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One pot three-component regioselective and diastereoselective synthesis of halogenated pyrido[2,1-*b*][1,3]oxazines

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ABSTRACT

Three-component reactions of 3-substituted pyridines, dimethyl acetylenedicarboxylate (DMAD), and α-halo ketones led to regioselective and stereoselective synthesis of pyrido[2,1-*b*][1,3]oxazines in high to excellent yields under mild conditions. All the reactions gave the pyrido[2,1-*b*][1,3]oxazine derivatives without formation of any indolizine products.

1. Introduction

Fused [1,3]oxazines with a bridgehead nitrogen-atom exhibit remarkable biological and pharmacological properties, and have both natural and synthetic origins.[1–13] These properties include moxalactam as an antibiotic drug,[14–16] PA-824 as an antituberculosis drug,[17–20] the alkaloid of myrioneurinol with antitumor activity,[21] and hyperaspine, an alkaloid released from a kind of ladybird beetle to repel predators and competitors.[22] Due to importance of these compounds as useful and key intermediates, synthesis of the fused [1,3]oxazines has received much attention in organic synthesis.[23–30]

The reported procedures for the synthesis of fused [1,3]oxazines include: multi-step reactions,[31–38] the use of microwave irradiation,[39,40] specific catalysts,[41–45] and using oxidation reagents in the reaction media.[46,47] In 1932, Diels and Alder reported the formation of 1,4-dipolar intermediates by reacting pyridine with dimethyl acetylenedicarboxylate (DMAD).[48] In 1967, Huisgen et al. prepared these 1,4-dipolar intermediates from reaction of nitrogen-heterocycles such as pyridine and isoquinoline with DMAD and treated them with different dipolarophiles such as carbon dioxide, phenyl isocyanate, diethyl mesoxalate, and dimethyl azodicarboxylate.[49] Recently, the 1,4-dipolar intermediates derived by reacting various aromatic *N*-heterocycles such as pyridine, quinoline, isoquinoline, 1-alkyl imidazoles, thiazole, benzothiazole, and phenanthridine with activated acetylenes, were trapped by electron-deficient carbonyl groups such as activated aldehydes and 1,2-diketone derivatives,[50–54] quinones,[55,56]ethyl pyruvate,[57,58] *N*-alkyl isatin,[59] benzoyl cyanide,[60]1,3-dimethylalloxan,[61] and benzofuran-2,3-diones[62] to produce the corresponding fused [1,3] oxazine derivatives. However, in 2006 Yavari et al. reported these reactions with ethyl bromopyruvate[63] and hexachloroacetone[64] as electron-deficient ketones to afford the indolizine products instead of the corresponding oxazine derivatives. The indolizine products have also been reported for the reaction of pyridine and acetylene esters with phenacyl bromide under microwave conditions using basic alumina.[65] These results encouraged us to study the reactions of pyridine derivatives with various α-chloro or α-bromo ketones and DMAD in more details. Herein, we report three-component reactions of pyridines **1a**–**d** and DMAD with different α-halo ketones **2a**–**f** leading to stereoselective and regioselective halogenated pyrido[2,1-*b*][1,3]oxazines **3aa**–**df** in high yields without formation of any corresponding indolizines **4** (Scheme 1).

Similarly, the reactions of pyridine and DMAD with α-bromo ketones **5a**–**c** afforded the corresponding pyrido[2,1-*b*][1,3]oxazine derivatives **6a**–**c** in good yields (Scheme 2).

2. Results and discussion

Initially the reaction of pyridine and DMAD with chloroacetone was carried out at room temperature for 8 h. The reaction

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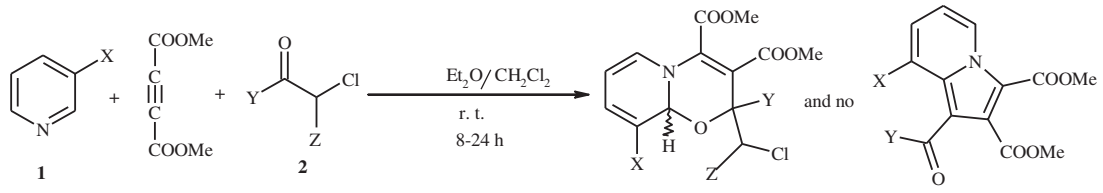
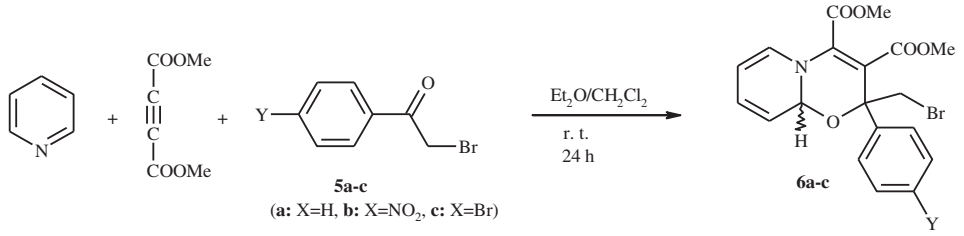


1	X
a	H
b	CH_3
c	Br
d	Cl

2	Y	Z
a	CH_3	H
b	CH_3	CH_3
c	CH_3	Cl
d	CH_2Cl	H
e	Ph	H
f	Ph	Cl

Scheme 1.



Scheme 2.

proceeded smoothly and afforded compound **3aa** in good yield with low stereoselectively (Table 1, entry 1). In order to examine the scope and limitations of these reactions, we extended our study to the other α-chloro and α-bromo ketones. Compared with **2a**, when the reaction was performed with 3-chlorobutan-2-one **2b**, which contains an electron-donating substituent (methyl group), the yield of the corresponding product **3ab** was decreased (Table 1, entry 2), while using 1,1-dichloroacetone **2c** or 1,3-dichloroacetone **2d**, having an electron–withdrawing substituent, the yields of the reaction products **3ac** and **3ad** were increased (Table 1, entries 3 and 4). The same trend was observed with 2-chloroacetophenone **2e** and 2,2-dichloroacetophenone **2f** (Table 1, entries 5 and 6). These results imply that the electrophilicity of the carbonyl group plays an important role in these reactions. However, using 3-substituted pyridines **1b–d** instead of pyridine **1a**, higher yields of the products with excellent stereoselectivity were observed (Table 1, entries **3ba–df**). On the other hand, these reactions with 3-substituted pyridines afforded the regioisomers **3** as sole product without formation of any other regioisomers **7** (Scheme 3). ^{1}H NMR spectra of all of the products **3ba–df** exhibited a singlet at 5.20–5.98 ppm for the methine proton of the NCHO group, confirming the observed regioselectivity in the formation of products **3**.

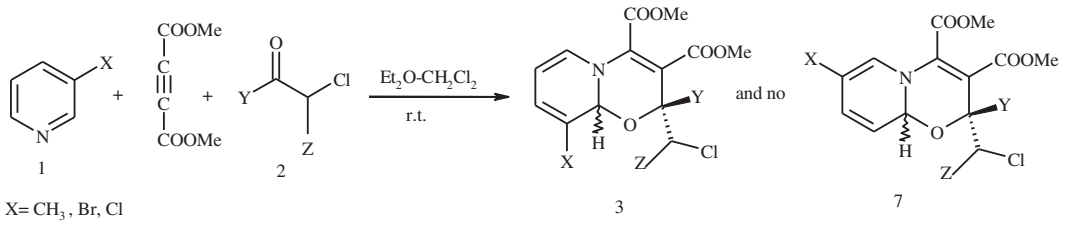
Table 1
Reactions of pyridine derivatives, DMAD, and α-chloro ketone derivatives

Entry	**1a–d**	**2a–f**	Product	Yield of **3** (%)[a]	Major diastereomer (%)/minor diastereomer (%)[b]
1	**1a**: (X=H)	**2a**	**3aa**	71	(61:39)
2		**2b**	**3ab**	50	(100:0)
3		**2c**	**3ac**	83	(67:33)
4		**2d**	**3ad**	82	(100:0)
5		**2e**	**3ae**	70	(90:10)
6		**2f**	**3af**	80	(64:36)
7	**1b**: (X=CH_3)	**2a**	**3ba**	74	(100:0)
8		**2b**	**3bb**	64	(100:0)
9		**2c**	**3bc**	87	(91: 9)
10		**2d**	**3bd**	85	(100:0)
11		**2e**	**3be**	72	(100:0)
12		**2f**	**3bf**	83	(100:0)
13	**1c**: (X=Br)	**2a**	**3ca**	87	(85:15)
14		**2b**	**3cb**	—	—
15		**2c**	**3cc**	93	(100:0)
16		**2d**	**3cd**	95	(100:0)
17		**2e**	**3ce**	80	(100:0)
18		**2f**	**3cf**	93	(100:0)
19	**1d**: (X=Cl)	**2a**	**3da**	85	(71:29)
20		**2b**	**3db**	—	—
21		**2c**	**3dc**	94	(100:0)
22		**2d**	**3dd**	95	(100:0)
23		**2e**	**3de**	—	—
24		**2f**	**3df**	91	(100:0)

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.

