Pergamon

Tetrahedron 57 (2001) 7501–7506

TETRAHEDRON

Process development of potassium channel opener, TCV-295, based on convenient ring formation of 2*H*-1,3-benzoxazine and selective *N*-oxidation of the pyridyl moiety

Hideya Mizufune,* Hiroyuki Irie, Susumu Katsube, Tadataka Okada, Yukio Mizuno and Miichiro Arita

Chemical Development Laboratories, Pharmaceutical Production Division, Takeda Chemical Industries Ltd, 2-17-85 Jusohonmachi, Yodogawaku, Osaka 532 8686, Japan

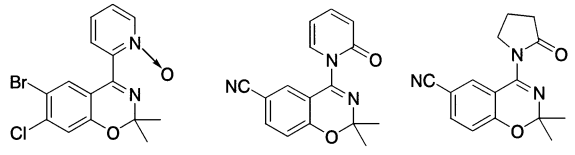
Received 11 June 2001; accepted 13 July 2001

Abstract—An efficient process for potassium channel opener, TCV-295, based on a novel and convenient 4-(2-pyridyl)-2*H*-1,3-benzoxazine ring formation from *o*-hydroxybenzoylpyridine by the NH_4I/piperidine/2,2-dimethoxypropane system and the following selective pyridine-*N*-oxidation using dimethyldioxirane, has been developed. Additionally, the combination reagent of ammonium halide and *sec*- or *tert*- amine conveniently converted *o*-hydroxyphenyl arylketones with several ketones (or benzaldehyde) to various novel 4-aryl-2*H*-1,3-benzoxazines. © 2001 Elsevier Science Ltd. All rights reserved.

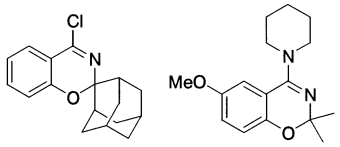
1. Introduction

TCV-295 **1** is the one of a series of 2*H*-1,3-benzoxazine derivatives[1] having potassium channel-activating activity expected as therapeutic agents for various diseases such as hypertension, angina pectoris, asthma and urinary incontinence. In its chemical structure, TCV-295 **1** is distinct from most 2*H*-1,3-benzoxazines, including potassium channel openers **2**[2a] and **3**,[2b] because the benzoxazine ring is linked with a pyridyl moiety, as a pendant group, via a carbon–carbon bond at the 4-position. Therefore, in medicinal chemistry research, some original synthetic routes to the novel benzoxazine skeleton were developed.[1a]

However, from the viewpoint of large-scale preparation of **1** as a drug candidate for further evaluation (e.g. toxicological and clinical studies), the original synthetic process for **1** has some drawbacks, such as low yield in the reaction for the benzoxazine ring formation, use of ammonia gas/acetone solution in a sealed tube, and also low chemoselectivity regarding the *N*-oxidation of the pyridyl moiety. Thus, herein, we wish to report an efficient process, based on a novel and convenient 2*H*-1,3-benzoxazine ring formation using the NH_4I/piperidine/2,2-dimethoxylpropane reagent and the selective pyridine *N*-oxidation by dimethyldioxirane, to supply the active chemical substances **1**. In addition, because of the usefulness of the 2*H*-1,3-benzoxazine ring as various materials, such as photochromic substance **4**[3a] and photofading-preventive material **5**,[3b] we also wish to demonstrate expansion of the novel ring formation using the convenient ammonium halide/amine system.



1 **2** **3**



4 **5**

2. Results and discussion

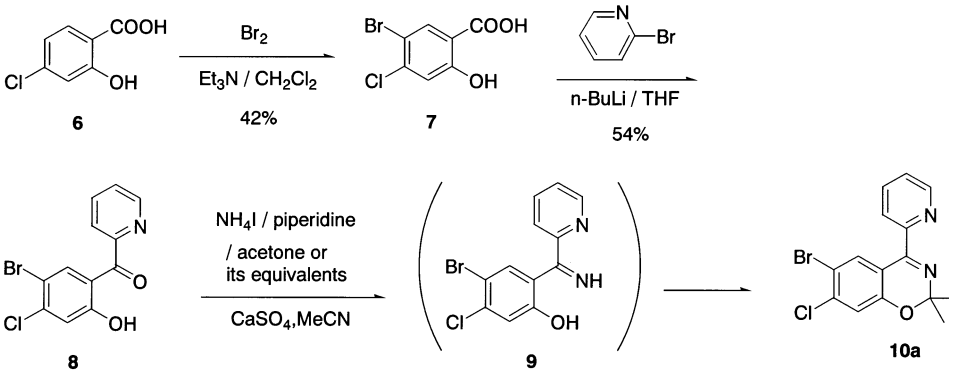
2.1. Process development of potassium channel opener 1

As shown in Scheme 1, the key intermediate, *o*-hydroxybenzoylpyridine **8**, was derived from 5-chlorosalicylic acid **6** via bromination in the $Br_2/Et_3N/CH_2Cl_2$ system at −70°C and the following coupling reaction with 2-lithiopyridine generated in situ at −70°C. Despite our modification of the reaction conditions of the original synthetic method,[1a] the synthesis of benzoylpyridine **8** suffered from low yield

Keywords: benzoxazines; ammonium salts; amines; *N*-oxides; dioxiranes.

