Convenient Synthesis of 1,2,3,4-Tetrahydropyrimidin-5-ylbenzoxazoles

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Dedicated to the memory of Professor Raymond N. Castle

2-Pyrimidin-5-ylbenzoxazoles **7** have been synthesized by condensation of 5-pyrimidinecarboxaldehyde **4** with substituted aminophenols **5** followed by oxidative cyclization of the resulting Schiff's bases **6** with iodobenzene diacetate. Subsequent formation of methylpyrimidinium salts **8** and reduction thereafter afforded tetrahydropyrimidinylbenzoxazoles **10**. This method has been utilized in the synthesis of M_1 muscarinic agonist candidates.

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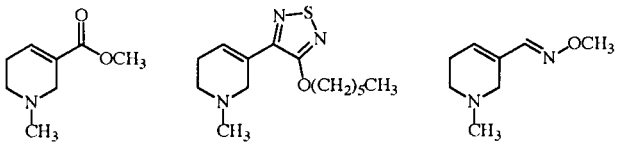
Recently, the demand for effective treatments of neurodegenerative diseases, particularly Alzheimer's disease (AD) is becoming more and more urgent. Among the researches for AD, muscarinic compounds not only are beneficial in the treatment of AD symptoms, but actually slow the progress of the disease [1].

Arecoline **1** (Figure 1), a naturally occurring alkaloid and unselective muscarinic agonist, had been used for AD patients in early clinical trials but proved to be problematic due to its low clinical efficacy, lack of subtype selectivity, and poor metabolic stability [2]. Continued research, in an effort to improve the pharmacological and pharmacokinetic properties toward a clinically more useful profile, has led to the emergence of xanomeline **2** [3] and milameline **3** [4] in which the alkoxythiadiazole, or alkoxyimino group is introduced to the tetrahydropyridine ring, respectively.