Under similar reaction conditions, we carried out the reactions of pyridine and DMAD with α-bromo ketone derivatives **5a–c** (Table 2). The results in the Table 2 show that the yields of the products decreased, which could be probably due to the lower electronegativity of the bromine atom, which makes the carbonyl group less electrophilic than that of the α-chloro ketones (cf. Table 1 vs Table 2). However, when 3-substituted pyridines **1b–d** were used in these reactions, in all cases a complex mixture was obtained, which could not be identified.

A proposed mechanism for the reactions is shown in Scheme 4. On the basis of the well-established chemistry of aromatic *N*-heterocycle nucleophiles,[48–65] it is reasonable to assume that the zwitterionic intermediate **8** results from an initial addition of the pyridines **1a–d** to DMAD. Then, intermediate **8** attacks the C=O group of the α-halo ketone, which leads to the dipolar species **9**. The negative oxygen atom of intermediate **9** can either attack at position 2 of the pyridinium ring (route a) to produce **3**, or at



Scheme 3.

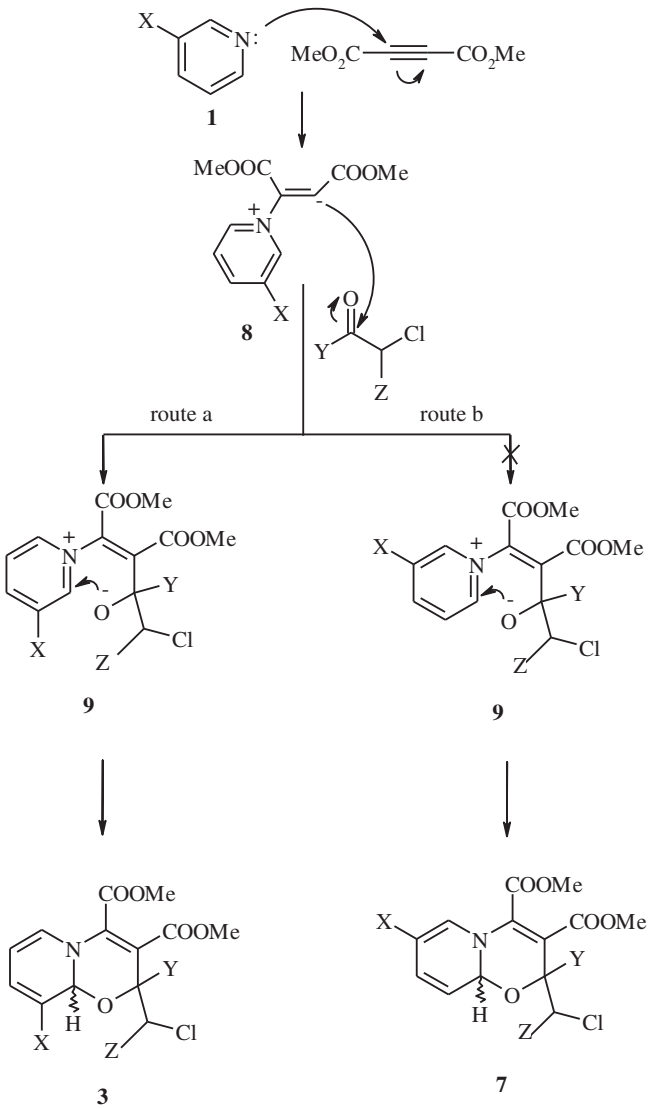
Table 2
Reactions of pyridine, dimethyl acetylenedicarboxylate, and α-bromo ketone derivatives

Entry	1	5a–d	Product	Yield of 6 (%)[a]	Major diastereomer (%)/minor diastereomer(%)[b]
1	1	5a, Y=H	6a	60	(100:0)
2		5b, Y=NO_2	6b	71	(74:26)
3		5c, Y=Br	6c	65	(87:13)

[a] Isolated yield.
[b] Determined by ^{1}H NMR spectroscopy.

position 6 of the pyridinium ring (route b) to form **7**. Since the ^{1}H NMR spectra of the products **3ba–df** exhibited a singlet for the methine proton of NCHO group, *route a* was confirmed for these reactions.

The structure of **3cd** was deuced from IR, ^{1}H, ^{13}C NMR, and mass spectroscopy, elemental analyses as well as X-ray diffraction analysis. The IR spectrum of **3cd** showed two strong signals at 1742 and 1702 cm^{-1} for the two carbonyl groups of the ester moieties. The ^{1}H NMR spectrum of **3cd** exhibited two singlets at 3.79 and 3.94 ppm for the two methoxy groups, two doublets at 3.94 and 4.16 ppm



Scheme 4.

($^2J_{HH}$=12.0 Hz) for CH_2Cl (AX system), an AB quartet system at 4.07 and 4.09 ppm ($^2J_{HH}$=11.2 Hz) for another CH_2Cl group, a singlet at 5.93 ppm for the methine proton of the NCHO group, a triplet at 5.26 ($^3J_{HH}$=7.2 Hz) and two doublets at 6.35 and 6.65 ppm ($^3J_{HH}$=7.2 Hz) for the 3CH groups of the pyridine moiety. The ^{13}C NMR spectrum of **3cd** exhibited 14 signals in agreement with the proposed structure. The mass spectrum of this compound displayed molecular ion peaks at 425 ($M^{+\bullet}$, 9), 427 ($M^{+\bullet}$+2, 15), 429 ($M^{+\bullet}$+4, 7), and 431 ($M^{+\bullet}$+6, 1), due to the existence of the isotopes of the chlorine atom (^{35}Cl and ^{37}Cl) and the bromine atom (^{79}Br and ^{81}Br).

Finally, the structure of **3cd** was confirmed by a single-crystal X-ray analysis (Fig. 1).

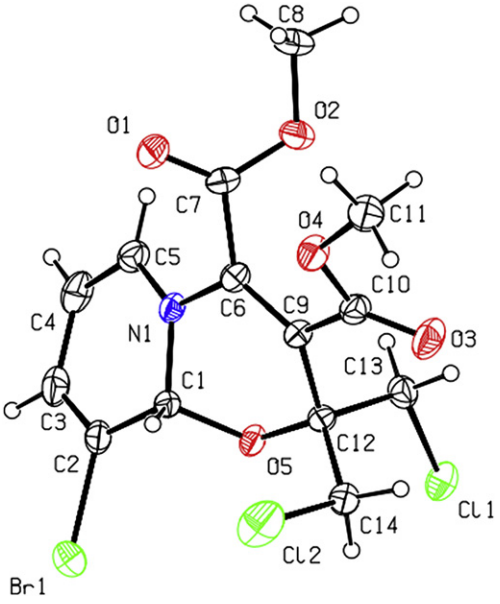


Fig. 1. ORTEP diagram of compound **3cd**.

However, compound **3cd** contains only one chiral center, but other products that were formed from asymmetric ketones (**2a**–**c** and **2e**–**f**), have two and three chiral centers, which could lead to a mixture of diastereomers. As shown in Fig. 2, compound **3cc**

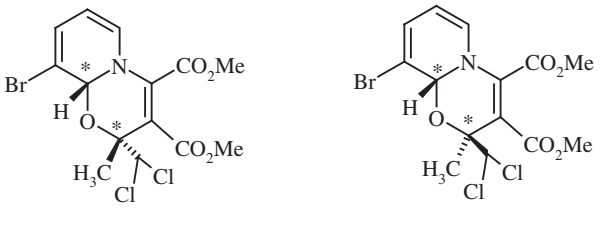


Fig. 2. Two diastereoisomers of **3cc**.

possesses two chiral centers and it can exist as two diastereoisomers, namely **3cc-I** (*RR*) or its enantiomer (*SS*), and **3cc-II** (*RS*) or its enantiomer (*SR*). The ^1H and ^{13}C NMR spectrum of **3cc** showed only one diastereoisomer. Thus, the reaction is diastereoselective. In order to determine the stereochemistry of the major products, the nuclear Overhauser effect (NOE) was measured for compound **3cc** as an example. The NOE measurement for **3cc** showed that, when the methine signal of NC*H*O was irradiated, the CH_3 protons were enhanced by 6%. Thus the methine proton and the CH_3 should be in the same side of the molecule as **3cc-I** or its enantiomer.

The ^1H and ^{13}C NMR spectra of **3aa**–**bf**, **3cd**–**df**, and **5a**–**d** were similar to those of **3cc** except to their substituents in pyridine and oxazine moieties, which showed characteristic resonances in the appropriate regions of the spectra.

3. Conclusions

In summary, we have developed a highly efficient procedure for the regioselective and diastereoselective synthesis of pyrido[2,1-*b*][1,3]oxazines involving various α-halo ketones and dimethyl acetylenedicarboxylate in the presence of pyridine and 3-substituted pyridines. Scope and limitations of the reaction are described. The simplicity of the present procedure also makes it an interesting alternative to other approaches.