* Corresponding author. Tel.: +81-6-6300-6378; fax: +81-6-6300-6251; e-mail: mizufune_hideya@takeda.co.jp

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00728-1



Scheme 1.

and the low temperature reaction. Therefore, our attention was focused on developing a facile process from benzoylpyridine **8** to the target compound **1**.

Our first task was to develop a novel and effective ring formation of 4-(2-pyridyl)-2*H*-1,3-benzoxazine **10a** from benzoylpridine **8**. In the medicinal chemistry process,[1a] benzoylpyridine **8** reacted with ammonia-saturated acetone solution in a sealed tube to give 2*H*-1,3-benzoxazine **10a** in 50% yield using chromatographic purification. From the viewpoint of large-scale production, to prepare the ammonia/acetone solution, which is unstable due to the self-Aldol condensation, to deal with the reaction in the closed vessel and to purify **10a** with column chromatography are disadvantages in a facility. Hence, to avoid using ammonia gas and a sealed tube, we investigated the reaction of the substrates [**8** and acetone (or its equivalents)] with ammonia generated in situ by combination of an ammonium halide and an amine. Additionally, we hoped that the amine or the amine-hydrohalide salt (generated in situ) might accelerate conversion of the ketimine **9**, derived from the ketone **8** and ammonia, to 2*H*-1,3-benzoxazine **10a** in good yield.

During some screening of the ammonium halide/amine system, we decided to choose a combination of ammonium iodide with piperidine in MeCN, because ammonium iodide was expected to be easily dissolved in a polar organic solvent such as MeCN; piperidine might be converted to the corresponding enamine of acetone, which cyclizes easily with the ketimime **9** to give the benzoxazine like Kabbe's synthesis of 4-chromanone.[4] Gratifyingly, **in an open vessel** for 5 h at rt, benzoylpyridine **8** reacted with ammonium iodide and piperidine in MeCN, to generate the corresponding ketimine **9**, which was observed by TLC. Then, to the mixture was added acetone or its equivalents (e.g. 2,2-dimethoxypropane and 2-methoxypropene), respectively, and refluxed for 3 h to give the desired 2*H*-1,3-benzoxazine **10a** in good yield. As shown in Table 1, among acetone and its equivalents, 2,2-dimethoxypropane presented the highest yield for construction of the 2*H*-1,3-benzoxazine ring; thus, it was chosen as the raw material in the large-scale preparation to give the 2*H*-1,3-benzoxazine **10a** 1.44 kg (82% yield) without chromatographic purification.

Table 1. The reaction of **8** with NH_4I, piperidine and acetone or its equivalents

Entry	Acetone or its equivalents	Isolated yield (%)
1	2,2-Dimethoxypropane[a]	82[b]
2	2,2-Dimethoxypropane[a]	77[c]
3	2,2-Diethoxypropane[a]	71[c]
4	2-Methoxypropene[a]	60[c]
5	Acetone[d]	61[c]

[a] Carried out by the general procedure in Section 4.
[b] **8** (1.55 kg, 4.97 mol) was used.
[c] **8** (10 g, 320 mmol) was used.
[d] Reacted at rt for 36 h with other materials.

Our next task was to improve the chemoselectivity in pyridine *N*-oxidation of 4-(2-pyridyl)-2*H*-1,3-benzoxazine **10a**. On the medicinal chemistry route, **10a** was oxidized by *m*-CPBA to give the potassium channel opener **1** in low yield (30%)[1a] with the by-product, dioxide **11**. At first, we investigated the reaction condition in the *m*-CPBA system and *N*-oxidation using other peracids (e.g. magnesium monoperoxybenzoic acid), but failed to improve the chemoselectivity. Thus, for the timely development of the potassium channel opener **1**, we prepared a sample for early toxicological and clinical study, by *m*-CPBA oxidation.