Figure 1
Muscarinic Agonists

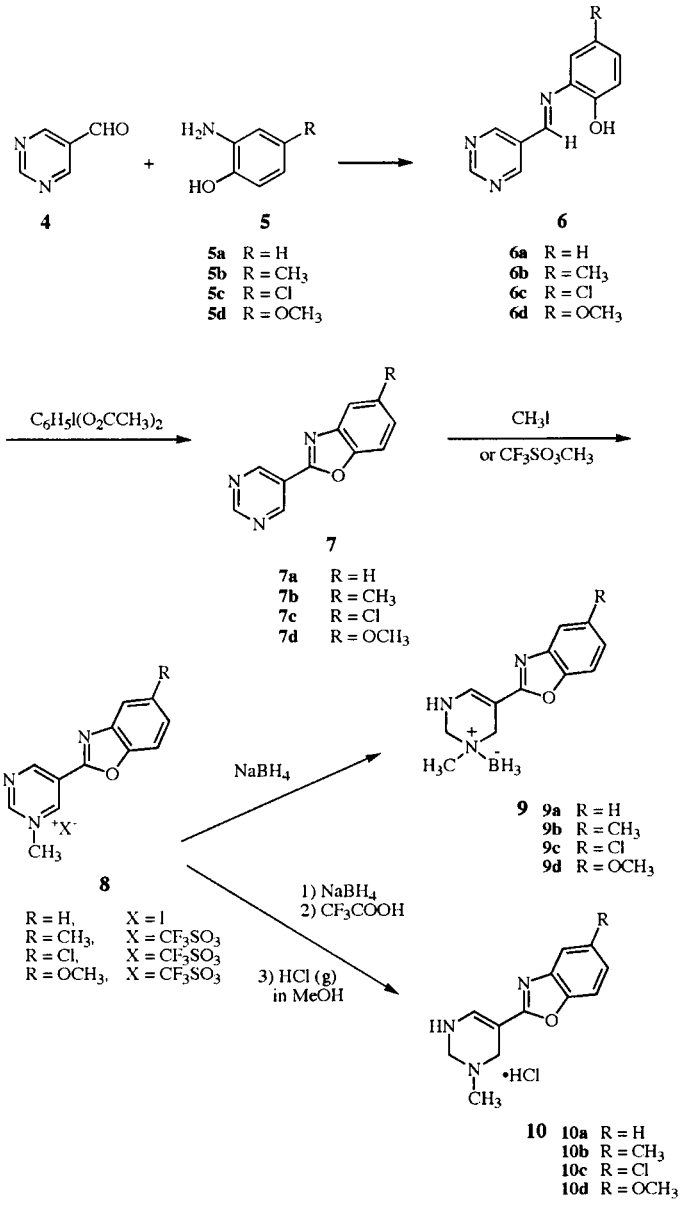


1 **2** **3**

Benzoxazoles are important structural moieties exhibiting interesting biological activity in many agrochemicals as well as in medicines [5]. In conjunction with our research for AD, a synthetic method to introduce of benzoxazole ring in place of the ester group would be useful for the preparation of other related compounds that might be used for M_1 muscarinic agonists in the treatment of AD. In our previous paper [6], we described the synthesis of tetrahydropyridinylbenzoxazoles. Herein, synthesis of pyrimidinylbenzoxazoles that are the bioisosteric congeners of pyridinylbenzoxazoles is reported as Scheme 1.

The starting material 5-pyrimidinecarboxaldehyde **4** was prepared from commercially available 4,6-dihydroxy-

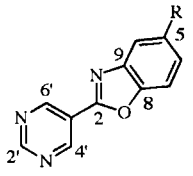
Scheme 1



pyrimidine according to a known procedure [7]. Although many reports are published on the oxidative cyclization of Schiff's bases obtained from *o*-aminophenols with variety of arylbenzoxazoles [8], the synthesis of pyrimidinylbenzoxazoles has not been reported. We obtained various Schiff's bases **6** from the reaction using 5-pyrimidinecarboxaldehyde **4** and substituted *o*-aminophenols **5** in ethyl alcohol. The resulting intermediate Schiff's bases were not isolated, but treated directly with iodobenzene diacetate to give 2-pyrimidin-5-ylbenzoxazoles **7** *via* hypervalent iodine oxidative intramolecular cyclization. The spectral data are summarized in Table 1.

Table 1

^{1}H NMR Data ($CDCl_3$) and ^{13}C NMR Data ($CDCl_3$) of Compound **7**



Compound	proton δ [ppm]					carbon δ [ppm]		
	2'-H	4',6'-H	C-2	C-8	C-9	C-2'	C-5'	C-4',6'
7a	9.37	9.53	158.0	150.7	141.4	160.1	122.1	155.4
7b	9.35	9.50	158.0	148.9	141.6	159.2	122.2	155.3
7c	9.39	9.52	159.8	149.7	143.0	160.8	122.1	155.0
7d	9.35	9.51	158.7	145.4	142.4	160.0	122.2	155.3

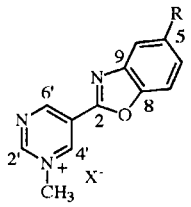
Compound **7a** (R = H) was further treated with the conventional method of methyl iodide in acetone to afford 3-methylpyrimidinium iodide **8a** in good yield. However, compounds **7b-7d** did not yield the pyrimidinium iodides. Thus, to circumvent the problem, methyl triflate in methylene chloride was used to give 3-methylpyrimidinium triflates **8b-8d**. It is noticeable that formation of the quarternary pyrimidinium occurs only at the 3-position of the pyrimidine ring. The pyrimidine rings have very different and characteristic chemical shifts corresponding to the C2, C4, and C6-positions. The chemical shifts assignments were made using 2D NMR. The spectral data of compound **8** are shown in Table 2.

Next, treatment of the methylpyrimidinium salts **8** with sodium borohydride in cold (-20 °C) tetrahydrofuran yielded borane complexes of 1,2,3,4-tetrahydropyrimidines **9**. Compound **9a** was determined by X-ray crystallography (Figure 2, see the Experimental), and typical B-H signals were observed in their IR (see the Experimental for detailed spectral data) and NMR spectra (typically observed as a broad peak at higher than 3.00 ppm). The spectral data of compound **9** are summarized in Table 3.