4. Experimental

4.1. General

Dimethyl acetylenedicarboxylates (DMAD), pyridine, β-chloro pyridine, β-bromo pyridine, β-methyl pyridine, chloroacetone (=1-chloropropan-2-one), 1,1-dichloroacetone (=1,1-dichloropropan-2-one), 1,3-dichloroacetone (=1,3-dichloropropan-2-one), 3-chlorobutan-2-one, 2-chloroacetophenone (=2-chloro-1-phenylethanone), 2,2-dichloroacetophenone (=2,2-dichloro-1-phenylethanone), 2-bromoacetophenone (=2-bromo-1-phenylethanone), 2-bromo-4-nitroacetophenone (=2-bromo-1-(4-nitrophenyl) ethanone), 2-bromo-4-chloroacetophenone (=2-bromo-1-(4-chlorophenyl) ethanone), and 2,4-dibromoacetophenone (=2-bromo-1-(4-bromophenyl) ethanone) were purchased from Fluka and Merck and used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^1H, 100.6 MHz for ^{13}C) with $CDCl_3$ as solvent. Chemical shifts are given in parts per million (δ) relative to TMS, and coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on an FT-IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heraeus CHN-O Rapid analyzer.

4.2. General procedure

To a stirred solution of the dimethyl acetylenedicarboxylate (0.25 g, 2 mmol) and the α-halo ketone derivative (2 mmol) in CH_2Cl_2/Et_2O (1:4) (10 ml) was added the pyridine derivative (2 mmol) at room temperature. After completion of the reaction (8–24 h) as indicated by TLC (*n*-hexane/EtOAc, 9:1), the solvent was removed under reduced pressure. For mono chloro ketones and bromo phenacyl derivatives, the residue was purified by column chromatography on silica gel (Merck, 230–240 mesh) using a mixture of *n*-hexane/EtOAc as eluent to afford pure product. For dichloro ketones, when 5 mL methanol was added to the residue, the products precipitated as yellow powders.

*4.2.1. Dimethyl 2-(chloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3aa**).* Yellow powder, yield (0.45 g, 71%). Mp 103–105 °C. IR (KBr) (ν_{max}/cm^{-1}): 1738 and 1702 (2C=O), 1654 (C=C), 1243 (C_{sp^2}–O), 773 (C–Cl). NMR data for the major isomer (61%): ^1H NMR (400.13 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.98 and 4.06 (AB quartet, $^2J_{HH}$=10.8Hz, 2H, CH_2Cl), 5.25–5.29 (m, 1H, CH), 5.56 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=0.8 Hz, 1H, NCHO), 5.61–5.64 (m, 1H, CH), 6.25–6.30 (m, 2H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.3 (CH_3),

50.8 (CH_2Cl), 52.0 and 53.3 ($2OCH_3$), 77.0 (NCHO), 77.6 (C_q), 100.9 (CH), 113.0 (NC=*C*COOMe), 116.8 (CH), 125.3 (CH), 125.5 (CH), 144.7 (N*C*=CCOOMe), 163.8 and 165.0 (2C=O). NMR data for the minor isomer (39%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.66 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.87 and 4.19 (AB quartet, $^2J_{HH}$=11.6 Hz, 2H, CH_2Cl), 5.25–5.29 (m, 1H, CH), 5.66–5.69 (m, 1H, CH), 5.91 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 6.25–6.30 (m, 2H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.90 (CH_3), 50.6 (CH_2Cl), 50.8 and 53.3 ($2OCH_3$), 75.6 (C_q), 78.3 (N*C*HO), 101.0 (CH), 112.6 (NC=*C*COOMe), 116.1 (CH), 124.9 (CH), 125.1 (CH), 143.9 (N*C*=CCOOMe), 163.8 and 164.8 (2C=O). MS: *m*/*z* (%) 315 ($M^{+\bullet}$+2, 8), 313 ($M^{+\bullet}$, 23), 300 (10), 298 (30), 278 (8), 264 (100), 222 (11), 202 (3), 190 (18), 162 (8), 111 (23), 80 (48). Anal. Calcd for $C_{14}H_{16}ClNO_5$ (313.73): C, 53.60; H, 5.14; N, 4.46%. Found: C, 53.40; H, 5.12; N, 4.28%.

*4.2.2. Dimethyl 2-(1-chloroethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ab**).* Yellow powder, yield (0.33 g, 50%). Mp 116–117 °C. IR (KBr) (ν_{max}/cm^{-1}): 1743 and 1697 (2C=O), 1655 (C=C), 1240 (C_{sp^2}–O), 1080 (C_{sp^3}–O), 771 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.41 (d, $^3J_{HH}$=6.8 Hz, 3H, CH_3), 1.69 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.90 (q, $^3J_{HH}$=6.8 Hz, 1H, CHCl), 5.28 (dd, $^3J_{HH}$=6.8 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 5.54 (dd, $^3J_{HH}$=3.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, NCHO), 5.67–5.70 (m, 1H, CH), 6.25–6.30 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.9 (CH_3), 24.9 (CH_3), 52.1 and 53.2 ($2OCH_3$), 63.2 (CHCl), 77.6 (N*C*HO), 78.7 (C_q), 101.1 (CH), 115.1 (NC=*C*COOMe), 116.5 (CH), 125.1 (CH), 125.3 (CH), 143.9 (N*C*=CCOOMe), 163.6 and 165.2 (C=O). MS: *m*/*z* (%) 329 ($M^{+\bullet}$+2, 7), 327 ($M^{+\bullet}$, 21), 264 (100), 222 (33), 190 (18), 163 (12), 111 (25), 80 (59), 59 (13). Anal. Calcd for $C_{15}H_{18}ClNO_5$ (327.76): C, 54.97; H, 5.54; N, 4.27%. Found: C, 54.82; H, 5.35; N, 4.13%.

*4.2.3. Dimethyl 2-(dichloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ac**).* Yellow powder, yield (0.58 g, 83%). Mp 138–140 °C. IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1693 (2C=O), 1657 (C=C), 1243 (C_{sp^2}–O), 1074 (C_{sp^3}–O), 770 (C–Cl). NMR data for the major isomer (67%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.74 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.30–5.34 (m, 1H, CH), 5.60 (dd, $^3J_{HH}$=3.4 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 5.70 (ddt, $^3J_{HH}$=10.0 Hz, $^3J_{HH}$=3.4 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.26–6.34 (m, 2H, 2CH), 6.58 (s, 1H, $CHCl_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 26.3 (CH_3), 52.3 and 53.3 ($2OCH_3$), 77.2 ($CHCl_2$), 79.4 (C_q), 80.0 (NCHO), 101.5 (CH), 112.6 (NC=*C*COOMe), 116.1 (CH), 125.2 (CH), 125.5 (CH), 145.5 (N*C*=CCOOMe), 163.4 and 164.9 (C=O). NMR data for the minor isomer (33%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.71 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.30–5.34 (m, 2H, CH and NCHO), 5.78–5.82 (m, 1H, CH), 6.31–6.35 (m, 2H, 2CH), 6.50 (s, 1H, $CHCl_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.1 (CH_3), 52.2 and 53.3 (OCH_3), 77.8 ($CHCl_2$), 77.9 (NCHO), 79.8 (C_q), 101.4 (CH), 112.6 (NC=*C*COOMe), 116.5 (CH), 124.8 (CH), 124.9 (CH), 143.8 (N*C*=CCOOMe), 163.6 and 164.4 (C=O). MS: *m*/*z* (%) 351 ($M^{+\bullet}$+4, 2), 349 ($M^{+\bullet}$+2, 11), 347 ($M^{+\bullet}$, 17), 336 (1), 334 (5), 332 (9), 320 (1), 318 (6), 316 (9), 264 (100), 222 (12), 190 (18), 162 (8), 111 (26), 80 (57), 59 (10). Anal. Calcd for $C_{14}H_{15}Cl_2NO_5$ (348.18): C, 48.29; H, 4.34; N, 4.02%. Found: C, 48.42; H, 4.51; N, 3.95%.

*4.2.4. Dimethyl 2,2-bis(chloromethyl)-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ad**).* Yellow powder, yield (0.57 g, 82%). Mp 99–101 °C. IR (KBr) (ν_{max}/cm^{-1}): 1743 and 1704 (2C=O), 1654 (C=C), 1222 (C_{sp^2}–O), 769 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.77 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.95 and 4.16 (AB quartet, $^2J_{HH}$=12.0 Hz, 2H, CH_2Cl), 4.00 and 4.11 (AB quartet, $^2J_{HH}$=10.8 Hz, 2H, CH_2Cl), 5.33 (td, $^3J_{HH}$=6.8 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 5.72–5.75 (m, 1H, CH), 5.92 (dd, $^3J_{HH}$=3.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, NCHO), 6.27–6.32 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 48.7 (CH_2Cl), 48.8 (CH_2Cl), 52.3 and 53.3 ($2OCH_3$), 77.7 (C_q), 78.8 (NCHO), 101.8 (CH), 108.9 (NC=*C*COOMe), 116.3 (CH), 125.1 (CH), 125.2 (CH), 146.7 (N*C*=CCOOMe), 163.4 and 164.5 (C=O). MS: *m*/*z* (%) 351 ($M^{+\bullet}$+4, 2), 349 ($M^{+\bullet}$+2, 11), 347 ($M^{+\bullet}$, 17), 300 (34), 298 (100), 254 (1), 252 (3), 234 (6), 202 (5), 190 (17), 176 (7), 143 (7), 111 (23), 79 (30), 59 (12). Anal. Calcd for $C_{14}H_{15}Cl_2NO_5$ (348.18): C, 48.29; H, 4.34; N, 4.02%. Found: C, 47.92; H, 4.18; N, 3.90%.

