Pergamon

Tetrahedron, Vol. 53, No. 20, pp. 6959-6970, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00395-5

Electrophilic Substitution of Imidazo[2,1-*b*]oxazoles

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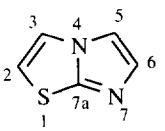
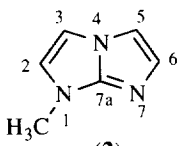
Abstract: The electrophilic substitutions of *di* and *tri* substituted imidazo[2,1-*b*]oxazoles were studied. Mannich, bromination, nitration, and the Vilsmeier-Haack formylation reactions occur at position-5 of this ring system to give a range of products in high yield. © 1997 Elsevier Science Ltd.

Investigations conducted earlier by Paolini and Lendvay,[1] and later by Meakins and co-workers[2] have revealed that the 5-position of the imidazo[2,1-*b*]thiazole (**1**) ring is the most susceptible site for electrophilic attack. A similar study by Miller and Bamburg[3] on analogous imidazo[1,2-*a*]imidazoles (**2**) has also shown that this ring is similarly prone to electrophilic attack at position-5.



(**1**)



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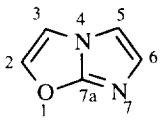
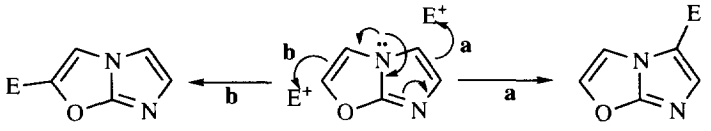


(**3**)

It was, therefore, reasonable to envision a similar pattern of reactivity for analogous π-excessive imidazo[2,1-*b*]oxazole (**3**) systems despite a significant possible deactivation incurred by the more inductively electron withdrawing oxygen atom at position-1. This reactivity can be rationalised through a mesomeric shift of the bridging nitrogen's lone pair of electrons towards the π-electrons of the heteroaromatic ring system. Indeed, these electron interactions may proceed in at least two ways. The first way may constitute an interaction with the π-electrons of the imidazole part of the molecule, which consequently activates position-

5. This electrophilic substitution at position-5 could be a three step mechanism perhaps involving also the nitrogen at position-7 before finally rearranging to **4**. Alternatively, reaction could also occur at position-2 as a result of the electron interactions with the oxazole nucleus of the molecule to give **5**.



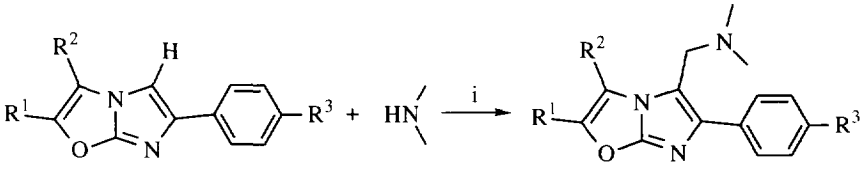
(**5**) (**3**) (**4**)

However, owing to the lack of synthetic access to these imidazo[2,1-*b*]oxazoles, to date there has been no report that deals with their chemistry. Herein, following our first efficient preparation of these fused heterocycles,[4] we report their electrophilic Mannich, bromination, nitration and the Vilsmeier-Haack substitution reactions, which were extended to the preparation of some novel compounds of potential biological interest.

Results and Discussion.

Mannich Reactions.

Imidazo[2,1-*b*]oxazoles (**6**) condense with formaldehyde and secondary amines under acidic conditions, in a similar procedure to the one used by Sakai[5] and co-workers with imidazo[2,1-*b*]benzothiazoles, to give the corresponding position-5 (in **6a**, **6b**) and position-3 (in **6c**, **6d**)[8] aminomethylated products **7a-h** as shown in scheme 1. These products were obtained as stable crystalline solids. The general scope of this reaction has been examined by preparing a range of derivatives. The identities of R^1, R^2 and R^3 along with the yields of the products are summarised in Table 1.



(**6a-d**) (**7a-h**)

Scheme 1. *Reagents and Conditions:* i, 1. HCHO/ CH_3COOH, CH_3CH_2OH/ 78 °C , 4 - 6 hrs 2. NaOH/ 5 °C

It was noted that the yield of product **7h**, when *N*,*N*-diethylamine was used as the amine component, was significantly lower than the other products. This is presumably a result of the relative instability of this compound which was observed whilst it was being purified. The site of this aminomethylation was unequivocally adduced from an analysis of their ^1H and ^{13}C nmr spectra. The ^1H nmr showed the absence of a sharp singlet signal attributed to H-5 (in **6a** and **6b**) or H-3 (in **6c** and **6d**),[8] usually appearing around 7.02-

7.25 ppm. Likewise, the ^{13}C nmr spectra showed the disappearance of the resonance corresponding to unsubstituted C-5 (in **6a** and **6b**) and C-3 (in **6c** and **6d**) around 101-105 ppm, which was easily identified with a DEPT experiment. This showed instead additional quaternary signals which appeared between 114.0-117.0 ppm and were assigned to C-5 (in **7a-c**) or C-3 (in **7d-h**).