Attempted hydrolysis of **9** to **10** under acidic conditions resulted exclusively in decomposition of materials. On the other hand, the pyrimidinium salts generated under the same conditions were treated with CF_3CO_2H to get rid of the borane moiety, and then subsequently treated with HCl (gas) in MeOH to obtain the HCl salts of tetrahydropyrimidinylbenzoxazoles **10**

Table 2

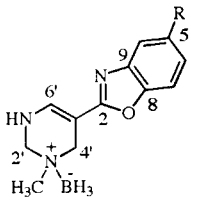
^{1}H NMR Data (CD_3OD) and ^{13}C NMR data (CD_3OD) of Compound **8**



Compound	proton δ [ppm]						carbon δ [ppm]		
	2'-H	4'-H	6'-H	C-2	C-8	C-9	C-2'	C-4'	C-6'
8a	6.36	7.93	8.76	160.1	152.1	142.8	84.3	128.9	151.9
8b	6.36	7.91	8.74	160.2	150.3	143.1	84.3	129.0	152.2
8c	6.32	7.93	8.71	161.6	150.7	144.1	84.2	129.5	152.2
8d	6.35	7.89	8.72	159.8	146.7	143.8	84.4	128.6	152.2

Table 3

^{1}H NMR Data and ^{13}C NMR Data of Compound **9**



Compound	proton δ [ppm]			carbon δ [ppm]				
	2'-H	4'-H	6'-H	C-2	C-8	C-9	C-2'	C-4'
9a	4.16	3.86	7.72	164.3	151.1	143.9	67.8	57.8
9b	3.90	3.41	7.46	163.4	147.6	142.6	66.4	56.5
9c	4.01	3.74	7.80	164.9	148.4	144.0	66.3	56.4
9d	4.15	3.85	7.69	164.5	144.6	143.8	66.9	56.8

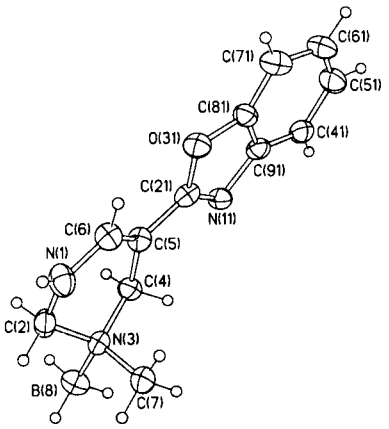


Figure 2. X-Ray crystallography of **9a**. (arbitary numbering system).

the HCl salts of tetrahydropyrimidinylbenzoxazoles **10** for the enhancement of stability. The spectral data was summarized in Table 4.

In summary, we have demonstrated a convenient synthesis of 1,2,3,4-tetrahydropyrimidin-5ylbenzoxazoles starting from 5-pyrimidinecarboxaldehyde and substituted *o*-aminophenols *via* oxidative hypervalent iodine cyclization, to form the methylpyrimidinium salts, and partial reduction thereafter.

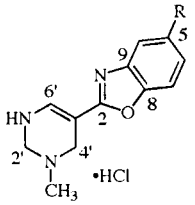
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Genesis II FTIR. Nuclear magnetic resonance spectra were measured on a Brucker AM-300 spectrometer. Mass spectra were determined on JEOL JMS-DX 303 Mass Spectrometer JEOL JMA-DA 5000 mass data system focusing high resolution mass spectrometer.

Single crystal X-ray diffractometry: The intensity data were collected at room temperature on a Siemens P4 four-circle X-ray diffractometer with graphite-monochrommated Mo Kα radiation (λ = 0.71073 Å). All calculations in the structural solution and refinement were performed using the Siemens SHELXTL crystallographic software package on a Silicon Graphics system. All the non-hydrogen atoms were refined anisotropically; all the hydrogen atoms fixed at the calculated positions with the isotripic thermal parameters were included in the final structure factor calculations.

Table 4

^{1}H NMR Data and ^{13}C NMR Data of Compound **10**



Compound	proton δ [ppm]			carbon δ [ppm]						
	2'-H	4'-H	6'-H	C-2	C-8	C-9	C-2'	C-4'	C-5'	C-6'
10a	4.88	4.44	8.35	164.4	149.6	147.3	62.6	50.1	84.5	133.2
10b	4.90	4.46	8.33	164.2	147.9	146.4	62.5	50.2	84.9	138.8
10c	4.26	4.15	7.73	163.9	148.3	143.6	60.5	49.0	87.4	138.2
10d	4.86	4.43	8.28	164.4	145.9	143.8	62.4	50.5	84.9	134.5

General Procedure for Preparation of 2-Pyrimidin-5-ylbenzoxazoles (**7**).