On the other hand, we undertook use of dimethyldioxirane[5] which has been recently studied for highly selective oxidation of various substrates.[6] After intensive study of the reaction conditions such as the solvent, buffer salt and procedure, 4-(2-pyridyl)-2*H*-1,3-benzoxazine **10a** was converted to potassium channel opener **1** in high yield (84%) by dimethyldioxirane which was in situ generated in acetone/

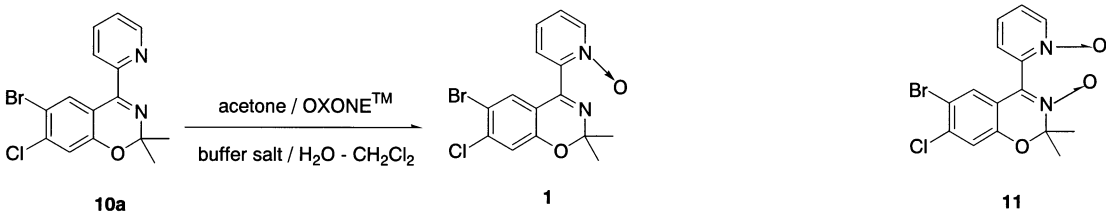


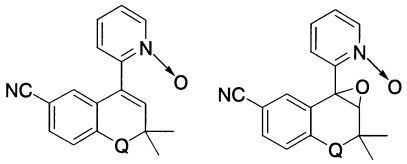
Table 2. Selective *N*-oxidation of benzoxazine **10a**

Entry	Oxidizer	Buffer salt		Ratio by HPLC		
				10a	**1**	**11**
1	m-CPBA[a]	Without		14	47 (41)[b]	26
2	OXONE™/acetone[c]	$NaHCO_3$	6.4 equiv.	18	76	4
3		Na_2HPO_4	6.4 equiv.	15	79	2
4			8.0 equiv.	7	86 (84)[b]	3
5			9.2 equiv.	9	84	3
6		K_2HPO_4	6.4 equiv.	15	79	2

[a] CH_2Cl_2 was used as solvent.
[b] Isolated yield.
[c] Acetone, OXONE™ (2.3 equiv.), buffer salt, H_2O and CH_2Cl_2 were used.

OXONE™ ($2KH_2SO_5 \cdot KHSO_4 \cdot K_2SO_4$)/aq. Na_2HPO_4-CH_2Cl_2 system. As shown in Table 2, the system requires a basic buffer salt, such as Na_2HPO_4, K_2HPO_4 and $NaHCO_3$, to keep dimethyldioxirane stable against the acidic medium due to OXONE™. Additionally, it is important to dropwise slowly aq. OXONE™ to the mixture of benzoxazine, acetone, aq.buffer salt and CH_2Cl_2 for completion of *N*-oxidation.

Additionally, the selective *N*-oxidation using dimethyldioxirane might be useful for synthesis of other potassium channel openers[7], **12a** and **12b**, which have a pyridine-*N*-oxide moiety and are derived by *m*-CPBA oxidation from the corresponding pyridine derivatives, with the by-products **13a** and **13b**.



12a: Q=O,
12b: Q=C(O)

13a: Q=O,
13b: Q=C(O)

2.2. Further study of the novel 2*H*-1,3-benzoxazine ring formation

In addition to the potassium channel opener, the 2*H*-1,3-benzoxazine ring is useful as an anti-inflammatory agent,[3c] photochromic substance **4**[3a] and photofading-preventive material **5**.[3b] However, these 2*H*-1,3-benzoxazine rings are linked to the substituents at the 4-position via C–heteroatom bonds. Thus, our novel cyclization method for 2*H*-1,3-benzoxazine bearing the substituent linked with the C–C bond may be effective for syntheses of various new materials.

We investigated the reagent composition for our convenient annulation reaction and its application to syntheses of other benzoxazines. First, a combination of ammonium halides and amines was extensively studied for synthesis of benzoxazine **10a**, the precursor of the potassium channel opener **1**. As shown in Table 3, ammonium iodide and ammonium bromide are useful in combination with various secondary or tertiary amines and cyclic or linear amines, such as piperidine, morpholine, dibutylamine and triethylamine. The combination of ammonium chloride and morpholine also gave benzoxazine **10a**, but needed longer time to give the ketimine **9**, than the other combinations. Generally, regarding ammonium halide, ammonium iodide was preferable to the others because it provided high yield and required short reaction time. On the other hand, regarding the suitable amines for the benzoxazine annulation, we predicted that a secondary amine might be particularly effective due to the enamine formation[4] with acetone. However, we found no difference between secondary amines and tertiary ones in the effect for the benzoxazine annulation.