*4.2.5. Dimethyl 2-(chloromethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ae**).* Yellow powder, yield (0.52 g, 70%). Mp 108–110 °C. IR (KBr) (ν_{max}/cm^{-1}): 1738 and 1709 (2C=O), 1649 (C=C), 1265 (C_{sp^2}–O), 1109 (C_{sp^3}–O), 770 (C–Cl). NMR data for the major isomer (90%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.35 and 4.50 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.21 (td, $^3J_{HH}$=6.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 5.38–5.44 (m, 1H, CH), 5.45 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 6.15–6.19 (m, 1H, CH), 6.26 (dt, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 7.31–7.39 (m, 5H, 5CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.5 (CH_2Cl), 52.1 and 53.3 ($2OCH_3$), 78.0 (NCHO), 80.7 (C_q), 101.1 (CH), 108.3 (NC=*C*COOMe), 116.1 (CH), 125.1 (CH), 125.3 (CH), 127.7 (2CH), 128.5 (CH), 128.6 (2CH), 142.0 (C_q), 146.2 (N*C*=CCOOMe), 164.0 and 165.4 (2C=O). NMR data for the minor isomer (10%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.52 and 4.63 (AB quartet, $^2J_{HH}$=12.0 Hz, 2H, CH_2Cl), 5.21 (td, $^3J_{HH}$=6.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 5.33–5.35 (m, 1H, CH), 5.45 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 6.29–6.30 (m, 1H, CH), 6.35–6.38 (m, 1H, CH), 7.31–7.39 (m, 5H, 5CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.3 (CH_2Cl), 51.9 and 53.2 ($2OCH_3$), 79.4 (N*C*HO), 80.7 (C_q), 101.6 (CH), 108.3 (NC=*C*COOMe), 116.7 (CH), 124.9 (CH), 125.0 (CH), 127.0 (2CH), 127.9 (CH), 128.1 (2CH), 140.9 (C_q), 144.9 (N*C*=CCOOMe), 163.7 and 165.4 (2C=O). MS: *m*/*z* (%) 377 ($M^{+\bullet}$+2, 4), 375 ($M^{+\bullet}$, 11), 340 (19), 326 (100), 309 (3), 300 (3), 298 (22), 280 (8), 262 (15), 247 (23), 190 (12), 162 (5), 111 (15), 105 (100), 77 (31), 59 (8). Anal. Calcd for $C_{19}H_{18}ClNO_5$ (375.80): C, 60.72; H, 4.83; N, 3.73%. Found: C, 60.52; H, 4.68; N, 3.62%.

*4.2.6. Dimethyl 2-(dichloromethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3af**).* Yellow powder, yield (0.65 g, 80%). Mp 103–105 °C. IR (KBr) (ν_{max}/cm^{-1}): 1740 and 1701 (2C=O), 1653 (C=C), 1271 (C_{sp^3}–O), 769 (C–Cl). NMR data for the major isomer (64%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.32 (td, $^3J_{HH}$=6.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 5.66 (dd, $^3J_{HH}$=3.4 Hz, $^4J_{HH}$=0.8 Hz, 1H, NCHO), 5.82 (ddt, $^3J_{HH}$=9.0 Hz, $^3J_{HH}$=3.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.30 (dt, $^3J_{HH}$=6.8 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 6.37–6.39 (m, 1H, CH), 6.99 (s, 1H, $CHCl_2$), 7.30–7.41 (m, 3H, 3CH), 7.52–7.55 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.5 and 53.3 ($2OCH_3$), 76.8 ($CHCl_2$), 79.3 (NCHO), 80.7 (C_q), 101.4 (CH), 114.5 (NC=*C*COOMe), 115.1 (CH), 125.8 (CH), 125.9 (CH), 126.6 (2CH), 128.2 (CH), 128.7 (2CH), 140.1 (C), 143.8 (N*C*=CCOOMe), 163.2 and 166.5 (2C=O). NMR data for the minor isomer (36%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.70 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 5.45 (td, $^3J_{HH}$=6.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.45 (dd, $^3J_{HH}$=3.8 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 5.94–5.98 (m, 1H, CH), 6.33–6.37 (m, 1H, CH), 6.37–6.39 (m, 1H, CH), 6.41 (s, 1H, $CHCl_2$), 7.30–7.41 (m, 3H, 3CH), 7.52–7.55 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.2 and 53.2 ($2OCH_3$), 77.3 ($CHCl_2$), 76.6 (NCHO), 82.6 (C_q), 102.2 (CH), 114.6 (NC=*C*COOMe), 116.7 (CH), 125.0 (CH), 125.9 (CH), 126.7 (2CH), 128.0 (CH), 128.6 (2CH), 141.2 (C), 143.9 (N*C*=CCOOMe), 163.3 and 164.1 (C=O). MS: *m*/*z* (%) 413 ($M^{+\bullet}$+4, 1), 411 ($M^{+\bullet}$+2, 6), 409 ($M^{+\bullet}$, 9), 376 (3), 374 (8), 326 (100), 298 (6), 264 (4), 221 (4), 190 (11), 162 (6), 129 (8), 111 (21), 105 (100), 77 (49), 63 (8), 51 (12). Anal. Calcd for $C_{19}H_{17}Cl_2NO_5$ (410.25): C, 55.63; H, 4.18; N, 3.41%. Found: C, 55.42; H, 4.06; N, 3.30%.

*4.2.7. Dimethyl 2-(chloromethyl)-2,9-dimethyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ba**).* Yellow powder, yield (0.49 g,

74%). Mp 76–78 °C. IR (KBr) (ν_{max}/cm^{-1}): 1738 and 1707 (2C=O), 1664 (C=C), 1230 (C_{sp^2}–O), 1040 (C_{sp^3}–O), 755 (C–Cl). NMR data for the major isomer (75%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.95 and 4.05 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.22 (dd, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=6.0 Hz, 1H, CH), 5.98–6.00 (m, 1H, CH), 5.34 (s, 1H, NCHO), 5.98–6.00 (m, 1H, CH), 6.16 (d, $^3J_{HH}$=7.6 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.9 (CH_3), 24.2 (CH_3), 50.8 (CH_2Cl), 51.0 (OCH_3), 53.2 (OCH_3), 80.7 (NCHO), 81.0 (C_q), 101.5 (CH), 112.1 (NC=*C*COOMe), 121.1 (CH), 123.0 (CH), 125.1 (C), 145.1 (N*C*=CCOOMe), 164.1 and 165.1 (2C=O). NMR data for the minor isomer (25%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.78 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.95 and 4.05 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.23 (t, $^3J_{HH}$=6.4 Hz, 1H, CH), 5.34 (s, 1H, NCHO), 5.98–6.00 (m, 1H, CH), 6.14 (d, $^3J_{HH}$=7.2 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.0 (CH_3), 24.5 (CH_3), 50.2 (CH_2Cl), 50.6 (OCH_3), 50.8 (OCH_3), 75.7 (NCHO), 77.6 (C_q), 101.6 (CH), 111.8 (NC=*C*COOMe), 120.6 (CH), 122.6 (CH), 125.9 (C), 143.5 (N*C*=CCOOMe), 164.0 and 165.0 (2C=O). MS: *m*/*z* (%) 329 ($M^{+\bullet}$+2, 6), 327 ($M^{+\bullet}$, 18), 314 (9), 312 (26), 292 (7), 278 (100), 236 (10), 204 (15), 176 (7), 147 (7), 111 (14), 94 (40), 77 (4). Anal. Calcd for $C_{15}H_{18}ClNO_5$ (327.76): C, 54.97; H, 5.54; N, 4.27%. Found: C, 54.68; H, 5.30; N, 4.10%.