A mixture of 5-pyrimidinecarboxldehyde (**4**) (5.0 mmol) and *o*-hydroxyaniline (**5**) (5.0 mmol) in ethanol (100 ml) was stirred at room temperature for 1 hour. To the reaction mixture was added iodobenzene diacetate (7.5 mmol). After 30 minutes stirring, the solvent was removed under reduced pressure, the residue was diluted with ethyl acetate and then washed with aqueous $NaHCO_3$ solution. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate) to give the title compounds **7**.

2-Pyrimidin-5-ylbenzoxazole (**7a**).

This compound was obtained as a brown power, yield 25%, mp 164-166 °C; ir (potassium bromide) ν 3150 (CH), 1560, 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.53 (s, 2H, C4'-H, C6'-H), 9.37 (s, 1H, C2'-H), 7.84-7.41 (m, 4H, C4-H, C5-H, C6-H, C7-H); ^{13}C nmr (deuteriochloroform): δ 160.1 (C-2'), 158.0 (C-2), 155.4 (C-4', C-6'), 150.7 (C-8), 141,4 (C-9), 122.1 (C-5'), 126.3, 125.2, 120.5, 110.0 (C-4, C-5, C-6, C-7).

Anal. Calcd. for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 67.01; H, 3.27; N, 20.84.

5-Methyl-2-pyrimidin-5-ylbenzoxazole (**7b**).

This compound was obtained as yellow crystals, yield 15%, mp 161-162 °C; ir (potassium bromide) ν 3050 (CH), 1560, 1400 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.50 (s, 2H, C4'-H, C6'-H), 9.35 (s, 1H, C2'-H), 7.58 (s, 1H, C4-H), 7.50 (d, 1H, C7-H), 7.23 (d, 1H, C6-H), 2.50 (s, 3H, CH_3); ^{13}C nmr (deuteriochloroform): δ 159.9 (C-2'), 158.0 (C-2), 155.3 (C-4', C-6'), 148.9 (C-8), 141,6 (C-9), 135.2 (C-5), 122.2 (C-5'), 127.4, 120.3, 110.2 (C-4, C-6, C-7), 21.4 (CH_3).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.38; H, 4.12; N, 19.47.

5-Chloro-2-pyrimidin-5-ylbenzoxazole (**7c**).

This compound was obtained as yellow crystals, yield 30%, mp 202-204 °C; ir (potassium bromide) ν 3100 (CH), 1590, 1410 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.52 (s, 2H, C4'-H, C6'-H), 9.39 (s, 1H, C2'-H), 7.80 (d, 1H, C4-H, J = 2.0 Hz), 7.57 (d, 1H, C7-H, J = 8.7 Hz), 7.40 (dd, 1H, C6-H, J = 2.0 Hz, 8.7 Hz); ^{13}C nmr (deuteriochloroform): δ 160.8 (C-2'), 159.8 (C-2), 155.0 (C-4', C-6'), 149.7 (C-8), 143.0 (C-9), 131.2 (C-5), 122.1 (C-5'), 127.1, 120.9, 112.1 (C-4, C-6, C-7).

Anal. Calcd. for $C_{11}H_6ClN_3O$: C, 57.04; H, 2.61; N, 18.14. Found: C, 56.77; H, 2.77; N, 17.76.

5-Methoxy-2-pyrimidin-5-ylbenzoxazole (**7d**).

This compound was obtained as yellow crystals, yield 38 %, mp 165-166 °C; ir (potassium bromide) ν 3100 (CH), 1610, 1480 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.51 (s, 2H, C4'-H, C6'-H), 9.35 (s, 1H, C2'-H), 7.52 (d, 1H, C7-H, J = 8.9 Hz), 7.28 (d, 1H, C4-H, J = 2.4 Hz), 7.03 (dd, 1H, C6-H, J = 2.4 Hz, 8.9 Hz), 3.89 (s, 3H, OCH_3); ^{13}C nmr (deuteriochloroform): δ 160.0 (C-2'), 158.7 (C-2), 157.9 (C-5), 155.3 (C-4', C-6'), 145.4 (C-8), 142.4 (C-9), 122.2 (C-5'), 115.3, 111.1, 103.0 (C-4, C-6, C-7), 56.0 (OCH_3).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.44; H, 3.90; N, 18.32.