Table 3. Syntheses of benzoxazine **10a** using various ammonium halides and amines

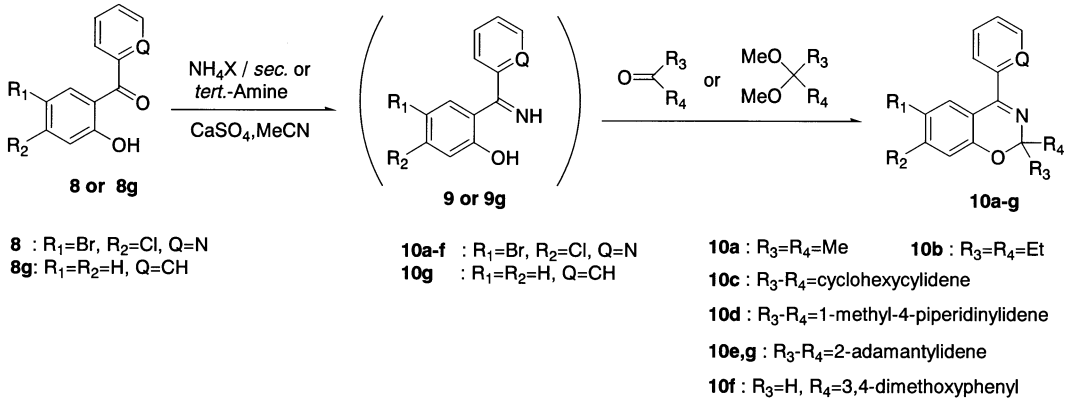
Entry	NH_4X	Amine	Reaction time (h)		Isolated yield (%)
			Imination[a]	Acetonidation[b]	
1	NH_4I	Piperidine	2.5	3	77
2		Morpholine	4	3	61
3		Dibutylamine	2	2	75
4		Diethylamine	3	6	76
5		Tributylamine	3	4	72
6		Triethylamine	2	3	78
7		DBU	2	2	77
8	NH_4Br	Piperidine	7	9	62
9		Morpholine	7	6	61
10		Dibutylamine	3	4	77
11		Triethylamine	5	5	75
12	NH_4Cl	Morpholine	12	6	66
13		Triethylamine	8	15	33

[a] **8** was reacted with NH_4X (5 equiv.), amine (5 equiv.) and $CaSO_4$ (Drierite™) in MeCN at rt.
[b] To the mixture was added 2,2-dimethoxypropane (10 equiv.) and refluxed.

Table 4. Syntheses of benzoxazines **10b–g** bearing various substituents

Entry	Substrate	NH_4X/amine	Ketones or benzaldehyde	Benzoxazines	Isolated yield (%)
1	**8**	NH_4I/Et_3N	3-Pentanone (10 equiv.)[a]	**10b**	58
2	**8**	NH_4I/Et_3N	Cyclohexanone (10 equiv.)[a]	**10c**	79
3	**8**	NH_4I/Et_3N	1-Methyl-4-piperidone (10 equiv.)[b]	**10d**	70
4	**8**	NH_4I/piperidine	2-Admantanone (3 equiv.)[a]	**10e**	82
5	**8**	NH_4I/piperidine	3,4-Dimethoxybenzaldehyde (3 equiv.)[a]	**10f**	88
6	**8g**	NH_4I/piperidine	2-Admantanone (3 equiv.)[a]	**10g**	70

[a] Carried out by the general procedure in Section 4.
[b] Reacted at rt for 38 h with other materials.



Next, syntheses of various benzoxazines were investigated to expand the novel benzoxazine annulation method using our combination reagents of ammonium halides and amines which are optimized by the above result of Table 3. As shown in Table 4, benzoylpyridine **8** reacted with various carbonyl compounds to give novel 4-pyridylbenzoxazines **10b-f** bearing, respectively, diethyl, cyclohexylidene, 1-methyl-4-piperidinylidene, 2-adamantylidene and 3,4-dimethoxyphenyl moiety. Benzophenone **8g** was also converted to novel 4-phenylbenzoxazine **10g**.

We also investigated the role of the amine-hydrohalides salt generated in situ in our combination reagent of ammonium halides and amines. The benzoylpyridine **8** reacted with ammonia gas dissolved in EtOH to give the ketimine **9**, which was readily converted to the benzoxazine **10f** by veratraldehyde/morpholine–HCl salt systems in 61% yield based on **8**. Hence, in our convenient benzoxazine synthesis, amine–hydrohalides salt generated in situ from ammonium halides and amines can accelerate cyclization of the ketimines generated in situ to various carbonyl compounds.