*4.2.8. Dimethyl 2-(1-chloroethyl)-2,9-dimethyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3bb**).* Yellow powder, yield (0.44 g, 64%). Mp 117–119 °C. IR (KBr) (ν_{max}/cm^{-1}): 1739 and 1702 (2C=O), 1667 (C=C), 1239 (C_{sp^2}–O), 1076 (C_{sp^3}–O), 798 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.40 (d, $^3J_{HH}$=6.8 Hz, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.92 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.52 (q, $^3J_{HH}$=6.8 Hz, 1H, CHCl), 5.22 (dd, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=6.4 Hz, 1H, CH), 5.36 (s, 1H, NCHO), 5.99 (dd, $^3J_{HH}$=6.0 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 6.14 (d, $^3J_{HH}$=7.6 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.8 (CH_3), 18.9 (CH_3), 24.7 (CH_3), 52.0 and 53.2 ($2OCH_3$), 63.3 (CHCl), 78.7 (NCHO), 80.6 (C_q), 101.7 (CH), 113.8 (NC=*C*COOMe), 120.7 (CH), 122.7 (CH), 125.8 (C), 144.3 (N*C*=CCOOMe), 163.9 and 165.3 (C=O). MS: *m*/*z* (%) 343 ($M^{+\bullet}$+2, 9), 341 ($M^{+\bullet}$, 27), 328 (4), 326 (11), 278 (100), 262 (3), 236 (16), 204 (18), 176 (10), 111 (20), 94 (54), 77 (4). Anal. Calcd for $C_{16}H_{20}ClNO_5$ (341.79): C, 56.23; H, 5.90; N, 4.10%. Found: C, 55.96; H, 5.65; N, 3.95%.

*4.2.9. Dimethyl 2-(dichloromethyl)-2,9-dimethyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3bc**).* Yellow powder, yield (0.63 g, 87%). Mp 136–138 °C. IR (KBr) (ν_{max}/cm^{-1}): 1735 and 1698 (2C=O), 1667 (C=C), 1244 (C_{sp^2}–O), 1072 (C_{sp^3}–O), 781 (C–Cl). NMR data for the major isomer (91%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 1.95 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.27 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.4 Hz, 1H, CH), 5.42 (s, 1H, NCHO), 6.03 (dd, $^3J_{HH}$=6.2 Hz, $^4J_{HH}$=1.6 Hz, 1H, CH), 6.17 (d, $^3J_{HH}$=7.6 Hz, 1H, CH), 6.59 (s, 1H, $CHCl_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.9 and 24.0 ($2CH_3$), 52.1 and 53.3 ($2OCH_3$), 77.3 ($CHCl_2$), 79.9 (C_q), 80.9 (CHNO), 102.2 (CH), 111.5 (NC=*C*COOMe), 121.2 (CH), 122.7 (CH), 125.2 (C), 145.8 (N*C*=CCOOMe), 163.7 and 165.0 (2C=O). NMR data for the minor isomer (9%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.70 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.27 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.4 Hz, 1H, CH), 5.42 (s, 1H, NCHO), 6.03 (dd, $^3J_{HH}$=6.2 Hz, $^4J_{HH}$=1.6 Hz, 1H, CH), 6.17 (d, $^3J_{HH}$=7.6 Hz, 1H, CH), 6.52 (s, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 17.7 and 26.4 ($2CH_3$), 52.1 and 53.3 ($2OCH_3$), 77.6 ($CHCl_2$), 79.9 (C_q), 78.6 (CHNO), 102.2 (CH), 116.8 (NC=*C*COOMe), 120.7 (CH), 122.7 (CH), 128.8 (C_q), 145.8 (N*C*=CCOOMe), 163.7 and 165.0 (2C=O). MS: *m*/*z* (%) 365 ($M^{+\bullet}$+4, 2), 363 ($M^{+\bullet}$+2, 13), 361 ($M^{+\bullet}$, 18), 350 (2), 348 (12), 346 (18), 334 (1), 332 (6), 330 (9), 278 (100), 248 (7), 236 (16), 204 (24), 176 (13), 147 (7), 111 (21), 94 (51), 83 (7), 65 (11). Anal. Calcd for $C_{15}H_{17}Cl_2NO_5$ (362.21): C, 49.74; H, 4.73; N, 3.87%. Found: C, 49.63; H, 4.58; N, 3.72%.

*4.2.10. Dimethyl 2,2-bis(chloromethyl)-9-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3bd**).* Yellow powder, yield (0.62 g, 85%). Mp 128–130 °C. IR (KBr) (ν_{max}/cm^{-1}): 1744 and 1705 (2C=O), 1665 (C=C), 1267 (C_{sp^2}–O), 1053 (C_{sp^3}–O), 758 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ1.99 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.01 (d, $^2J_{HH}$=12.0 Hz, 1H, CHCl), 4.06 and 4.12 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 4.17 (d, $^2J_{HH}$=12.4 Hz, 1H, CHCl), 5.29 (dd, $^3J_{HH}$=7.6 Hz, $^3J_{HH}$=6.4 Hz, 1H, CH), 5.98 (s, 1H, NCHO), 6.01–6.03 (m, 1H, CH), 6.18 (d, $^3J_{HH}$=7.6 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.0 (CH_3), 48.3 and 48.5 ($2CH_2Cl$), 52.2 and 53.3 ($2OCH_3$),77.8 (C_q), 81.5 (NCHO), 102.4 (CH), 107.9 (NC=*C*COOMe), 120.9 (CH), 122.5 (CH), 125.8 (C), 147.0 (N*C*=CCOOMe), 163.6 and 164.7 (C=O). MS: *m*/*z* (%) 365 ($M^{+\bullet}$+4, 1), 363 ($M^{+\bullet}$+2, 6), 361 ($M^{+\bullet}$, 9), 314 (62), 312 (100), 274 (5), 254 (8), 204 (15), 176 (8), 119 (17), 111 (20), 93 (50), 78 (24), 65 (18). Anal. Calcd for $C_{15}H_{17}Cl_2NO_5$ (362.21): C, 49.74; H, 4.73; N, 3.87%. Found: C, 49.62; H, 4.58; N, 3.75%.

*4.2.11. Dimethyl 2-(chloromethyl)-9-methyl-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3be**).* Yellow powder, yield (0.56 g, 72%). Mp 110–112 °C IR (KBr) (ν_{max}/cm^{-1}): 1737 and 1709 (2C=O), 1667 (C=C), 1243 (C_{sp^2}–O), 1051 (C_{sp^3}–O), 774 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.62 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.35 and 4.51 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.16 (dd, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=6.0 Hz, 1H, CH), 5.20 (br s, 1H, NCHO), 5.87–5.89 (m, 1H, CH), 6.16 (d, $^3J_{HH}$=7.6 Hz, 1H, CH), 7.31–7.41 (m, 5H, aromatic). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 18.7 (CH_3), 49.6 (CH_2Cl), 52.0 and 53.3 ($2OCH_3$), 80.8 (NCHO), 81.1 (C_q), 101.7 (CH), 107.1 (NC=*C*COOMe), 120.9 (CH), 122.9 (CH), 125.0 (C), 128.0 (2CH), 128.4 (2CH), 128.5 (CH), 142.1 (C), 146.7 (N*C*=CCOOMe), 164.3 and 165.6 (C=O). MS: *m*/*z* (%) 391 ($M^{+\bullet}$+2, 5), 389 ($M^{+\bullet}$, 15), 355 (25), 340 (100), 294 (9), 278 (11), 262 (13), 247 (20), 204 (15), 176 (8), 129 (7), 111 (25), 105 (100), 77 (34), 59 (8). Anal. Calcd for $C_{20}H_{20}ClNO_5$ (389.82): C, 61.62; H, 5.17; N, 3.59%. Found: C, 61.30; H, 4.85; N, 3.28%.

*4.2.12. Dimethyl 2-(dichloromethyl)-9-methyl-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (3**bf**).* Yellow powder, yield (0.70 g, 83%). Mp 112–113 °C. IR (KBr) (ν_{max}/cm^{-1}): 1731 and 1717 (2C=O), 1663 (C=C), 1265 (C_{sp^2}–O), 1054 (C_{sp^3}–O) 760 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 2.05 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.24 (dd, $^3J_{HH}$=7.4 Hz, $^3J_{HH}$=6.4 Hz, 1H, CH), 5.51 (s, 1H, NCHO), 6.0 (m, 1H, CH), 6.16 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.93 (s, 1H, $CHCl_2$), 7.34–7.44 (m, 3H, 3CH), 7.61–7.64 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.9 (CH_3), 52.4 and 53.3 ($2OCH_3$), 81.9 ($CHCl_2$), 82.6 (C_q), 83.5 (CHNO), 102.0 (CH), 111.8 (NC=*C*COOMe), 121.8 (CH), 123.4 (CH), 124.7 (C), 127.9 (2CH), 128.1 (C), 128.3 (2CH), 128.7 (CH), 144.6 (NC=CCOOMe), 163.6 and 166.4 (2C=O). MS: *m*/*z* (%) 427 ($M^{+\bullet}$+4, 1), 425 ($M^{+\bullet}$+2, 6), 423 ($M^{+\bullet}$, 9), 390 (2), 388 (6), 340 (71), 318 (50), 278 (11), 260 (12), 233 (8), 204 (12), 176 (6), 143 (10), 111 (13), 105 (100), 77 (50), 59 (17). Anal. Calcd for $C_{20}H_{19}Cl_2NO_5$ (424.27): C, 56.62; H, 4.51; N, 3.30%. Found: C, 56.55; H, 4.34; N, 3.18%.