Table 1. Products of Mannich reactions of imidazo[2,1-*b*]oxazoles.

Starting Compound **6**	R^1	R^2	R^3	Amine / HN\	Product **7**	Yield %
a	H	CH_3	Cl	piperidino	**a**	96
	H	CH_3	Cl	morpholino	**b**	93
b	CH_3	CH_3	Cl	piperidino	**c**	86
c	-$(CH_2)_4$-		Cl	piperidino	**d**	89
	-$(CH_2)_4$-		Cl	morpholino	**e**	95
d	-$(CH_2)_4$-		Br	piperidino	**f**	98
	-$(CH_2)_4$-		Br	morpholino	**g**	95
	-$(CH_2)_4$-		Br	N,N-diethylamino	**h**	55

Under electron impact (70 eV), this class of compounds (**7a-h**) exhibited the general mass fragmentation pattern illustrated in Figure 2. Fragment **8** was often the base peak presumably due to strong stabilisation rendered through resonance.

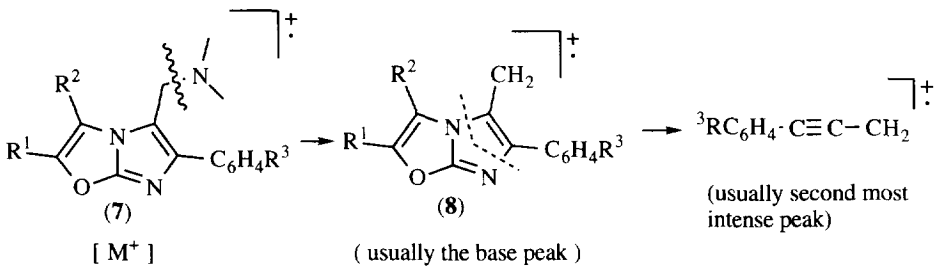
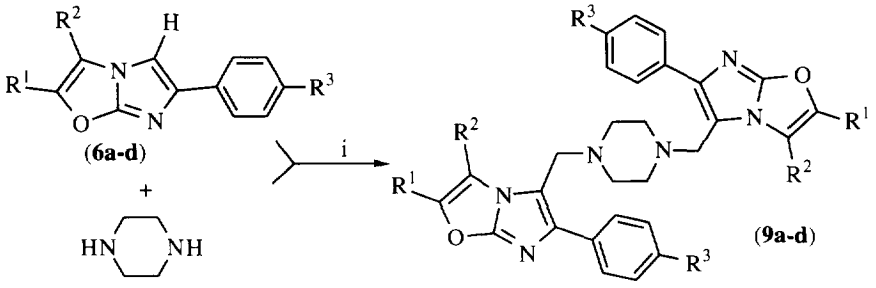


Figure 2

When **6a** was reacted with excess aminomethylating agents under reflux for several hours, the only products formed were the corresponding derivatives of **7**.

Our ongoing search for new biologically active molecules led us to design and prepare novel compounds for biological evaluation. Compounds possessing rigid structural features sometimes show enhanced biological

activity, particularly in their selectivity.[6] In the light of this property, we desired to prepare compounds incorporating two potentially active pharmacophore units within the same molecule joined by a piperazine spacer. This was achieved through a double Mannich reaction with piperazine as a secondary amine component. Using two equivalents of imidazo[2,1-*b*]oxazoles and formaldehyde, compounds **9a,b** were prepared in good yields (scheme 2). Compounds **9c,d**, which have a more rigid structural feature, were also obtained in the same manner. The structures of these products were unequivocally confirmed by their spectral analysis. The high degree of symmetry exhibited in the ^{1}H and ^{13}C nmr spectra of compounds **9a-d**, indicates that these molecules are free of steric interactions which would result in restricted rotation.

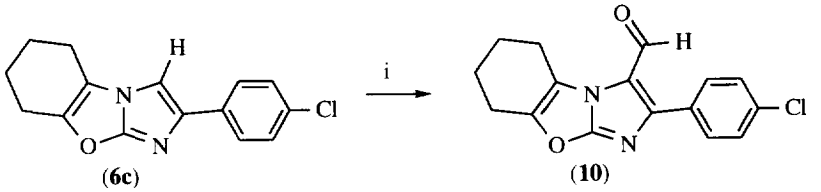


Scheme 2. *Reagents and Conditions:* i, 1. HCHO/CH_3COOH, CH_3CH_2OH/ 78 °C , 2 - 3 hrs 2. NaOH/ 5 °C

9	R^1	R^2	R^3	Yield
a	H	CH_3	Cl	57
b	CH_3	CH_3	Cl	74
c		-$(CH_2)_4$-	Cl	74
d		-$(CH_2)_4$-	Br	80

Miscellaneous Reactions.