3. Conclusions

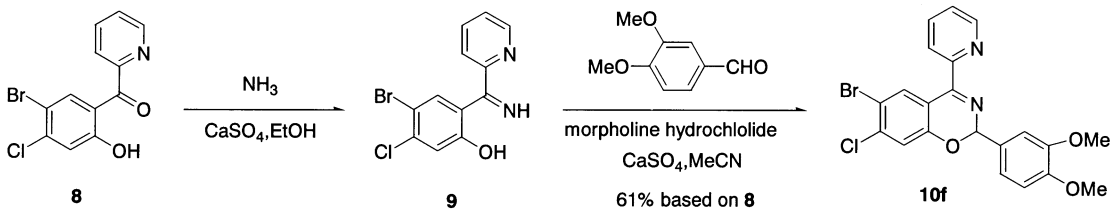
In conclusion, we have developed an efficient process for potassium channel opener, TCV-295, based on a novel and convenient 4-(2-pyridyl)-2*H*-1,3-benzoxazine ring formation from *o*-hydroxybenzoylpyridine by the NH_4I/piperidine/2,2-dimethoxypropane system and the following selective pyridine-*N*-oxidation using dimethyldioxirane. Additionally, the combination reagent of ammonium halide and *sec*- or *tert*- amine conveniently converted *o*-hydroxyphenyl arylketones and several ketones (or benzaldehyde) to various novel 4-aryl-2*H*-1,3-benzoxazines. Now we are expanding the convenient synthetic method and investigating its application to various materials.

4. Experimental

4.1. Data of compounds

Melting points were recorded on a Yanagimoto micro melting apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^1H NMR spectra were recorded on a Bruker DPX-300 spectrometer. Elemental analyses and mass spectra were analyzed by Takeda Analytical Research Ltd. HPLC was performed on a YMC-Pack ODS-A302 column (150 mm×4.6 mm I.D.) with 0.05 M KH_2PO_4 aq. soln.-MeCN (50:50) at 25°C. Detection was effected with a Hitachi spectrophotometric detector at 254 nm.

4.1.1. 5-Bromo-4-chlorosalicylic acid (7). 4-Chlorosalicylic acid (2.70 kg, 15.7 mol) and triethylamine



(1.75 kg, 17.3 mol) was dissolved in CH_2Cl_2 (60 L). After cooling at −70°C, bromine (2.50 kg, 15.6 mol) in CH_2Cl_2 (12.5 L) was dropped to the mixture. After stirring at the same temperature for 1 h, the reaction mixture was concentrated in vacuo. To the residue was added water (50 L) and conc. HCl (5 L), and extracted with AcOEt (15 and 10 L). The combined organic layer was washed with brine (30 L) twice, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was washed with *n*-hexane (12.5 L) and MeCN (3 L) to give the title compound (1.66 kg, yield 42%). ^{1}H NMR (DMSO-d_6, TMS, 300 MHz), δ (ppm):7.30 (1H, s), 8.02 (1H, s).

4.1.2. 2-(5-Bromo-4-chloro-2-hydroxybenzoyl)pyridine (8). Under argon atmosphere, 2-bromopyridine (5.15 kg, 32.6 mol) was dissolved in THF (21 L), stirred and cooled at −78°C. To the solution was added dropwise 1.6 M *n*-BuLi hexane solution (12.0 kg, 27.9 mol), maintaining the temperature at under than −70°C, and stirred at this temperature for 0.5 h. Then, 5-bromo-4-chloro-salicylic acid (1.17 kg, 4.65 mol) in THF (5 L) was added dropwise, and the resultant mixture was stirred at this temperature for 1 h before being allowed to warm to −20°C. At −20°C, MeOH (2.3 L) and water (30 L) were added to the reaction mixture which was allowed to warm to room temperature and extracted with AcOEt (25, 12.5 and 12.5 L). The combined organic layers were washed with 5% HCl aq. (2×17 L) and water (2×30 L), and concentrated in vacuo. The residue was recrystallized from EtOH to give the title compound (790 g, yield 54%) as a yellow crystalline powder: mp 123–124°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz),δ (ppm):7.20 (1H, s), 7.57–7.61 (1H, m), 7.98–8.01 (1H, m), 8.07–8.10 (1H, m), 8.60 (1H, s), 8.73–8.75 (1H, m), 13.0 (1H, br), IR (KBr, cm^{-1}) 1585, 1440, 1378, MS (EI, *m/z*): 315 (M+4), 313 (M+2), 311 (M), elemental analysis: calcd for $C_{12}H_7NO_2BrCl$; C: 46.11, H: 2.26, N: 4.48, found for C: 46.03, H: 2.27, N: 4.52.

