 133.5, 133.6, 141.3, 144.7, 159.0, 166.0, 166.4 ppm. IR (KBr) 2926, 2856, 1707, 1619, 1464, 1377, 1332, 1264, 1201, 1149, 1096, 1050, 1008 cm^{-1}. MS (ESI): 317 $[M+H]^+$; HRMS-ESI calcd for $C_{18}H_{21}O_5$ $[M+H]^+$ 317.1311; found 317.1393.

*4.4.12. (3Z,4E)-Ethyl 9-allyl-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3l**).* Colorless solid; R_f (20% EtOAc/hexane) 0.68; mp 81–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=6.9 Hz, 3H, OCH_2CH_3), 1.39 (t, J=7.2 Hz, 3H, OCH_2CH_3), 3.44 (d, J=6.6 Hz, 2H, CH_2Ar), 4.22 (q, J=6.9 Hz, 2H, OCH_2CH_3), 4.32 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.00–5.08 (m, 2H, CH=CH_2), 5.26 (s, 2H, OCH_2), 5.86–6.02 (m, 1H, CH_2CH=CH_2), 6.52 (s, 1H, C=CH), 6.92–6.98 (m, 1H, Ar), 7.14–7.24 (m, 2H, Ar), 7.55 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.4, 34.4, 60.4, 61.3, 67.2, 115.9, 121.3, 122.3, 123.9, 130.9, 132.8, 133.8, 136.5, 141.0, 144.9, 158.8, 166.2, 166.5, 166.6 ppm. IR (KBr) 2980, 2927, 1710, 1612, 1455, 1380, 1280, 1201, 1152, 1055, 1010 cm^{-1}. MS (ESI): 343 $[M+H]^+$, 365 $[M+Na]^+$. HRMS-ESI calcd for $C_{20}H_{22}O_5$ Na $[M+Na]^+$ 365.13594; found 365.13513.

*4.4.13. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-8-(methoxymethoxy)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3m**).* Yellow solid; R_f (20% EtOAc/hexane) 0.62; mp 81–82 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 3.48 (s, 3H, OCH_3), 4.22 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.30 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.15 (s, 2H, OCH_2), 5.23 (s, 2H, OCH_2), 6.54 (s, 1H, C=CH), 6.62–6.74 (m, 2H, Ar), 7.26 (d, J=8.7 Hz, 1H, Ar), 7.58 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 56.2, 60.4, 61.3, 66.4, 94.1, 106.2, 110.9, 117.3, 121.5, 128.2, 137.2, 141.0, 143.9, 160.5, 162.1, 166.0, 166.5 ppm. IR (KBr) 2982, 1704, 1610, 1579, 1548, 1283, 1217, 1162, 1112, 1024 cm^{-1}. MS (ESI): 363 $[M+H]^+$, 385 $[M+Na]^+$. HRMS-ESI calcd for $C_{19}H_{22}O_7Na$ $[M+Na]^+$ 385.12577; found 385.12631.

*4.4.14. (3Z,4E)-Ethyl 8-(allyloxy)-3-(2-ethoxy-2-oxoethylidene)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3n**).* Yellow solid; R_f (20% EtOAc/hexane) 0.58; mp 114–115 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=6.9 Hz, 3H, OCH_2CH_3), 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.21 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.29 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.53 (d, J=5.1 Hz, 2H, OCH_2CH=CH_2), 5.23 (s, 2H, OCH_2), 5.26–5.46 (m, 2H, CH=CH_2), 5.92–6.08 (m, 1H, CH=CH_2), 6.54 (s, 1H, C=CH), 6.54–6.62 (m, 2H, Ar), 7.20–7.30 (m, 1H, Ar), 7.58 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.4, 61.2, 66.4, 68.9, 104.3, 110.5, 116.4, 118.2, 121.3, 127.7, 132.4, 137.2, 141.2, 143.9, 162.1, 162.3, 166.4, 166.5 ppm. IR (KBr) 2981, 1703, 1612, 1580, 1548, 1362, 1282, 1218, 1167, 1115, 1055 cm^{-1}. MS (ESI): 359 $[M+H]^+$, 381 $[M+Na]^+$; HRMS-ESI calcd for $C_{20}H_{23}O_6$ $[M+H]^+$ 359.1416; found 359.1499.