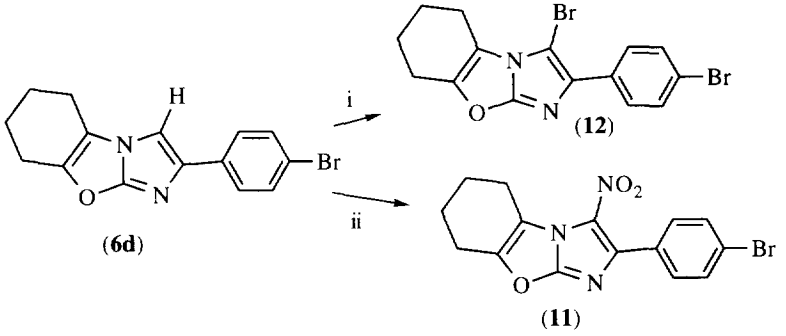
Compound **6c** was formylated under Vilsmeier-Haack[7] conditions to give a 3-carboxaldehyde substituted imidazo[2,1-*b*]oxazole (**10**) in good yield (scheme 3).



Scheme 3. *Reagents and Conditions*: i, 1. $POCl_3$/DMF, 60 °C, 2 hr; 2. NaOH/ 5 °C

The site of this formylation was clearly established by the usual ^{1}H and ^{13}C nmr analysis. The collapse of the H-3 resonance which appeared at 7.11 ppm in **6c**, and the appearance of a signal at 9.69 ppm, attributed to the aldehyde proton, was clear evidence for this substitution. Also, the ^{13}C nmr shows the disappearance of the unsubstituted C-3 signal at 101.1 ppm in **6c** and the appearance of a carbonyl resonance at 177.4 ppm as anticipated for the CHO group in **10**.

Compound **6d** was subjected to nitration in a mixture of nitric acid (70% w/w) and sulfuric acid at 0 ^{0}C, scheme 4. The product **11** was isolated in low yield, due to extensive decomposition. In addition, the high instability of **11** at ambient temperature, made purification difficult under a variety of techniques. Thus, it was impossible to isolate an analytically pure sample for satisfactory correct elemental analysis.



Scheme 4. *Reagents and Conditions:* i, Br_2/CH_2Cl_2, 0 - 25 ^{0}C, 15 min.; ii, 1. HNO_3/H_2SO_4, 0 ^{0}C, 1 hr. 2. NaOH/ 5 ^{0}C

Bromination of compound **6d** was carried out in dichloromethane at room temperature to give product **12** in good yield, scheme 4. The site of this substitution was confirmed by ^{1}H and ^{13}C nmr analysis. In the ^{13}C nmr spectrum of **12**, the appearance of an additional quaternary signal, evidenced by a DEPT experiment, was consistent with the substitution of the C-3 atom which was originally a C-H positive resonance of compound **6d** at 101.2 ppm in the DEPT spectra. The presence of an additional bromine atom was also evident from the mass spectrum, which shows the $M^{+\cdot}$, $[M+2]^{+\cdot}$ and $[M+4]^{+\cdot}$ intensity ratio (1:2:1) according to the expected isotope distribution.

The present study clearly demonstrates that imidazo[2,1-*b*]oxazoles are quite susceptible to electrophilic attack most preferentially at position-5. These reactions thus provide an entry to the preparation of additional derivatives.

EXPERIMENTAL

Melting points were recorded on a Leitz hot stage microscope and are uncorrected. Elemental analysis were carried out by the Microanalytical Laboratory, University of New South Wales. Infrared spectra were obtained from a Perkin Elmer 298 Infrared Spectrophotometer and mass spectra from an AEI MS 12 mass spectrometer at 70 eV. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker CXP 300 (300 MHz) or a Bruker

AM 500 (500 MHz) spectrometer. ^{1}H nmr data are reported as follows: chemical shift measured in parts per million (ppm) downfield from TMS (δ), multiplicity, observed coupling constant (*J*) in Hertz (Hz), proton count. Multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C nmr chemical shifts (δ) are reported in ppm downfield from TMS and identifiable carbons are given. Column chromatography was carried out using Merck silica gel 7736 60H, whilst preparative thin layer chromatography (ptlc) was performed using Merk silica gel 7730 60 GF_{254}. Starting materials were analytical grade reagents and were checked for purity before use and all solvents were distilled before use. All imdazo[2,1-*b*]oxazoles (**6a-d**) were made according to our own procedure as described in the literature.[4]

6-(4'-Chlorophenyl)-3-methyl-5-(N-piperidinomethyl)imidazo[2,1-*b*]oxazole (7a).