4.1.3. 6-Bromo-7-chloro-4-(2-pyridyl)-2,2-dimethyl-2*H*-1,3-benzoxazine (9). Piperidine (2.11 kg, 24.8 mol) was added to the stirred suspension of 2-(5-bromo-4-chloro-2-hydroxybenzoyl)pyridine (1.55 kg, 4.97 mol), NH_4I (3.60 kg, 24.8 mol), $CaSO_4$ (Drierite™) (3.11 kg, 22.8 mol) and MeCN (31 L), and stirred at room temperature for 5 h. To the resulting mixture was added 2,2-dimethoxypropane (5.17 kg, 49.6 mol) and refluxed for 3 h. After allowing to cool to room temperature, the precipitate was filtered off and washed with MeCN (7.8 L). The mixture of the filtrate and washings was concentrated in vacuo. To the residue were added diisopropyl ether (31 L) and 0.1N-NaOH (16 L) and the organic and aqueous layers were separated. The organic layer was washed with 0.1N-NaOH (2×16 L) and water (2×16 L), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOH (1.6 L) to give the title compound (1.44 kg, yield 82%) as a colorless crystalline powder: mp 101–102°C. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm):1.66 (6H, s), 7.01 (1H, s), 7.38–7.41 (1H, m), 7.81–7.83 (2H, m), 8.08 (1H, s), 8.68–8.70 (1H, m). IR (KBr, cm^{-1}) 1590, 1365, 1265. Elemental analysis: calcd for $C_{15}H_{12}N_2OBrCl$; C: 51.24, H: 3.44, N: 7.97, found for C: 51.26, H: 3.69, N: 8.00.

4.1.4. 2-(6-Bromo-7-chloro-2,2-dimethyl-2*H*-1,3-benzoxazine-4-yl)pyridine-1-oxide (TCV-295). 6-Bromo-7-chloro-4-(2-pyridyl)-2,2-dimethyl-2H-1,3-benzoxazine (30 g, 85.3 mmol) was dissolved in CH_2Cl_2 (600 ml). To the solution were added acetone (300 ml), Na_2HPO_4 (97.2 g, 685 mmol) and water (300 ml); and then OXONE™ ($2KH_2SO_5{\cdot}KHSO_4{\cdot}K_2SO_4$) (120 g, 195 mmol) in water (600 ml) was added dropwise at room temperature for 4 h. After additional stirring for 4 h, the reaction mixture was separated into the organic and aqueous layers. The aqueous layer was extracted with CH_2Cl_2 (2×300 ml). The combined organic layer was washed with $Na_2S_2O_3$ (50 g) in water (1 L) and water (2×300 ml), dried over anhydrous Mg_2SO_4 and concentrated in vacuo. The residue was purified with silica-gel chromatography (eluent; MeCN) and the combined fraction was concentrated in vacuo. The residue was recrystallized from EtOH (140 ml) and water (280 ml) to give the title compound (26.5 g, yield 84%) as a colorless crystalline powder: mp 182–183°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 1.68 (6H, s), 7.00 (1H, s), 7.15 (1H, s), 7.33–7.41 (3H, m), 8.25–8.28 (1H, m), IR (KBr, cm^{-1}) 1617, 1432, 989, MS (EI, *m/z*): 370 (M+4), 368 (M+2), 366 (M), Elemental analysis: calcd for $C_{15}H_{12}N_2O_2BrCl$; C: 49.01, H: 3.29, N: 7.62, found for C: 49.24, H: 3.35, N: 7.78.

4.2. General procedure for 4-(2-pyridyl)-2*H*-1,3-benzoxazines (10a–f) (Tables 1, 3 and 4)

Appropriate amine (160 mmol) was added to the stirred suspension of 2-(5-bromo-4-chloro-2-hydroxybenzoyl)-pyridine **8** (10 g, 32 mmol), various ammonium halide (160 mmol), $CaSO_4$ (Drierite™) (20 g) and MeCN (200 ml), and stirred at room temperature for 2–12 h. To the resulting mixture was added desired ketone, aldehyde or its equivalents (96–320 mmol) and refluxed for 2–15 h. After allowing to cool to room temperature, the insoluble matter in the reaction mixture was filtered off and washed with MeCN. The mixture of the filtrate and washings was concentrated in vacuo. To the residue were added diisopropyl ether and 0.1N-NaOH; and separated into the organic and aqueous layers. The organic layer was washed with 0.1N-NaOH and water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was recrystallized from EtOH or washed with EtOH to give the target compound.