General Procedure for Preparation of Pyrimidium Salts (**8**).

Iodomethane Method.

2-(3-Methylpyrimidinium-5-yl)benzoxazole Iodide (**8a**).

To a stirred solution of (**7a**) (6.0 mmol) in acetone (30 ml) was added a solution of iodomethane (48.0 mmol) in acetone (10 ml), the mixture was stirred overnight at room temperature. The pricipitate was filtered, the filter cake was washed with acetone, then dried under reduced pressure to give **8a**, yield 83%, mp 223-225 °C; ir (potassium bromide) ν 3150 (CH), 1690, 1560, 1010 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.76 (s, 1H, C6'-H), 7.93 (s, 1H, C4'-H), 7.75-7.40 (m, 4H, C4-H, C5-H, C6-H, C7-H), 6.36 (s, 1H, C2'-H), 3.65 (s, 3H, NCH_3); ^{13}C nmr (deuteriomethanol): δ 160.1 (C-2), 152.1 (C-8), 151.9(C-6'), 142.8 (C-9), 128.9 (C-4'), 127.8, 127.7, 126.6, 121.3, 112.0 (C-5', C-4, C-5, C-6, C-7), 84.3 (C-2'), 41.4 (NCH_3).

Anal. Calcd. for $C_{12}H_{10}IN_3O$: C, 42.50; H, 2.97; N, 12.39. Found: C, 42.04; H, 3.03; N, 12.28.

Methyl Trifluoromethanesulfonate Method.

To a cooled (-30 °C) and stirred solution of methyl trifluoromethanesulfonate (1 mmol) in methylene chloride (15 ml) was added (**7b-7d**) (1 mmol) under N_2. The reaction mixture was slowly warmed to room temperature and stirring was continued for 4 hours. The precipitate was filtered to give **8b-8d**.

5-Methyl-2-(3-methylpyrimidinium-5-yl)benzoxazole Triflate (**8b**).

This compound was obtained as white power, yield 73%, mp 256-258 °C; ir (potassium bromide) ν 3070 (CH), 1260, 1040 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.74 (s, 1H, C6'-H), 7.91 (s, 1H, C4'-H), 7.54 (s, 1H, C4-H), 7.52 (d, 1H, C7-H), 7.28 (d, 1H, C6-H), 6.36 (s, 1H, C2'-H), 3.67 (s, 3H, NCH_3), 2.50 (s, 3H, CH_3); ^{13}C nmr (deuteriomethanol): δ 160.2 (C-2), 150.3 (C-8), 152.2 (C-6'), 143.1 (C-9), 136.9 (C-5), 129.0 (C-4'), 129.1, 128.7, 121.2, 111.5 (C-5', C-4, C-6, C-7), 84.3 (C-2'), 41.3 (NCH_3), 21.8 (CH_3).

Anal. Calcd. For $C_{14}H_{12}F_3N_3O_4S$: C, 44.80; H, 3.22; N, 11.20; S, 8.54. Found: C, 44.78; H, 3.33; N, 11.04; S, 8.65.

5-Chloro-2-(3-methylpyrimidinium-5-yl)benzoxazole Triflate (**8c**).

This compound was obtained as yellow power, yield 96%, mp 270 °C ir (potassium bromide) ν 3070 (CH), 1260, 1160, 1035 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.71 (s, 1H, C6'-H), 7.93 (s, 1H, C4'-H), 7.72 (d, 1H, C4-H, J = 2.0 Hz), 7.62 (d, 1H, C7-H, J = 8.0 Hz), 7.42 (dd, 1H, C6-H, J = 2.0 Hz, 8.0 Hz), 6.32 (s, 1H, C2'-H), 3.64 (s, 3H, N CH_3); ^{13}C nmr (deuteriomethanol): δ 161.6 (C-2), 152.2 (C-6'), 150.7 (C-8), 144.1 (C-9), 131.9 (C-5), 129.5 (C-4'), 127,9, 127.8, 121.1, 113.1 (C-5', C-4, C-6, C-7), 84.2 (C-2'), 41.2 (NCH_3).