*4.2.13. Dimethyl 9-bromo-2-(chloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ca**).* Yellow powder, yield (0.68 g, 87%). Mp 107–109 °C. IR (KBr) (ν_{max}/cm^{-1}): 1738 and 1706 (2C=O), 1651 (C=C), 1241 (C_{sp^2}–O), 1078 (C_{sp^3}–O), 755 (C–Cl), 531 (C–Br). NMR data for the major isomer (85%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.61 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.95 and 4.14 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.20 (t, $^3J_{HH}$=7.0 Hz, 1H, CH), 5.50 (s, 1H, NCHO), 6.35 (d, $^3J_{HH}$=7.6 Hz, 1H, CH), 6.63 (d, $^3J_{HH}$=6.8 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$):

δ 23.7 (CH_3), 50.3 (CH_2Cl), 52.2 and 53.3 ($2OCH_3$), 77.9 (NCHO), 81.2 (C_q),100.3 (CH), 109.7 (C), 116.2 (NC=CCOOMe), 125.1 (CH), 128.0 (CH), 143.5 (NC=CCOOMe), 163.3 and 164.8 (2C=O). NMR data for the minor isomer (15%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.59 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 3.95 and 4.14 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.25 (t, $^3J_{HH}$=7.0 Hz, 1H, CH), 5.55 (s, 1H, NCHO), 6.35 (d, $^3J_{HH}$=7.6 Hz, 1H, CH), 6.62 (d, $^3J_{HH}$=7.2 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.7 (CH_3), 50.3 (CH_2Cl), 52.2 (OCH_3), 53.3 (OCH_3), 77.9 (NCHO), 81.5 (C_q), 101.0 (CH), 108.0 (C), 116.5 (NC=CCOOMe), 124.8 (CH), 128.2 (CH), 143.5 (NC=CCOOMe), 163.3 and 164.8 (2C=O). MS: *m*/*z* (%) 395 ($M^{+\bullet}$+4, 4), 393 ($M^{+\bullet}$+2, 15), 391 ($M^{+\bullet}$, 11), 344 (100), 342 (100), 300 (9), 298 (9), 270 (6), 268 (6), 211 (3), 209 (3), 158 (20), 111 (23), 78 (16), 59 (10). Anal. Calcd for $C_{14}H_{14}ClBrNO_5$ (392.62): C, 42.83; H, 3.85; N, 3.57%. Found: C, 42.65; H, 3.77; N, 3.48%.

*4.2.14. Dimethyl 9-bromo-2-(dichloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3cc**).* Yellow powder, yield (0.80 g, 93%). Mp 167–169 °C. IR (KBr) (ν_{max}/cm^{-1}): 1732 and 1704 (2C=O), 1652 (C=C), 1266 (C_{sp^2}–O), 1054 (C_{sp^3}–O), 770 (C–Cl); ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.76 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.25 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.55 (s, 1H, NCHO), 6.34 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.57 (s, 1H, $CHCl_2$), 6.65 (d, $^3J_{HH}$=6.8 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.4 (CH_3), 52.4 and 53.4 ($2OCH_3$), 76.8 ($CHCl_2$), 80.6 (C_q), 81.5 (NCHO), 101.0 (CH), 109.8 (NC=CCOOMe), 115.5 (C_q), 124.8 (CH), 128.2 (CH), 144.2 (NC=CCOOMe), 163.0 and 164.7 (C=O). MS: *m*/*z* (%) 431 ($M^{+\bullet}$+6, 1), 429 ($M^{+\bullet}$+4, 7), 427 ($M^{+\bullet}$+2, 14), 425 ($M^{+\bullet}$, 8), 400 (2), 398 (14), 396 (30), 394 (18), 344 (100), 342 (100), 302 (6), 300 (6), 270 (9), 268 (9), 242 (4), 240 (4), 158 (28), 131 (7), 111 (45), 78 (19), 51 (17). Anal. Calcd for $C_{14}H_{14}Cl_2BrNO_5$ (427.07): C, 39.37; H, 3.30; N, 3.28%. Found: C, 39.10; H, 3.21; N, 3.18%.

*4.2.15. Dimethyl 9-bromo-2,2-bis(chloromethyl)-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3cd**).* Yellow powder, yield (0.81 g, 95%). Mp 172–174 °C. IR (KBr) (ν_{max}/cm^{-1}): 1742 and 1702 (2C=O), 1650 (C=C), 1264 (C_{sp^2}–O), 1059 (C_{sp^3}–O), 767 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.94 (d, $^2J_{HH}$=12.0 Hz, 1H, CHCl), 4.07 and 4.09 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 4.16 (d, $^2J_{HH}$=12.0 Hz, 1H, CHCl), 5.26 (t, $^3J_{HH}$=7.2 Hz, 1H, CH), 5.93 (s, 1H, NCHO), 6.35 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.65 (d, $^3J_{HH}$=6.8 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ48.2 and 48.4 (CH_2Cl), 52.4 and 53.5 ($2OCH_3$), 78.7 (C_q), 82.1 (NCHO), 101.2 (CH), 109.9 (NC=CCOOMe), 117.3 (C), 124.7 (CH), 127.9 (CH), 145.7 (NC=CCOOMe), 163.0 and 164.4 (C=O). MS: *m*/*z* (%) 431 ($M^{+\bullet}$+6, 1), 429 ($M^{+\bullet}$+4, 7), 427 ($M^{+\bullet}$+2, 15), 425 ($M^{+\bullet}$, 9), 380 (28), 378 (100), 376 (76), 334 (1), 332 (4), 330 (3), 312 (1), 310 (3), 270 (7), 268 (7), 241 (5), 239 (5), 211 (7), 209 (7), 159 (18), 131 (5), 111 (33), 78 (16), 59 (22). Anal. Calcd for $C_{14}H_{14}Cl_2BrNO_5$ (427.07): C, 39.37; H, 3.30; N, 3.28%. Found: C, 39.12; H, 3.15; N, 3.10%. Crystal data for **3cd** $C_{14}H_{14}Cl_2BrNO_5$ (CCDC 878070): M_w=427.06, orthorhombic, space group $P2_12_12_1$, unit cell dimensions a=7.3176(5) Å, b=13.9308(9) Å, c=16.3749(15) Å, $\alpha=\beta=\gamma$=90.00°; V=1669.3(2) Å^3, Z=4, D_{calcd}=1.699 g cm^{-3}; F(000)=856, crystal dimension 0.35×0.25×0.15 mm, radiation, Mo Kα (λ=0.71073 Å), 2.92≤2θ≤29.28, intensity data were collected at 298(2) K with a STOE IPDS-II diffractometer, and employing $\omega/2\theta$ scanning technique, in the range of −10≤h≤8; −19≤k≤16; −22≤l≤18; the structure was solved by a rotation method, all non-hydrogen atoms were positioned and anisotropic thermal parameters refined from 2487 observed reflections with R(into)=0.0609 by a full-matrix least-squares technique converted to R=0.1256 and Raw=0.1122 [I>2σ(I)].

*4.2.16. Dimethyl 9-bromo-2-(chloromethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3ce**).* Yellow powder, yield (0.73 g, 80%). Mp 113–115 °C. IR (KBr) (ν_{max}/cm^{-1}): 1740 and 1705 (2C=O), 1651 (C=C), 1261 (C_{sp^2}–O), 1062 (C_{sp^3}–O), 780 (C–Cl), 556 (C–Br). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.77 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.35 and 4.51 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.13 (dd, $^3J_{HH}$=7.8 Hz, $^4J_{HH}$=6.8 Hz, 1H, CH), 5.38 (d, $^4J_{HH}$=0.8 Hz, 1H, NCHO), 6.32 (dd, $^3J_{HH}$=7.4 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 6.53 (d, $^3J_{HH}$=6.4 Hz, 1H, CH), 7.35–7.43 (m, 5H, 5CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.4 (CH_2Cl), 52.3 and 53.4 ($2OCH_3$), 81.0 (NCHO), 81.7 (C_q), 100.4 (CH), 110.0 (NC=CCOOMe), 110.8 (C), 125.0 (CH), 128.0 (CH), 128.1 (2CH), 128.4 (2CH), 128.8 (CH), 140.8 (C), 145.4 (NC=CCOOMe), 163.7 and 165.3 (C=O). MS: *m*/*z* (%) 457 ($M^{+\bullet}$+4, 1), 455 ($M^{+\bullet}$+2, 6), 453 ($M^{+\bullet}$, 4), 406 (33), 404 (33), 362 (6), 360 (26), 358 (19), 247 (24), 213 (13), 185 (9), 159 (16), 129 (9), 111 (16), 105 (100), 77 (24), 59 (11). Anal. Calcd for $C_{19}H_{17}ClBrNO_5$ (454.69): C, 50.19; H, 3.77; N, 3.08%. Found: C, 49.85; H, 3.60; N, 2.92%.