To a stirred mixture of 6-(4'-chlorophenyl)-3-methylimidazo[2,1-*b*]oxazole (**6a**) (500 mg, 2.15 mmol), piperidine (183 mg, 2.15 mmol) and glacial acetic acid (1 ml) in absolute ethanol (10 ml) was added formaldehyde solution (0.30 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 4.5 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold viscous residue was triturated with a small amount of water and made basic to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was filtered off, washed with water and recrystallised from methanol/chloroform (4:1, v/v). This gave **7a** as colourless crystals (680 mg, 96%) mp 109-110 ^{0}C; ir (potassium bromide): 735, 785, 825, 985, 1040, 1090, 1400, 1580, 3100 cm^{-1}; ms: m/z (%): 331 (M+2, 4), 329 (M$^+$, 10), 247 (28), 245 (M-84, 100), 210 (245-Cl, 14), 151 (17), 149 (245-96, $BrPhCCCH_2$, 49), 141 (14), 114 (15), 55 (13), 42 (18); ^{1}H NMR ($CDCl_3$): δ 1.40-1.49 (m, 6H, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.35 (b, 4H, $C\underline{H}_2NC\underline{H}_2$), 2.44 (s, 3H, CH_3-3), 3.59 (s, 2H, NCH_2C-5), 7.00 (s, 1H, H-2), 7.32 (d, *J* = 8.3 Hz, 2H, aromatic H), 7.63 (d, *J* = 8.3 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 8.8 (CH_3-3), 24.2 ($NCH_2CH_2\underline{C}H_2$), 25.9 ($NCH_2\underline{C}H_2$), 51.9 ($N\underline{C}H_2$C-5), 53.8 ($N\underline{C}H_2CH_2$), 116.3 (C-5), 122.6 (C-6), 128.1 (C-3', aromatic C), 129.2 (C-2', aromatic C), 132.4 (C-4', aromatic C), 132.9 (C-2), 133.4 (C-1', aromatic C), 140.6 (C-3), 155.1 (C-7a). Anal. Calcd. for $C_{18}H_{20}N_3OCl$: C, 65.55; H, 6.11; N, 12.74. Found: C, 65.15; H, 6.46; N, 12.39.

6-(4'-Chlorophenyl)-3-methyl-5-(N-morpholinomethyl)imidazo[2,1-*b*]oxazole (7b).

To a stirred mixture of 6-(4'-chlorophenyl)-3-methylimidazo[2,1-*b*]oxazole (**6a**) (500 mg, 2.15 mmol), morpholine (190 mg, 2.15 mmol) and glacial acetic acid (1 ml) in absolute ethanol (10 ml) was added formaldehyde solution (0.30 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 3 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold viscous residue was triturated with a small amount of water and made basic to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was filtered off, washed with water, and recrystallised from aqueous methanol. This gave **7b** as pale yellowish crystals (660 mg, 93%) mp 133-134 ^{0}C; ir (potassium bromide): 705, 830, 1000, 1085, 1115, 1410, 1580 cm^{-1}; ms: m/z (%): 333 (M+2, 2), 331 (M$^+$, 5), 247 (29), 245 (M-86, 100), 210 (245-Cl, 13), 151 (12), 149 ($ClPhCCCH_2$, 36), 141 (10), 114 (13), 56 (11); ^{1}H NMR ($CDCl_3$): δ 2.45 (t, *J* = 4.5 Hz, 4H, $NC\underline{H}_2C\underline{H}_2O$), 2.49 (d, *J* = 1.4 Hz, 3H, CH_3-3), 3.66 (t, *J* = 4.6 Hz, 4H, $NCH_2C\underline{H}_2O$), 3.71 (s, 2H, NCH_2C-5), 7.07 (d, *J* = 1.4 Hz, 1H, H-2), 7.36 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.62 (d, *J* = 8.5 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 9.1 (CH_3-3), 51.7 ($N\underline{C}H_2$C-5), 53.0 ($N\underline{C}H_2CH_2O$), 67.0 ($NCH_2\underline{C}H_2O$), 115.0 (C-5), 122.5 (C-6), 128.4 (C-3', aromatic C), 129.3 (C-2',

aromatic C), 132.9 (C-4', aromatic C), 133.2 (C-2), 141.5 (C-3), 155.4 (C-7a). Anal. Calcd. for $C_{17}H_{18}N_3O_2Cl$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.41; H, 5.72; N, 12.50.

6-(4'-Chlorophenyl)-2,3-dimethyl-5-(N-piperidinomethyl)imidazo[2,1-*b*]oxazole (7c).

To a stirred mixture of 6-(4'-chlorophenyl)-2,3-dimethylimidazo[2,1-*b*]oxazole (**6b**) (1.0 g, 4.05 mmol), piperidine (345 mg, 4.05 mmol) and glacial acetic acid (1.5 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.50 ml of 40% diluted with 10 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 6 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold brown residue was triturated with water and made basic to *p*H 9-10 with sodium hydroxide solution. The precipitated solid was filtered off, washed with water, and recrystallised from aqueous methanol. This gave **7c** as colourless needles (1.20 g, 86%) mp 164-165 ^{0}C; ir (potassium bromide): 730, 845, 1090, 1415, 1590 cm^{-1}; ms: m/z (%): 345 (M+2, 12), 343 (M^+, 29), 306 (7), 304 (21), 261 (33), 259 (M-84, 100), 224 (259-Cl, 14), 151 (12), 149 ($ClPhCCCH_2$, 36), 98 (13), 55 (15), 43 (20); ^{1}H NMR ($CDCl_3$): δ 1.42-1.54 (m, 6H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.28 (s, 3H, CH_3-3), 2.29-2.38 (m, 4H, $NC\underline{H}_2CH_2$), 2.42 (s, 3H, CH_3-2), 3.61 (s, 2H, NCH_2C-5), 7.33 (d, J = 8.6 Hz, 2H, aromatic H), 7.64 (d, J = 8.6 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 8.5 (CH_3-3), 10.7 (CH_3-2), 24.4 ($NCH_2CH_2\underline{C}H_2$), 26.1 ($NCH_2\underline{C}H_2$), 52.1 ($N\underline{C}H_2$C-5), 53.9 ($N\underline{C}H_2CH_2$), 116.1 (C-5), 116.7 (C-6), 128.3 (C-3', aromatic C), 129.3 (C-2', aromatic C), 132.3 (C-4', aromatic C), 133.8 (C-1', aromatic C), 139.8 (C-2), 141.9 (C-3), 154.2 (C-7a). Anal. Calcd. for $C_{19}H_{22}N_3OCl$: C, 66.37; H, 6.45; N, 12.21. Found: C, 66.47; H, 6.56; N, 11.70.