4.2.1. 6-Bromo-7-chloro-4-(2-pyridyl)-2,2-diethyl-2*H*-1,3-benzoxazine (10b). A colorless crystalline powder: mp 110–111°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 1.00 (6H, t, J=7.4 Hz), 1.95 (4H, q, J=7.4 Hz), 6.99 (1H, s), 7.38–7.43 (1H, m), 7.83–7.84 (2H, m), 8.18 (1H, s), 8.69–8.71 (1H, m), IR (KBr, cm^{-1}) 2971, 1621, 985, Elemental analysis: calcd for $C_{17}H_{16}N_2OBrCl$; C: 53.78, H: 4.25, N: 7.38, found for C: 53.88, H: 4.27, N: 7.42,

4.2.2. Spiro[6-bromo-7-chloro-4-(2-pyridyl)-2*H*-1,3-benzoxazine-2,1′-cyclohexane] (10c). A colorless crystalline powder: mp 116–117°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 1.45–2.03 (10H, m), 7.06 (1H, s), 7.38–7.42 (1H, m), 7.80–7.89 (2H, m), 8.11 (1H, s), 8.68–8.70 (1H, m), IR (KBr, cm^{-1}) 2925, 1589, 985, MS (EI, *m/z*): 394 (M+4), 394 (M+2), 390 (M), Elemental analysis: calcd for $C_{18}H_{16}N_2OBrCl$; C: 55.20, H: 4.12, N: 7.15, found for C: 54.95, H: 4.00, N: 7.25.

4.2.3. Spiro[6-bromo-7-chloro-4-(2-pyridyl)-2*H*-1,3-benzoxazine-2,4′-(1′-methylpiperidine)] (10d). A colorless crystalline powder: mp 155–156°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 2.05–2.18 (4H, m), 2.37 (3H, s), 2.46–2.54 (2H, m), 2.66–2.73 (2H, m), 7.08 (1H, s), 7.38–7.43 (1H, m), 7.80–7.91 (2H, m), 8.14 (1H, s), 8.68–8.70 (1H, m), IR (KBr, cm^{-1}) 2798, 1589, 1010, MS (EI, *m/z*): 409 (M+4), 407 (M+2), 405 (M), Elemental analysis: calcd for $C_{18}H_{17}N_3OBrCl$; C: 53.16, H: 4.21, N: 10.33, found for C: 53.41, H: 4.30, N: 10.67.

4.2.4. Spiro[6-bromo-7-chloro-4-(2-pyridyl)-2*H*-1,3-benzoxazine-2,2′-adamantane] (10e). A colorless crystalline powder: mp 145–146°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 1.58–1.78 (6H, m), 1.93–1.97 (2H, m), 2.22–2.26 (4H, m), 2.36–2.40 (2H, m), 7.10 (1H, s), 7.37–7.42 (1H, m), 7.80–7.86 (1H, m), 7.98–8.01 (1H, m), 8.22 (1H, s), 8.67–8.69 (1H, m), IR (KBr, cm^{-1}) 2904, 1590, 1006, MS (EI, *m/z*): 446 (M+4), 444 (M+2), 442 (M), Elemental analysis: calcd for $C_{22}H_{20}N_2OBrCl$; C: 59.54, H: 4.54, N: 6.31, found for C: 59.57, H: 4.59, N: 6.37.

4.2.5. 6-Bromo-7-chloro-2-(3,4-dimethoxyphenyl)-4-(2-pyridyl)-2*H*-1,3-benzoxazine (10f). A yellow crystalline powder: mp 218–220°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 3.96 (3H, s), 3.98 (3H, s), 6.70–6.74 (1H, m), 6.93–6.98 (1H, m), 7.02–7.04 (1H, m), 7.15 (1H, s), 7.26 (1H, d, J=1.8 Hz), 7.30–7.33 (1H, m), 7.88–7.90 (1H, m), 7.94 (1H, s), 8.28–8.30 (1H, m), IR (KBr, cm^{-1}) 1511, 1265, 1027, MS (EI, *m/z*): 462 (M+4), 460 (M+2), 458 (M), Elemental analysis: calcd for; C: 54.87, H: 3.51, N: 6.09, found for C: 54.95, H: 3.55, N: 6.16,

4.2.6. Spiro[4-phenyl-2*H*-1,3-benzoxazine-2,2′-adamantane](10g). Triethylamine (25.5 g, 252 mmol) was added to the stirred suspension of 2-hydroxybenzo-phenone **8f** (10 g, 50.4 mmol), ammonium iodide (36.5 g, 252 mmol), $CaSO_4$ (Drierite™) (31.6 g, 232 mmol) and MeCN (150 ml), and stirred at room temperature for 44.5 h. To the resulting mixture was added 2-adamatanone (22.7 g, 151 mmol) and MeCN (50 ml), and refluxed for 3 h. After allowing to cool to room temperature, the insoluble matter in the reaction mixture was filtered off and washed with MeCN. The mixture of the filtrate and washings was concentrated in vacuo. To the residue were added diisopropyl ether and 0.1N-NaOH; and separated into the organic and aqueous layers. The organic layer was washed with 0.1N-NaOH and water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was washed with EtOH to give the target compound **10f** (11.6 g, yield 70%) as a colorless crystalline powder: mp 171–173°C, ^{1}H NMR ($CDCl_3$, TMS, 300 MHz), δ (ppm): 1.57–1.59 (6H, m), 1.93–1.98 (2H, m), 2.23–2.30 (4H, m), 2.44–2.48 (2H, m), 6.92–7.01 (2H, m), 7.23–7.26 (2H, m), 7.38–7.46 (3H, m), 7.63–7.66 (2H, m), IR (KBr, cm^{-1}) 2902, 1610, 1334, 700, MS (EI, *m/z*):329 (M^+), Elemental analysis: calcd for; C: 83.85, H: 7.04, N: 4.25, found for C: 83.80, H: 6.91, N: 4.07.