*4.2.17. Dimethyl 9-bromo-2-(dichloromethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3cf**).* Yellow powder, yield (0.91 g, 93%). Mp 154–156 °C. IR (KBr) (ν_{max}/cm^{-1}): 1734 and 1712 (2C=O), 1643 (C=C), 1262 (C_{sp^2}–O), 1059 (C_{sp^3}–O), 740 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 3.81 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.26 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.70 (s, 1H, NCHO), 6.36 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.70 (d, $^3J_{HH}$=6.8 Hz, 1H, CH), 6.92 (s, 1H, $CHCl_2$), 7.36–7.42 (m, 3H, 3CH), 7.74–7.76 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.8 and 53.5 ($2OCH_3$), 76.7 ($CHCl_2$), 82.3 (NCHO), 83.1 (C_q), 100.8 (CH), 108.7 (C_q), 117.9 (NC=CCOOMe), 125.9 (CH), 127.3 (2CH), 128.5 (2CH), 128.9 (CH), 129.1 (CH), 138.9 (C_q), 142.1 (NC=CCOOMe), 162.7 and 166.3 (C=O). MS: *m*/*z* (%) 503 ($M^{+\bullet}$+6, 1), 501 ($M^{+\bullet}$+4, 7), 489 ($M^{+\bullet}$+2, 15), 487 ($M^{+\bullet}$, 9), 456 (1), 454 (5), 452 (9), 406 (65), 404 (65), 340 (25), 312 (27), 183 (8), 181 (8), 159 (24), 157 (24), 129 (13), 111 (25), 105 (100), 77 (54), 51 (37). Anal. Calcd for $C_{19}H_{16}Cl_2BrNO_5$ (489.14): C, 46.65; H, 3.30; N, 2.86%. Found: C, 46.48; H, 3.15; N, 2.78%.

*4.2.18. Dimethyl 9-chloro-2-(chloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3da**).* Yellow powder, yield (0.60 g, 85%). Mp 111–113 °C. IR (KBr) (ν_{max}/cm^{-1}): 1742 and 1711 (2C=O), 1655 (C=C), 1242 (C_{sp^2}–O), 1061 (C_{sp^3}–O), 772 (C–Cl). NMR data for the major isomer (71%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.61 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 and 4.14 (AB quartet, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 5.26 (t, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.43 (s, 1H, NCHO), 6.29 (d, $^3J_{HH}$=6.8 Hz, 1H, CH), 6.42 (d, $^3J_{HH}$=6.8 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.9 (CH_3), 50.2 (CH_2Cl), 52.2 and 53.4 ($2OCH_3$), 77.5 (NCHO), 80.2 (C_q), 99.8 (CH), 116.0 (NC=CCOOMe), 120.4 (C), 124.1 (CH), 124.7 (CH), 143.5 (NC=CCOOMe), 163.4 and 164.9 (C=O). NMR data for the minor isomer (29%): ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.76 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.94 and 4.14 (AB quartet, $^2J_{HH}$=11.2Hz, 2H, CH_2Cl), 5.31 (t, $^3J_{HH}$=6.8Hz, 1H, CH), 5.48 (s, 1H, NCHO), 6.27 (d, $^3J_{HH}$=6.8Hz, 1H, CH), 6.45 (d, $^3J_{HH}$=6.8Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.5 (CH_3), 51.2 (CH_2Cl), 52.4 and 53.5 ($2OCH_3$), 77.8 (NCHO), 80.5 (C_q), 100.5 (CH), 115.3 (NC=CCOOMe), 121.3 (C), 124.2 (CH), 124.3 (CH), 143.5 (NC=CCOOMe), 163.4 and 164.9 (C=O). MS: *m*/*z* (%) 350 ($M^{+\bullet}$+4, 1), 349 ($M^{+\bullet}$+2, 7), 347 ($M^{+\bullet}$, 9), 336 (2), 334 (12), 332 (18), 314 (2), 312 (6.6), 300 (35), 298 (100), 258 (2), 256 (6), 226 (3), 224 (10), 214 (1), 212 (3), 111 (22), 78 (8), 59 (8). Anal. Calcd for $C_{14}H_{15}Cl_2NO_5$ (348.17): C, 48.29; H, 4.34; N, 4.02%. Found: C, 48.65; H, 3.67; N, 3.42%.

*4.2.19. Dimethyl 9-chloro-2-(dichloromethyl)-2-methyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3dc**).* Yellow powder, yield (0.72 g, 94%). Mp 163–165 °C. IR (KBr) (ν_{max}/cm^{-1}): 1733 and 1705 (2C=O), 1655 (C=C), 1267 (C_{sp^2}–O), 1060 (C_{sp^3}–O), 771 (C–Cl). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.76 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.30 (dd, $^3J_{HH}$=7.6 Hz, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.48 (s, 1H, NCHO), 6.29 (dd, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=0.4 Hz, 1H, CH), 6.45 (d,

$^3J_{HH}$=6.4 Hz, 1H, CH), 6.58 (s, 1H, $CHCl_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.5 (CH_3), 52.8 and 53.4 ($2OCH_3$), 76.8 ($CHCl_2$), 80.4 (C_q), 80.5 (NCHO), 100.5 (CH), 115.5 (NC=*C*COOMe), 120.5 (C), 124.2 (CH), 124.3 (CH), 144.3 (N*C*=CCOOMe), 163.0 and 164.7 (C=O). MS: *m*/*z* (%) 385 ($M^{+\bullet}$+4, 1.5), 383 ($M^{+\bullet}$+2, 5), 381 ($M^{+\bullet}$, 5), 300 (33), 298 (100), 258 (2), 256 (5), 226 (7), 224 (6), 167 (4),111 (19), 78 (7), 59 (7). Anal. Calcd for $C_{14}H_{14}Cl_3NO_5$ (382.62): C, 43.95; H, 3.69; N, 3.66%. Found: C, 43.68; H, 3.52; N, 3.48%.

*4.2.20. Dimethyl 9-chloro-2,2-bis(chloromethyl)-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3dd**).* Yellow powder, yield (0.72 g, 95%). Mp 164–166 °C. IR (KBr) (ν_{max}/cm^{-1}): 1742 and 1704 (2C=O), 1653 (C=C), 1266 (C_{sp^2}–O), 1064 (C_{sp^3}–O), 783 (C–Cl). ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.79 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.94 (d, $^2J_{HH}$=12.0 Hz, 1H, CHCl), 4.07 and 4.09 (d, $^2J_{HH}$=11.2 Hz, 2H, CH_2Cl), 4.16 (d, $^2J_{HH}$=12.0 Hz, 1H, CHCl), 5.31 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.87 (s, 1H, NCHO), 6.30 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.44 (d, $^3J_{HH}$=6.8 Hz, 1H, CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 48.3 (CH_2Cl), 48.4 (CH_2Cl), 52.4 and 53.5 ($2OCH_3$), 78.6 (C_q), 81.2 (NCHO), 100.6 (CH), 111.8 (NC=*C*COOMe), 120.8 (C), 126.0 (CH), 124.0 (CH), 145.8 (N*C*=CCOOMe), 163.0 and 164.4 (C=O). MS: *m*/*z* (%) 387 ($M^{+\bullet}$+6, 1), 385 ($M^{+\bullet}$+4, 9), 383 ($M^{+\bullet}$+2, 27), 381 ($M^{+\bullet}$, 27), 336 (11), 334 (67), 332 (100), 352 (3), 350 (3), 288 (4), 286 (6), 226 (3), 224 (8), 151 (18), 129 (12), 111 (19), 77 (12), 79 (4), 51 (13). Anal. Calcd for $C_{14}H_{14}Cl_3NO_5$ (382.62): C, 43.95; H, 3.69; N, 3.66%. Found: C, 43.65; H, 3.55; N, 3.48%.

*4.2.21. Dimethyl 9-chloro-2-(dichloromethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**3df**).* Yellow powder, yield (0.81 g, 91%). Mp 149–151 °C. IR (KBr) (ν_{max}/cm^{-1}): 1733 and 1705 (2C=O), 1645 (C=C), 1260 (C_{sp^2}–O), 1063 (C_{sp^3}–O), 769 (C–Cl). ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.32 (dd, $^3J_{HH}$=7.2 Hz, $^3J_{HH}$=6.8 Hz, 1H, CH), 5.64 (s, 1H, NCHO), 6.31 (d, $^3J_{HH}$=7.2 Hz, 1H, CH), 6.50 (d, $^3J_{HH}$=6.8 Hz, 1H, CH), 6.93 (s, 1H, CH), 7.36–7.42 (m, 3H, 3CH), 7.70–7.72 (m, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 52.8 and 53.5 ($2OCH_3$), 76.7 ($CHCl_2$), 81.6 (NCHO), 83.0 (Cq), 100.2 (CH), 117.9 (NC=*C*COOMe), 119.7 (C_q), 125.0 (CH), 125.4 (CH), 127.0 (2CH), 128.6 (2CH), 128.8 (CH), 139.1 (C_q), 14.1 (N*C*=CCOOMe), 162.8 and 166.4 (C=O). MS: *m*/*z* (%) 447 ($M^{+\bullet}$+4, 3), 445 ($M^{+\bullet}$+2, 9), 443 ($M^{+\bullet}$, 9), 412 (1), 410 (6), 408 (9), 362 (27), 360 (82), 348 (23), 332 (1), 330 (3), 295 (5), 247 (12), 224 (7), 167 (6), 139 (12), 111 (24), 105 (100), 77 (73), 51 (31). Anal. Calcd for $C_{19}H_{16}Cl_3NO_5$ (444.69): C, 51.32; H, 3.63; N, 3.15%. Found: C, 51.12; H, 3.51; 2.98%.