2-(4'-Chlorophenyl)-3-(N-piperidinomethyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (7d).

To a stirred mixture of 2-(4'-chlorophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6c**) (0.50 g, 1.83 mmol) and glacial acetic acid (1 ml) in absolute ethanol (10 ml) was added formaldehyde solution (0.25 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 3 hrs. The solvent was removed by evaporation in vacuo and the ice cold brownish residue was triturated with a small amount of water and made basic to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was filtered off, washed with water and dried *in vacuo*. This gave **7d** as a colourless solid (600 mg, 89%). It was recrystallised from aqueous methanol and had mp 146-147 ^{0}C; ir (potassium bromide): 725, 790, 840, 1090, 1130, 1380, 1420, 1580 cm^{-1}; ms: m/z (%): 371 (M+2, 6), 369 (M^+, 15), 287 (34), 285 (M-84, 100), 250 (285-Cl, 12), 151 (12), 149 ($ClPhCCCH_2$, 33), 114 (8), 97 (9), 77 (11), 67 (12), 60 (16), 43 (25); ^{1}H NMR ($CDCl_3$): δ 1.44-1.57 (m, 6H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.85-1.91 (m, 4H, H-6 and H-7), 2.38 (b, 4H, $NC\underline{H}_2CH_2$), 2.66 (b, 2H, H-5), 2.89 (b, 2H, H-8), 3.59 (s, 2H, NCH_2C-3), 7.35 (d, J = 8.5 Hz, 2H, aromatic H), 7.67 (d, J = 8.5 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.1, 22.2, 24.3, 26.1, one methylene signal obscured, 52.5 ($N\underline{C}H_2$C-3), 54.1 ($N\underline{C}H_2CH_2$), 115.9 (C-3), 119.2 (C-2), 128.3 (C-3', aromatic C), 129.2 (C-2', aromatic C), 132.3 (C-4', aromatic C), 133.8 (C-1', aromatic C), 139.2 (C-8a), 145.2 (C-4a), 154.4 (C-9a). Anal. Calcd. for $C_{21}H_{24}N_3OCl$: C, 68.19; H, 6.54; N, 11.36. Found: C, 67.66; H, 6.86; N, 11.14.

2-(4'-Chlorophenyl)-3-(N-morpholinomethyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (7e).

To a stirred mixture of 2-(4'-chlorophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6c**) (500 mg, 1.83 mmol), morpholine (160 mg, 1.84 mmol) and glacial acetic acid (1 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.25 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 3 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold brownish residue was triturated with a small amount of water followed by basification to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was collected by filtration and washed with water. This gave **7e** as an off-white solid (650 mg, 95%) mp 153-154 ^{0}C; ir (potassium bromide): 725, 800, 830, 860, 915, 1005, 1110, 1135, 1260, 1290, 1375, 1420, 1570 cm^{-1}; ms: m/z (%): 371 (M^+, 5), 287 (31), 285 (M-86, 100), 250 (285-Cl, 13), 151 (12), 149 ($ClPhCCCH_2$, 31), 114 (8), 77 (11), 67 (11), 56 (14); ^{1}H NMR ($CDCl_3$): δ 1.89-1.91 (b, 4H, H-6 and H-7), 2.44-2.47 (b, 4H, NCH_2CH_2O), 2.66-2.67 (b, 2H, H-5), 2.83 (b, 2H, H-8), 3.64-3.65 (b, 4H, NCH_2CH_2O), 3.67 (s, 2H, NCH_2C-3), 7.33 (d, J = 8.3 Hz, 2H, aromatic H), 7.65 (d, J = 8.3 Hz, 2H aromatic H); ^{13}C NMR ($CDCl_3$): δ 20.8, 22.1, 22.3, 52.1 (NCH_2C-3), 53.1 NCH_2CH_2O), 66.9 (NCH_2CH_2O), 114.6 (C-3), 119.0 (C-2), 128.3 (C-3', aromatic C), 129.1 (C-2', aromatic C), 132.4 (C-4', aromatic C), 133.5 (C-1', aromatic C), 139.8 (C-8a), 145.4 (C-4a), 154.4 (C-9a). Anal. Calcd. for $C_{20}H_{22}N_3O_3Cl$: C, 64.60; H, 5.96; N, 11.30. Found: C, 64.34; H, 6.06; N, 11.08.