*4.4.15. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-8-(3-methylbut-2-enyloxy)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3o**).* Yellow solid; R_f (20% EtOAc/hexane) 0.58; mp 83–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.74 (s, 3H, CH_3), 1.80 (s, 3H, CH_3), 4.21 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.29 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.49 (d, J=6.6 Hz, 2H, OCH_2), 5.23 (s, 2H, OCH_2), 5.38–5.48 (m, 1H, OCH_2CH=C), 6.50–6.58 (m, 2H, Ar), 6.54 (s, 1H, C=CH), 7.24 (d, J=8.7 Hz, 1H, Ar), 7.59 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 14.4, 18.2, 25.7, 59.9, 60.7, 64.9, 66.2, 104.0, 110.4, 116.1, 119.4, 121.2, 127.4, 136.9, 137.8, 141.2, 143.9, 162.4, 162.5, 165.8, 166.0 ppm. IR (KBr) 2979, 2917, 1702, 1611, 1546, 1380, 1281, 1216, 1163, 1111, 1023 cm^{-1}. MS (ESI): 387 $[M+H]^+$, 409 $[M+Na]^+$. HRMS-ESI calcd for $C_{22}H_{26}O_6Na$ $[M+Na]^+$ 409.16216; found 409.16141.

*4.4.16. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-7-phenyl-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3p**).* Yellow solid; R_f (20% EtOAc/hexane) 0.62; mp 51–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.40 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.23 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.32 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.27 (s, 2H, OCH_2), 6.56 (s, 1H, C=CH), 7.11 (d, J=8.3 Hz, 1H, Ar), 7.24–7.34 (m, 1H, Ar), 7.38 (t, J=8.3 Hz, 1H, Ar), 7.48–7.58 (m, 4H, Ar), 7.66 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.5, 61.5, 66.6, 120.1, 122.3, 123.3, 126.7, 127.3, 128.8, 130.9, 131.3, 134.1, 135.5, 139.6, 140.9, 143.84, 160.0, 166.3, 166.4 ppm. IR (KBr) 2984, 1710, 1618, 1478, 1377, 1290, 1219, 1150, 1124, 1061, 1006 cm^{-1}. MS (ESI): 379 $[M+H]^+$, 401 $[M+Na]^+$. HRMS-ESI calcd for $C_{23}H_{22}O_5Na$ $[M+Na]^+$ 401.13594; found 401.13558.

*4.4.17. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-7-(pyrimidin-2-yl)-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**3q**).* Brown solid; R_f (20% EtOAc/hexane) 0.38; mp 141–142 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.41 (t, J=7.2 Hz, 3H, OCH_2CH_3), 4.24 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.34 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.29 (s, 2H, OCH_2), 6.58 (s, 1H, C=CH), 7.20 (d, J=8.3 Hz, 1H, Ar), 7.48–7.60 (m, 2H, Ar), 7.64 (s, 1H, CHAr), 8.90 (br s, 2H, Ar), 9.15 (s, 1H, Ar) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.7, 61.7,

66.6, 121.2, 123.0, 123.8, 128.4, 130.3, 132.3, 133.0, 134.0, 139.8, 143.2, 154.5, 157.4, 161.1, 166.1, 166.3 ppm. IR (KBr) 2924, 2854, 1711, 1615, 1459, 1376, 1262, 1212, 1150, 1052 cm^{-1}. MS (ESI): 381 $[M+H]^+$.

*4.4.18. (1E,3Z)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-3,4-dihydronaphtho[2,1-b]oxepine-2-carboxylate (**3r**).* Pale yellow solid; R_f (20% EtOAc/hexane) 0.46; mp 53–54 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.44 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.24 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.38 (q, J=6.9 Hz, 2H, OCH_2CH_3), 5.47 (s, 2H, OCH_2), 6.50 (s, 1H, C=CH), 7.22 (d, J=8.9 Hz, 1H, Ar), 7.41 (t, J=7.9 Hz, 1H, Ar), 7.57 (t, J=7.4 Hz, 1H, Ar), 7.76 (s, 1H, Ar), 7.78 (d, J=2.5 Hz, 1H, Ar), 8.13 (d, J=8.8 Hz, 1H, Ar), 8.42 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.4, 61.5, 70.9, 117.8, 119.7, 120.3, 122.7, 124.8, 127.7, 128.8, 130.2, 131.5, 133.2, 133.6, 135.1, 146.3, 161.4, 166.6, 167.2 ppm. IR (KBr) 2976, 2926, 1712, 1609, 1555, 1461, 1388, 1279, 1216, 1151, 1056, 1014 cm^{-1}. MS (ESI): 353 $[M+H]^+$, 375 $[M+Na]^+$; HRMS-ESI calcd for $C_{21}H_{20}O_5$ Na $[M+Na]^+$ 375.1203; found 375.1215.