Anal. Calcd. For $C_{13}H_9ClF_3N_3O_4S$: C, 39.46; H, 2.29; N, 10.62; S, 8.54. Found: C, 39.88; H, 2.33; N, 10.59, S, 8.28.

5-Methoxy-2-(3-methylpyrimidinium-5-yl)benzoxazole Triflate (**8d**).

This compound was obtained as white power, yield 59%, mp 243-245 °C; ir (potassium bromide) ν 3150 (CH), 1600, 1280, 1260 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.72 (s, 1H, C6'-H), 7.89 (s, 1H, C4'-H), 7.54 (d, 1H, C7-H, J = 8.9 Hz), 7.25 (d, 1H, C4-H, J = 2.4 Hz), 7.04 (dd, 1H, C6-H, J = 2.4 Hz, 8.9 Hz), 6.35

(s, 1H, C2'-H), 3.87 (s, 3H, OCH_3), 3.65 (s, 3H, NCH_3); ^{13}C nmr (deuteriomethanol): δ 160.8 (C-5), 159.8 (C-2), 152.2 (C-6'), 146.7 (C-8), 143.8 (C-9), 128.6 (C-4'), 116.4, 112.3, 107.8, 104.2 (C-5', C-4, C-6, C-7), 84.4 (C-2'), 56.9 (CH_3), 41.2 (NCH_3); $C_{12}H_9N_3O_2(-CF_3SO_3CH_3)$(227.0695), MS: m/z = 227.0698.

General Procedure for Preparation of Borane Complexes of 1,2,3,4-Tetrahydropyrimidinbenzoxazoles (**9**).

To a cooled (-20 °C) and stirred suspension of (**8**) (1.0 mmol) in tetrahydrofuran (30 ml) was added portionwise sodium borohydride (1.5 mmol). After stirring for 3 hours at room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with aqueous $NaHCO_3$ solution. The organic layer was washed with brine, dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was recrystallized from methanol to give the adduct **9**.

2-(3-Methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Trihydroborane Complex (**9a**).

This compound was obtained as white crystals, yield 37%, mp 151-152 °C; ir (potassium bromide) ν 3360 (CH), 2380 (borane), 1640, 1510 cm^{-1}; ^1H nmr (deuterioacetone): δ 7.72 (brs, 1H, C6'-H), 7.53-7.21 (m, 4H, arom. H), 6.90 (brs, 1H, NH), 4.16 (s, C2'-H), 3.86 (ABq, 2H, C4'-H), 2.62 (s, 3H, NCH_3); ^{13}C nmr (deuterioacetone): δ 164.3 (C-2), 151.1 (C-8), 143.9 (C-9), 137.1, 137.0 (C-5', C-6'), 125.2, 124.7, 119.5, 110.7 (C-4, C-5, C-6, C-7), 67.8 (C-2'), 57.8 (C-4'), 46.1 (NCH_3).

Anal. Calcd. for $C_{12}H_{16}BN_3O$: C, 62.92; H, 7.04; N, 18.34. Found: C, 63.18; H, 6.82; N, 18.23.

Crystal Data and Structure Refinement for **9a**.

Empirical formula	$C_{12}H_{16}BN_3O$
Formula weight	229.09
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	a = 20.009(5) Å α = 90°.
	b = 5.5681(17) Å β = 104.53(2)°.
	c = 11.733(4) Å γ = 90°
Volume, Z	1265.4(7) $Å^3$, 4
Calculated density	1.203 Mg/m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	488
Crystal size	0.2 x 0.2 x 0.2 mm
θ Range for data collection	2.10 to 25.02°
Limiting indices	$-23 \le h \le 1, -6 \le k \le 1, -13 \le l \le 13$
Reflections collected	1493
Independent reflections	1221 [R_{int} = 0.0768]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1221 / 2 / 143
Goodness-of-fit on F^2	1.046
Final R indices [I>2σ(I)]	R1 = 0.0636, wR2 = 0.1459
R indices (all data)	R1 = 0.1052, wR2 = 0.1701
Absolute structure parameter	0(4)
Extinction coefficient	0.0051(18)
Largest diff. peak and hole	0.244 and -0.194 $e.A^{-3}$

5-Methyl-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Trihydroborane Complex (**9b**).