2-(4'-Bromophenyl)-3-(N-piperidinomethyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (7f)

To a stirred mixture of 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (500 mg, 1.58 mmol), piperidine (140 mg, 1.64 mmol) and glacial acetic acid (1 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.25 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 4 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold yellowish residue was triturated with a small amount of water and made basic to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was filtered off, washed with water and dried *in vacuo*. This gave **7f** as a white solid (640 mg, 98%). It was recrystallised from aqueous methanol as colourless needles mp 109-110 ^{0}C; ir (potassium bromide): 725, 785, 820, 840, 1065, 1095, 1130, 1210, 1410, 1580 cm^{-1}; ms: m/z (%): 415 (M+2, 15), 413 (M^+, 17), 332 (18), 331 (93), 329 (M-84, 100), 250 (329-Br, 36), 249 (25), 207 (12), 195 (34), 193 ($BrPhCCCH_2$, 37), 114 (18), 97 (17), 84 (18), 69 (20), 67 (26), 55 (41), 41 (37); ^{1}H NMR ($CDCl_3$): δ 1.44-1.56 (m, 6H, $NCH_2CH_2CH_2$), 1.89-1.92 (m, 4H, H-6 and H-7), 2.39 (b, 4H, NCH_2CH_2), 2.65-2.67 (b, 2H, H-5), 2.86-2.88 (b, 2H, H-8), 3.59 (s, 2H, NCH_2C-3), 4.82 (bs, H_2O), 7.51 (d, J = 8.5 Hz, 2H, aromatic H), 7.66 (d, J = 8.5 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.1, 22.3, 24.3, 26.1, one methylene signal obscured, 52.5 (NCH_2C-3), 54.2 (NCH_2CH_2), 116.1 (C-3), 119.2 (C-2), 120.4 (C-4', aromatic C), 129.4 (C-3', aromatic C), 131.2 (C-2', aromatic C), 134.4 (C-1', aromatic C), 139.3 (C-8a), 145.2 (C-4a), 154.4 (C-9a). Anal. Calcd. for $C_{21}H_{24}N_3OBr.H_2O$: C, 58.34; H, 6.06; N, 9.72. Found: C, 58.72; H, 6.13; N, 9.38.

2-(4'-Bromophenyl)-3-(N-morpholinomethyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (7g).

To a stirred mixture of 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (500 mg, 1.58 mmol), morpholine (140 mg, 1.61 mmol) and glacial acetic acid (1 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.25 ml of 40% diluted with 5 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 3 hrs. The solvent was removed by evaporation *in vacuo* and the ice cold viscous residue was triturated with a small amount of water and made basic to *p*H 9-10 with 2*M* sodium hydroxide solution. The precipitated solid was filtered off, washed with water and dried *in vacuo*. This gave **7g** as a colourless solid (620 mg, 95%). A small sample was recrystallised from aqueous ethanol as white crystals 146-147 ^{0}C; ir (potassium bromide): 715, 790, 825, 855, 910, 1000, 1060, 1105, 1130, 1255, 1370, 1415, 1570 cm^{-1}; ms: m/z (%): 417 (M+2, 4), 415 (M$^+$, 5), 331 (91), 329 (M-86, 100), 316 (17), 250 (329-Br, 38), 249 (26), 195 (34), 193 (BrPhCCCH$_2$, 37), 128 (10), 114 (17), 77 (25), 67 (26), 56 (34); ^{1}H NMR ($CDCl_3$): δ 1.91 (b, 4H, H-6 and H-7), 2.46 (t, *J* = 4.10 Hz, 4H, NC$\underline{H}_2$CH$_2$O), 2.68 (b, 2H, H-5), 2.85 (b, 2H, H-8), 3.66-3.69 (m, 6H, NCH$_2$C$\underline{H}_2$O and NC$\underline{H}_2$C-3), 7.52 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.63 (d, *J* = 8.5 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.1, 22.3, 52.2 (N$\underline{C}$H$_2$C-3), 53.1 (N$\underline{C}$H$_2$CH$_2$O), 67.0 (NCH$_2\underline{C}$H$_2$O), 114.6 (C-3), 119.1 (C-2), 120.7 (C-4', aromatic C), 129.4 (C-3', aromatic C), 131.4 (C-2', aromatic C), 134.1 (C-1', aromatic C), 139.9 (C-8a), 145.5 (C-4a), 154.5 (C-9a). Anal. Calcd. for $C_{20}H_{22}N_3O_2Br$: C, 57.70; H, 5.33; N, 10.09. Found: C, 57.64; H, 5.39; N, 9.90.

2-(4'-Bromophenyl)-3-(N,N-diethylaminomethyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (7h).