*4.2.22. Dimethyl 2-(bromomethyl)-2-phenyl-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**6a**).* Yellow powder, yield (0.50 g, 60%). Mp 127–129 °C. IR (KBr) (ν_{max}/cm^{-1}): 1741 and 1707 (2C=O), 1649 (C=C), 1263 (C_{sp^2}–O), 1107 (C_{sp^3}–O), 524 (C–Br). ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.28 and 4.44 (AB quartet, $^2J_{HH}$=10.4 Hz, 2H, CH_2Br), 5.22 (td, $^3J_{HH}$=6.8 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 5.36–5.40 (m, 1H, CH), 5.42 (dd, $^3J_{HH}$=3.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.17 (ddt, $^3J_{HH}$=8.8 Hz, $^3J_{HH}$=6.0 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.26 (dt, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 7.29–7.39 (m, 5H, 5CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ39.1 (CH_2Br), 52.1 and 53.3 ($2OCH_3$), 78.0 (N*C*HO), 80.0 (C_q), 101.1 (CH), 109.2 (NC=*C*COOMe), 116.1 (CH), 125.1 (CH), 125.3 (CH), 127.7 (2CH), 128.5 (CH), 128.6 (2CH), 141.9 (C_q), 146.0 (N*C*=CCOOMe), 160.0 and 165.4 (2C=O). MS: *m*/*z* (%) 421 ($M^{+\bullet}$+2, 7), 419 ($M^{+\bullet}$, 7), 419 (94), 329 (100), 308 (5), 280 (16), 262 (20), 248 (7), 234 (4), 190 (10), 162 (5), 145 (6), 129 (8), 111 (16), 105 (100), 77 (30), 59 (9). Anal. Calcd for $C_{19}H_{18}BrNO_5$ (420.25): C, 54.30; H, 4.32; N, 3.33%. Found: C, 53.95; H, 4.05; N, 3.21%.

*4.2.23. Dimethyl 2-(bromomethyl)-2-(4-nitrophenyl)-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**6b**).* Yellow powder, yield (0.66 g, 71%). Mp 127–129 °C. IR (KBr) (ν_{max}/cm^{-1}): 1739 and 1695 (2C=O), 1655 (C=C), 1240 (C_{sp^2}–O), 1107 (C_{sp^3}–O), 525 (C–Br). NMR data for the major isomer (74%): ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.77 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.26 and 4.39 (AB quartet, $^2J_{HH}$=10.4 Hz, 2H, CH_2Br), 5.28 (td, $^3J_{HH}$=6.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 5.36 (dd, $^3J_{HH}$=2.8 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 5.41–5.43 (m, 1H, CH), 6.22 (ddt, $^3J_{HH}$=9.6 Hz, $^3J_{HH}$=6.0 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.28 (dt, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 7.61 (d, $^3J_{HH}$=9.2 Hz, 2H, 2CH), 8.25 (d, $^3J_{HH}$=9.2 Hz, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.3 (CH_2Br), 52.3 and 53.5 ($2OCH_3$), 78.4 (NCHO), 79.1 (C_q), 101.7 (CH), 107.7 (NC=*C*COOMe), 115.8 (CH), 123.8 (CH), 125.1 (CH), 125.5 (2CH), 128.7 (CH), 128.8 (2CH), 146.7 (C_{ipso}), 148.5 (N*C*=CCOOMe), 163.6 and 165.0 (2C=O). NMR data for the minor isomer (26%): ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.37 and 4.55 (AB quartet, $^2J_{HH}$=11.6 Hz, 2H, CH_2Br), 5.77–5.81 (m, 1H, CH), 6.02 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 5.38–5.40 (m, 1H, CH), 6.31–6.36 (m, 1H, CH), 6.38 (dt, $^3J_{HH}$=7.2 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 7.73 (d, $^3J_{HH}$=9.2 Hz, 2H, 2CH), 8.18 (d, $^3J_{HH}$=9.2 Hz, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.6 (CH_2Br), 52.1 and 54.3 ($2OCH_3$), 77.2 (NCHO), 79.2 (C_q), 102.4 (CH), 107.7 (NC=*C*COOMe), 116.6 (CH), 123.6 (CH), 124.1 (CH), 124.8 (2CH), 125.2 (CH), 126.0 (2CH), 146.7 (C_q), 147.6 (N*C*=CCOOMe), 163.6 and 165.0 (2C=O). MS: *m*/*z* (%) 466 ($M^{+\bullet}$+2, 2), 464 ($M^{+\bullet}$, 2), 385 (27), 371 (31), 325 (7), 222 (7), 191 (15), 150 (100), 111 (100), 79 (100), 52 (93). Anal. Calcd for $C_{19}H_{17}BrN_2O_5$ (465.25): C, 49.05; H, 3.68; N, 6.02%. Found: C, 48.65; H, 3.48; N, 5.85%.

*4.2.24. Dimethyl 2-(bromomethyl)-2-(4-bromophenyl)-2H,9aH-pyrido[2,1-b][1,3]oxazine-3,4-dicarboxylate (**6c**).* Yellow powder, yield (0.65 g, 65%). Mp 129–131 °C. IR (KBr) (ν_{max}/cm^{-1}): 1739 and 1695 (2C=O), 1655 (C=C), 1240 (C_{sp^2}–O), 1107 (C_{sp^3}–O), 525 (C–Br). NMR data for the major isomer (87%): ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.74 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 4.22 and 4.39 (AB quartet, $^2J_{HH}$=10.40 Hz, 2H, CH_2Br), 5.24 (td, $^3J_{HH}$=7.0 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 5.35–5.39 (m, 2H, CH and NCHO), 6.16–6.21 (m, 1H, CH), 6.26 (dt, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 7.27 (d, $^3J_{HH}$=8.8 Hz, 2H, 2CH), 7.51 (d, $^3J_{HH}$=8.8 Hz, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.7 (CH_2Br), 52.2 and 53.4 ($2OCH_3$), 78.1 (NCHO), 79.1 (C_q), 101.4 (CH), 108.4 (NC=*C*COOMe), 116.0 (CH), 122.8 (CH), 125.2 (CH), 125.3 (2CH), 129.5 (CH), 131.7 (2CH), 140.9 (C_q), 146.3 (N*C*=CCOOMe), 163.9 and 165.2 (2C=O). NMR data for the minor isomer (13%): ^1H NMR (400.13 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.37 and 4.46 (AB quartet, $^2J_{HH}$=11.6 Hz, 2H, CH_2Br), 5.75 (td, $^3J_{HH}$=9.8 Hz, $^3J_{HH}$=3.6 Hz, $^4J_{HH}$=0.8 Hz, 1H, CH), 6.05 (dd, $^3J_{HH}$=3.2 Hz, $^4J_{HH}$=1.2 Hz, 1H, NCHO), 5.35–5.39 (m, 1H, CH), 6.30 (ddt, $^3J_{HH}$=10.0 Hz, $^3J_{HH}$=6.0 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 6.34 (dt, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.2 Hz, 1H, CH), 7.27 (d, $^3J_{HH}$=8.8 Hz, 2H, 2CH), 7.51 (d, $^3J_{HH}$=8.8 Hz, 2H, 2CH). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 37.4 (CH_2Br), 52.0 and 53.3 ($2OCH_3$), 79.5 (N*C*HO), 77.2 (C_q), 101.9 (CH), 108.4 (NC=*C*COOMe), 116.6 (CH), 122.0 (CH), 124.9 (CH), 125.0 (CH), 129.2 (CH), 131.1 (2CH), 139.8 (C_q), 144.1 (N*C*=CCOOMe), 163.4 and 164.3 (2C=O). MS: *m*/*z* (%) 501 ($M^{+\bullet}$+4, 1), 449 ($M^{+\bullet}$+2, 2), 497 ($M^{+\bullet}$, 1), 420 (20), 418 (20), 405 (19), 403 (19), 360 (3), 358 (3), 339 (4), 280 (2), 278 (4), 276 (2), 262 (14), 185 (100), 183 (100), 157 (21), 155 (21), 111 (38), 79 (48). Anal. Calcd for $C_{19}H_{17}Br_2NO_5$ (499.15): C, 45.72; H, 3.43; N, 2.81%. Found: C, 45.51; H, 3.35; N, 2.70%.

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