This compound was obtained as yellow crystals, yield 38%, mp 161-163 °C; ir (potassium bromide) ν 3360 (CH), 2380 (borane), 1635, 1160 cm^{-1}; ^1H nmr (deuteriomethanol + deuteriodimethyl sulfoxide): δ 7.46 (s, 1H, C6'-H), 7.17-6.85 (m, 3H, arom. H), 3.90-3.41 (m, 4H, C2'-H, C4'-H), 2.42 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 163.4 (C-2), 147.6 (C-8), 142.6 (C-9), 136.6 (C-6'), 133.5 (C-5'), 124.4, 118.3, 109.3, 89.3 (C-4, C-5, C-6, C-7), 66.4 (C-2'), 56.5 (C-4'), 45.4 (NCH_3), 21.4 (CH_3).

Anal. Calcd. for $C_{13}H_{18}BClN_3O$: C, 64.23; H, 7.46; N, 17.28. Found: C, 63.98; H, 7.73; N, 17.10.

5-Chloro-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Trihydroborane Complex (**9c**).

This compound was obtained as white crystals, yield 27%, mp 158-160 °C ir (potassium bromide) ν 3360 (CH), 2380 (borane), 1630, 1510 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 7.80 (brs, 1H, C6'-H), 7.79-7.21 (m, 3H, arom. H), 4.01 (s, C2'-H), 3.74 (ABq, 2H, C4'-H), 2.47 (s, 3H, NCH_3); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 164.9 (C-2), 148.4 (C-8), 144.0 (C-9), 137.9 (C-6'), 128.5 (C-5'), 123.2, 117.8, 111.0, 88.4 (C-4, C-5, C-6, C-7), 66.3 (C-2'), 56.3 (C-4'), 45.5 (NCH_3).

Anal. Calcd. for $C_{12}H_{15}BClN_3O$: C, 54.69; H, 5.74; N, 15.95. Found: C, 54.66; H, 6.12; N, 15.63.

5-Methoxy-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Trihydroborane Complex (**9d**).

This compound was obtained as white crystals, yield 53%, mp 154-155 °C; ir (potassium bromide) ν 3360 (CH), 2375 (borane), 1640, 1150 cm^{-1}; ^1H nmr (deuterioacetone): δ 7.69 (d, 1H, C6'-H, J = 3.7 Hz), 7.35 (d, 1H, C7-H, J = 8.8 Hz), 7.06 (d, 1H, C4-H, J = 2.5 Hz), 6.88 (brs, 1H, NH), 6.80 (dd, 1H, C6-H, J = 2.5 Hz, 8.8 Hz), 4.15 (s, C2'-H), 3.85 (ABq, 2H, C4'-H), 3.83 (s, 3H, OCH_3), 2.62 (s, 3H, NCH_3); ^{13}C nmr (deuterioacetone): δ 164.5 (C-2), 157.5 (C-5), 144.6 (C-8), 143.8 (C-9), 135.9 (C-6'), 111.1, 109.7, 102.5 (C-4, C-6, C-7), 91.3 (C-5'), 66.9 (C-2'), 56.8 (C-4'), 55.5 (OCH_3), 45.5 (NCH_3); $C_{13}H_{18}BN_3O_2$ (258.1528), MS: m/z = 258.1525.

General Procedure for Preparation of 2-(3-Methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazoles Hydrochlorides (**10**).

To a cooled (-20 °C) and stirred suspension of (**8**) (1.0 mmol) in 30 ml methanol, 1.5 mmol $NaBH_4$ was added portionwise. After 3 hours stirring, was added 1.7 mmol of trifluoroacetic acid to the reaction mixture at the same temperature. The reaction was allowed to come to room temperature, stirring was continued for 3 hours then water was added. After 30 minutes stirring, the reaction mixture was neutralized with 50% NaOH. extracted with methylene chloride, the organic layer was washed with $NaHCO_3$, dried over anhydrous Na_2SO_4, then concentrated. The residue was subjected to column chromatography on silica gel (hexane:ethyl acetate) to give the 2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazoles. This was dissolved in methanol then treated with HCl (gas) in methanol to give fine precipitate that was collected by filtration then dried under vacuum to give the title compounds **10**.

2-(3-Methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Hydrochloride (**10a**).