This was prepared in a similar manner to compound **7d** from 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (500 mg, 1.58 mmol), diethylamine (120 mg, 1.64 mmol) and formaldehyde solution (0.25 ml of 40 % w/v). The crude **7d** (600 mg, 95 %) was recrystallised from aqueous ethanol and formed yellow crystals mp 125-127 ^{0}C; ir (potassium bromide): 725, 830, 1035, 1125, 1190, 1370, 1420, 1585, 1595 cm^{-1}; ms: m/z (%): 404 (M+2, 40), 402 (M$^+$, 44), 331 (98), 329 (M-73, 100); ^{1}H NMR ($CDCl_3$): δ 0.94 (t, *J* = 7.1 Hz, 6H, NCH$_2$C$\underline{H}_3$), 1.87 (b, 4H, H-6 and H-7), 2.45-2.52 (q, *J* = 7.1 Hz, 4H, NC$\underline{H}_2$CH$_3$), 2.64 (b, 2H, H-5), 2.83 (b, 2H, H-8), 3.70 (s, 2H, NCH$_2$C-3), 7.47 (d, *J* = 8.4 Hz, 2H, aromatic H), 7.59 (d, *J* = 8.5 Hz, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 11.4 (CH$_3$), 21.2, 22.1, 22.3, 46.1, 47.8, 116.7, 119.3, 120.4, 129.5 (C-3', aromatic C), 131.2 (C-2', aromatic C), 134.3, 139.3 (C-4a), 145.1 (C-8a), 154.4 (C-9a). Anal. Calcd. for $C_{20}H_{24}N_3OBr$: C, 59.71; H, 6.01; N, 10.44. Found: C, 59.47; H, 6.28; N, 10.12.

Bis-1,4-[(6'-(4''-chlorophenyl)-3'-methyl-5'-imidazo[2,1-*b*]oxazolyl)methyl]piperazine (9a).

To a stirred mixture of 6-(4'-chlorophenyl)-3-methylimidazo[2,1-*b*]oxazole (**6a**) (1.0 g, 4.3 mmol), piperazine (190 mg, 2.15 mmol) and glacial acetic acid (1.5 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.60 ml of 40% diluted with 10 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 2.5 hrs., and cooled to room temperature. The resulting solid was filtered off and washed with sodium hydroxide solution (2*M*, 15 ml) and dried in vacuo. This gave **9a** as off-white crystals (700 mg, 57%) mp 270-272 ^{0}C (decomp.); ir (potassium bromide): 725, 845, 1000, 1090, 1140, 1375, 1585 cm^{-1}; ms: m/z (%): 575 (M$^+$, 6), 476 (21), 329 (33), 247 (33), 245 (100), 232 (17), 151 (16), 149 (47), 114 (13), 75 (12), 56 (13); ^{1}H NMR ($CDCl_3$): δ 2.42 (bs, 8H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.48 (d, *J* = 1.6 Hz, 6H,

3'-CH_3), 3.71 (s, 4H, NCH_2C-5'), 7.07 (q, J = 1.6 Hz, 2H, H-2), 7.36 (d, J = 8.5 Hz, 4H, aromatic H), 7.61 (d, J = 8.5 Hz, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 8.2 (3'-CH_3), 51.4 (N$\underline{C}H_2$C-5'), 52.8 (N$\underline{C}H_2\underline{C}H_2$N), 115.5 (C-5'), 122.6 (C-6'), 128.5 (C-3", aromatic C), 129.5 (C-2", aromatic C), 132.9 (C-4", aromatic C), 133.2 (C-2), 133.4 (C-1", aromatic C), 140.2 (C-3'), 155.5 (C-7'a). Anal. Calcd. for $C_{30}H_{28}N_6O_2Cl_2$: C, 62.62; H, 4.90; N, 14.60. Found: C, 62.23; H, 5.18; N, 14.34.

Bis-1,4-[(6'-(4''-chlorophenyl)-2',3'-dimethyl-5'-imidazo[2,1-*b*]oxazolyl)methyl]piperazine (9b).

To a stirred mixture of 6-(4'-chlorophenyl)-2,3-dimethylimidazo[2,1-*b*]oxazole (**6b**) (1.0 g, 4.10 mmol), anhydrous piperazine (174 mg, 2.03 mmol) and glacial acetic acid (1.5 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.50 ml of 40% diluted with 10 ml of ethanol) dropwise at room temperature. The mixture was heated under reflux for 1 hr, and cooled to room temperature. The resulting solid was filtered off and washed with 2*M* sodium hydroxide solution and dried *in vacuo*. This gave **9b** as shiny colourless crystals (900 mg, 74%). A small amount was recrystallised from aqueous dimethylformamide it had mp 273-274 ^{0}C; ir (potassium bromide): 705, 725, 820, 840, 1000, 1095, 1135, 1305, 1375, 1400, 1430(s), 1580 cm^{-1}; ms: m/z (%): 605 (M+2, 75), 603 (M^+, 100), 347 (15), 345 (35), 303 (68), 302 (100), 261 (18), 259 (59); ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 6H, 3'-CH_3), 2.40-2.46 (b, 14H, 2'-C$\underline{H}_3$ and NC$\underline{H}_2$C$\underline{H}_2$N), 3.67 (s, 4H, NCH_2C-5'), 7.37 (d, J = 8.5 Hz, 4H, aromatic H), 7.59 (d, J = 8.5 Hz, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 8.7 (3'-CH_3), 10.8 (2'-CH_3), 51.3 (N$\underline{C}H_2$C-5'), 52.6 (N$\underline{C}H_2\underline{C}H_2$N), 115.2 (C-5'), 116.5 (C-6'), 128.5 (C-3", aromatic C), 129.4 (C-2", aromatic C), 132.6 (C-4", aromatic C), 133.6 (C-1", aromatic C), 140.4 (C-2'), 142.2 (C-3'), 154.3 (C-7'a). Anal. Calcd. for $C_{32}H_{32}N_6O_2Cl_2$: C, 63.69; H, 5.34; N, 13.92. Found: C, 63.84; H, 5.31; N, 13.60.