*4.4.19. (3Z,4E)-Ethyl 3-(2-ethoxy-2-oxoethylidene)-2,3-dihydronaphtho[1,2-b]oxepine-4-carboxylate (**3s**).* Yellow liquid. R_f (20% EtOAc/hexane) 0.46; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=6.8 Hz, 3H, OCH_2CH_3), 1.44 (t, J=6.8 Hz, 3H, OCH_2CH_3), 4.21 (q, J=6.8 Hz, 2H, OCH_2CH_3), 4.38 (q, J=6.8 Hz, 2H, OCH_2CH_3), 5.47 (s, 2H, OCH_2), 6.50 (s, 1H, C=CH), 7.22 (d, J=9.0 Hz, 2H, Ar), 7.42 (t, J=7.6 Hz, 1H, Ar), 7.57 (t, J=7.6 Hz, 1H, Ar), 7.77 (d, J=9.0 Hz, 1H, Ar), 8.13 (d, J=8.3 Hz, 1H, Ar), 8.42 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 60.5, 61.4, 67.0, 117.2, 120.5, 121.9, 123.7, 126.2, 127.2, 128.3, 128.5, 130.6, 131.2, 133.1, 135.4, 141.4, 158.3, 166.6, 167.0 ppm. IR (KBr) 2974, 2922, 1718, 1603, 1548, 1452, 1372, 1260, 1222, 1156, 1043, 1014 cm^{-1}. MS (ESI): 353 $[M+H]^+$, 375 $[M+Na]^+$.

*4.4.20. (6E,8Z)-Ethyl 8-(2-ethoxy-2-oxoethylidene)-2,2-dimethyl-3,4,8,9-tetrahydro-2H-oxepino[3,2-g]chromene-7-carboxylate (**3t**).* Yellow liquid; R_f (20% EtOAc/hexane) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.34 (s, 6H, 2×CH_3), 1.38 (t, J=7.2 Hz, 3H, OCH_2CH_3), 1.80 (t, J=6.8 Hz, 2H, CH_2), 2.72 (t, J=6.8 Hz, 2H, CH_2Ar), 4.21 (q, J=7.2 Hz, 2H, OCH_2CH_3), 4.29 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.19 (s, 2H, OCH_2), 6.40 (s, 1H, Ar), 6.52 (s, 1H, C=CH), 7.05 (s, 1H, Ar), 7.55 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 14.3, 21.5, 26.9, 32.6, 60.3, 61.1, 66.4, 75.6, 107.0, 115.8, 116.4, 120.8, 127.1, 136.9, 141.5, 144.6, 158.1, 160.6, 166.6, 166.8 ppm. IR (KBr) 3451, 2923, 2852, 1709, 1616, 1552, 1495, 1458, 1207, 1126, 1058 cm^{-1}. MS (ESI): 387 $[M+H]^+$, 409 $[M+Na]^+$. HRMS-ESI calcd for $C_{22}H_{26}O_6Na$ $[M+Na]^+$ 409.16216; found 409.16175.

4.5. Typical procedure for the synthesis of (*E*)-ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylates (4a, 4f, 4g & 4j)

A mixture of ethyl 2-(chloromethyl)-2-hydroxy-2*H*-chromene-3-carboxylate **2a**, (268 mg, 1.0 mmol) and (1-ethoxycarbonylethylidene)triphenylphosphorane (506 mg, 1.4 mmol) in DCM (4 mL) were stirred at the room temperature for 6 h (TLC) under nitrogen atmosphere. After the completion of the reaction, the solvent was evaporated under reduced pressure, crude residue was purified by column chromatography (hexane/ethyl acetate 9:1) afford (*E*)-ethyl 3-oxo-2,3-dihydrobenzo[*b*]oxepine-4-carboxylate **4a** (190 mg, 82% yield) as yellow liquid.