This compound was obtained as white power, yield 18%, mp 154-156 °C; ir (potassium bromide) ν 3300 (CH), 1590 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.35 (s, 1H, C6'-H), 7.73-7.47 (m, 4H, arom. H), 4.88 (s, 2H, C2'-H), 4.44(s, 2H, C4'-H), 3.15 (s, 3H, NCH_3); ^{13}C nmr (deuteriomethanol): δ 164.4 (C-2), 149.6 (C-8), 147.3 (C-9), 133.2 (C-6'), 128.3, 127.7, 115.7, 112.8 (C-4, C-5, C-6, C-7), 84.5 (C-5'), 62.6 (C-2'), 50.1 (C-4'), 40.9 (NCH_3); $C_{12}H_{13}N_3O$(-HCl)(215.1059), MS: m/z = 215.1058.

5-Methyl-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Hydrochloride (**10b**).

This compound was obtained as white power, yield 19%, mp 173-175 °C; ir (potassium bromide) ν 3390 (CH), 1610, 1350 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.33 (s, 1H, C6'-H), 7.61 (d, 1H, C7-H), 7.48 (s, 1H, C4-H), 7.33 (d, 1H, C6-H), 4.90 (s, 2H, C2'-H), 4.46(s, 2H, C4'-H), 3.18 (s, 3H, NCH_3), 2.53 (s, 3H, CH_3); ^{13}C nmr (deuteriomethanol): δ 164.2 (C-2), 147.9 (C-8), 146.4 (C-9), 138.8 (C-6'), 133.6 (C-5), 128.4, 115.7, 112.1 (C-4, C-6, C-7), 84.9 (C-5'), 62.5 (C-2'), 50.2 (C-4'), 40.7 (NCH_3), 21.7 (CH_3); $C_{13}H_{15}N_3O$(-HCl)(229.1215), MS: m/z = 229.1215.

5-Chloro-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Hydrochloride (**10c**).

This compound was obtained as white power, yield 12%, mp 184-186 °C; ir (potassium bromide) ν 3020 (CH), 1590 cm^{-1}; ^1H nmr (deuteriodimethyl sulfoxide): δ 8.17 (brs, 1H, NH), 7.73 (d, 1H, C6'-H, J = 3.3 Hz), 7.62 (d, 1H, C4-H, J = 2.0 Hz), 7.60 (d, 1H, C7-H, J = 8.6 Hz), 7.27 (dd, 1H, C6-H, J = 2.0 Hz, 8.6 Hz), 4.26 (brs, 2H, C2'-H), 4.15 (ABq, 2H, C4'-H), 2.88 (s, 3H, NCH_3); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 163.9 (C-2), 148.3 (C-8), 143.6 (C-9), 138.2 (C-6'), 128.6 (C-5), 123.5, 117.8, 111.2 (C-4, C-6, C-7), 87.4 (C-5'), 60.5 (C-2'), 49.0 (C-4'), 38.8 (NCH_3); $C_{12}H_{12}ClN_3O$(-HCl)(249.0669), MS: m/z = 249.0671.

5-Methoxy-2-(3-methyl-1,2,3,4-tetrahydropyrimidin-5-yl)benzoxazole Hydrochloride (**10d**).

This compound was obtained as white power, yield 33%, mp 162-164 °C; ir (potassium bromide) ν 3430 (CH), 1610, 1200 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.28 (s, 1H, C6'-H), 7.59 (d, 1H, C7-H, J = 9.0 Hz), 7.15 (d, 1H, C4-H, J = 2.5 Hz), 7.04 (dd, 1H, C6-H, J = 2.5 Hz, 9.0 Hz), 4.86 (s, 2H, C2'-H), 4.43 (s, 2H, C4'-H), 3.89 (s, 3H, OCH_3), 3.15 (s, 3H, NCH_3); ^{13}C nmr (deuteriomethanol): δ 164.4 (C-2), 160.4 (C-5), 145.9 (C-8), 143.8 (C-9), 134.5 (C-6'), 114.6, 112.8, 99.7 (C-4, C-6, C-7), 84.9 (C-5'), 62.4 (C-2'), 56.8 (OCH_3), 50.5 (C-4'), 40.5 (NCH_3); $C_{13}H_{15}N_3O_2$(-HCl)(245.1164), MS: m/z = 245.1169.

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