4.2.7. Synthesis of benzoxazine (10e) via ketimine (9) derived benzoylpyrodine (8) and ammonia gas. In the stirred suspension of EtOH (400 ml) and $CaSO_4$ (Drierite™) (20 g), ammonia gas was bubbled for 1 h at 0–10°C. To the resulting mixture was added 2-(5-bromo-4-chloro-2-hydroxybenzoyl)pyridine **8** (20 g, 64 mmol) and stirred at room temperature for 1.5 h. The insoluble matter in the reaction mixture was filtered off and washed with EtOH. The mixture of the filtrate and washings was concentrated in vacuo to give the crude ketimine (**9**) (17.8 g) as a yellow solid: MS (EI, *m/z*): 314 (M+4), 312 (M+2), 310 (M), Elemental analysis: calcd for $C_{12}H_8N_2OBrCl$; C: 49.26, H: 2.59, N: 8.99, found for C: 46.03, H: 2.62, N: 8.33.

Morpholine hydrochloride (9.89 g, 80 mmol) was added to the stirred suspension of the crude ketimne (4.99 g, 32 mmol), 3,4-dimethoxybenzaldehyde (7.98 g, 48 mmol), $CaSO_4$ (Drierite™) (10.9 g) and MeCN (75 ml) and refluxed for 4.5 h. After allowing to cool to room temperature, the reaction mixture was concentrated in vacuo. To the residue was added CH_2Cl_2 and the insoluble matter was filtered off. The filtrate was washed with 0.1N-NaOH and water, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was washed with EtOH to give the target compound (4.51 g) (61% based on **8**) as a yellow crystalline powder.

References

1. (a) Yamamoto, S.; Hashiguchi, S.; Miki, S.; Igata, Y.; Watanabe, T.; Shiraishi, M. *Chem. Pharm. Bull.* **1996**, *44*, 734. (b) Kusumoto, K.; Awane, Y.; Kitayoshi, T.; Fujiwara, S.; Hashiguchi, S.; Terashita, Z.; Shiraishi, M.; Watanabe, T. *J. Cardiovasc. Pharmacol.* **1994**, *24*, 929.
2. (a) Baumgarth, M., Gericke, R., Bergmann, R., De Peyer, J., Ingeborg, L. DE3840011(CA114(17):164256m). (b) Englert, H. C., Mania, D., Lintz, W. DE4010488(CA116(5):41463k).
3. (a) Melzig, M. WO90-03379(CA114(5):42796s). (b) Kaneko, Y. JP88-284547(CA111(8):67818b). (c) Tachikawa, R.; Wachi, K.; Sato, S.; Terada, A. *Chem. Pharm. Bull.* **1981**, *29*, 3529.
4. Kabbe, H. J.; Widdig, A. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 247.
5. General review: (a) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res.* **1989**, *22*, 205. (b) Murray, R. W. *Chem. Rev.* **1989**, *89*, 1187. (c) Curci, R. *Pure Appl. Chem.* **1995**, *67*, 811.
6. Selective *N*-oxidation of pyridine derivatives bearing olefin moiety: (a) Ferrer, M.; Sanchez-Baeza, F.; Messrguer, A. *Tetrahedron* **1997**, *46*, 15877. Selective *N*-oxidation of 3- or 4-picolinaldehyde: (b) Dyker, G.; Hoelzer, B. *Tetrahedron* **1999**, *55*, 12557.
7. (a) Attwood, M. R.; Churcher, I.; Dunsdon, R. M.; Hurst, D. N.; Jones, P. S. *Tetrahedron Lett.* **1991**, *32*, 811. (b) Takahashi, T.; Koga, H.; Sato, H.; Ishizawa, T.; Taka, N. *Heterocycles* **1995**, *41*, 2405. (c) Almansa, C.; Gomez, L. A.; Cavalcanti, F. L.; Rodriguez, R.; Garcia-Rafanell, J.; Forn, J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1833.