*4.5.1. (E)-Ethyl 3-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**4a**).* Yellow liquid; R_f (20% EtOAc/hexane) 0.40; ^1H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, J=6.9 Hz, 3H, OCH_2CH_3), 4.34 (q, J=6.9 Hz, 2H, OCH_2CH_3), 4.58 (s, 2H, OCH_2), 7.12–7.24 (m, 2H, Ar), 7.38–7.52 (m, 2H, Ar), 7.89 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 61.2, 78.1, 120.4, 124.2, 125.7, 132.1, 133.4, 134.8, 145.3, 159.4, 165.3, 191.5 ppm. IR (KBr) 3451, 2981, 2925, 1728, 1675, 1605, 1565, 1482, 1447, 1394, 1284, 1250, 1189, 1115, 1041 cm^{-1}. MS (ESI): 233 $[M+H]^+$, 255 $[M+Na]^+$. HRMS-ESI calcd for $C_{13}H_{13}O_4$ $[M+H]^+$ 233.08084; found 233.08117.

*4.5.2. (E)-Ethyl 7-bromo-3-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**4f**).* Yield 226 mg (73%); colorless solid; R_f (20% EtOAc/hexane) 0.42; mp 68–69 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.0 Hz, 3H, OCH_2CH_3), 4.33 (q, J=7.0 Hz, 2H, OCH_2CH_3), 4.57 (s, 2H, OCH_2), 7.05 (d, J=8.7 Hz, 1H, Ar), 7.50 (dd, J=2.5, 8.7 Hz, 1H, Ar), 7.63 (d, J=2.0 Hz, 1H, Ar), 7.77 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 61.9, 78.5, 116.9, 122.5, 127.4, 131.7, 136.4, 136.8, 144.0, 158.4, 165.2, 192.1 ppm. IR (KBr) 2923, 2854, 2854, 1711, 1680, 1605, 1474, 1379, 1285, 1255, 1224, 1191, 1115, 1038 cm^{-1}. MS (ESI): 333, 335 $[M+Na]^+$. HRMS-ESI calcd for $C_{13}H_{11}BrO_4Na$ $[M+Na]^+$ 332.97329; found 332.97411.

*4.5.3. (E)-Ethyl 7-chloro-3-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**4g**).* Yield 234 mg (88%); colorless solid; R_f (20% EtOAc/hexane) 0.38; mp 54–55 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.37 (t, J=7.3 Hz, 3H, OCH_2CH_3), 4.32 (q, J=7.3 Hz, 2H, OCH_2CH_3), 4.56 (s, 2H, OCH_2), 7.09 (d, J=8.5 Hz, 1H, Ar), 7.35 (d, J=8.5 Hz, 1H, Ar), 7.47 (s, 1H, Ar), 7.76 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 61.8, 78.4, 122.1, 126.8, 129.6, 130.5, 133.3, 133.8, 143.7, 157.9, 165.0, 191.8 ppm. IR (KBr) 2922, 1714, 1681, 1607, 1477, 1384, 1274, 1193, 1105, 1033 cm^{-1}. MS (ESI): 267, 269 $[M+H]^+$, 289, 291 $[M+Na]^+$. HRMS-ESI calcd for $C_{13}H_{11}ClO_4Na$ $[M+Na]^+$ 289.02381; found 289.02356.

*4.5.4. (E)-Ethyl 7-methoxy-3-oxo-2,3-dihydrobenzo[b]oxepine-4-carboxylate (**4j**).* Yield 210 mg (80%); yellow liquid; R_f (20% EtOAc/hexane) 0.50; ^1H NMR (300 MHz, $CDCl_3$): δ 1.38 (t, J=7.0 Hz, 3H, OCH_2CH_3), 3.81 (s, 3H, OCH_3), 4.32 (q, J=7.0 Hz, 2H, OCH_2CH_3), 4.54 (s, 2H, OCH_2), 6.91–6.98 (m, 2H, Ar), 7.06 (d, J=8.8 Hz, 1H, Ar), 7.80 (s, 1H, CHAr) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3, 55.7, 61.6, 79.2, 117.6, 120.0, 121.6, 126.4, 128.1, 132.6, 145.2, 153.5, 155.9, 165.5 ppm. IR (KBr) 2924, 1729, 1675, 1607, 1571, 1496, 1464, 1389, 1244, 1209, 1164, 1039 cm^{-1}. MS (ESI): 263 $[M+H]^+$, 285 $[M+Na]^+$. HRMS-ESI calcd for $C_{14}H_{14}O_5Na$ $[M+Na]^+$ 285.07334; found 285.07257.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.05.047.

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