Bis-1,4-[(2'-(4''-chlorophenyl)-5',6',7',8'-tetrahydro-3'-imidazo[2,1-*b*]benzoxazolyl)methyl]piperazine (9c).

To a stirred mixture of 2-(4'-chlorophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6c**) (1.0 g, 3.67 mmol), anhydrous piperazine (160 mg, 1.83 mmol) and glacial acetic acid (1.5 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.46 ml of 40% diluted with 10 ml of ethanol) dropwise at room temperature. The reaction mixture was heated under reflux for 1.5 hrs, and cooled to room temperature. The resulting solid was filtered off, washed with 2*M* sodium hydroxide solution and dried in vacuo. This gave **9c** as shiny colourless crystals (700 mg, 74%). A small sample was recrystallised from aqueous methoxyethanol and had mp 278-280 ^{0}C; ir (potassium bromide): 730, 830, 850, 940, 1010, 1090, 1155, 1335, 1375, 1410, 1575 cm^{-1}; ms: m/z (%): 657 (M+2, 70), 655 (M^+, 100), 373 (16), 371 (29), 329 (97), 328 (100), 287 (20), 285 (53); ^{1}H NMR ($CDCl_3$): δ 1.91-1.93 (bm, 8H, H-6' and H-7'), 2.45 (bs, 8H, NC$\underline{H}_2$C$\underline{H}_2$N), 2.69 (bm, 4H, H-5'), 2.83 (bm, 4H, H-8'), 3.66 (s, 4H, NC$\underline{H}_2$C-3'), 4.85 (bs, H_2O), 7.36 (d, J = 8.5 Hz, 4H, aromatic H), 7.66 (d, J = 8.5 Hz, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 20.9, 22.2, 22.4, 51.8 (N$\underline{C}H_2$C-3'), 52.9 (N$\underline{C}H_2\underline{C}H_2$N), 115.3 (C-3'), 119.1 (C-2'), 128.5 (C-3", aromatic C), 129.3 (C-2", aromatic C), 132.5 (C-4", aromatic C), 133.8 (C-1", aromatic C), 139.8 (C-8'a), 145.4 (C-4'a), 154.6 (C-9'a). Anal. Calcd. for $C_{36}H_{36}N_6O_2Cl_2 \cdot 1/3H_2O$: C, 65.36; H, 5.63; N, 12.69; Found: C, 65.27; H, 5.87; N, 12.45.

Bis-1,4-[(2'-(4''-bromophenyl)-5',6',7',8'-tetrahydro-3'-imidazo[2,1-*b*]benzoxazolyl)methyl]piperazine (9d).

To a stirred mixture of 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (1.0 g, 3.15 mmol), anhydrous piperazine (140 mg, 1.58 mmol) and glacial acetic acid (1.5 ml) in absolute ethanol (15 ml) was added formaldehyde solution (0.4 ml of 40% diluted with 10 ml of ethanol) dropwise at room temperature. The reaction mixture was heated under reflux for 2 hrs, and cooled to room temperature. The resulting solid was filtered off, washed with 2*M* sodium hydroxide solution and dried *in vacuo*. This gave **9d** as a colourless solid (940 mg, 80%) mp 270-272 ^{0}C (decomp.); ir (potassium bromide): 725, 830, 1000, 1140, 1375, 1425, 1595 cm^{-1}; ms: m/z (%): 746 (M+4, 3.6), 744 (M+2, 6), 742 (M^+, 3.4), 660 (13), 648 (55), 646 (100), 644 (51), 579 (16), 567 (18), 536 (15), 525 (13); ^{1}H NMR ($CDCl_3$): δ 1.92-1.96 (bm, 8H, H-6' and H-7'), 2.44 (bs, 8H, NCH_2CH_2N), 2.66-2.68 (bm, 4H, H-5'), 2.83 (b, 4H, H-8'), 3.73 (s, 4H, NCH_2C-3'), 7.51 (d, *J* = 8.5 Hz, 4H, aromatic H), 7.68 (d, *J* = 8.5 Hz, 4H, aromatic H). Anal. Calcd. for $C_{36}H_{36}N_6O_2Br_2$: C, 58.08; H, 4.87; N, 11.28. Found: C, 58.05; H, 4.98; N, 11.02.

2-(4'-Bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole-3-carboxaldehyde (10) .

A solution of dry phosphorus oxychloride (810 mg , 5.3 mmol) in dry dimethyl formamide (15 ml) was added during 20 minutes to a stirred solution of the 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (1.5 g, 4.73 mmol) in dry dimethylformamide (10 ml) at 0 - 5 ^{0}C. The mixture was heated at 60 ^{0}C for 2 hrs, then poured into cold water (30 ml), and neutralised with sodium carbonate solution (10 % , 20 ml) while cooling. The precipitated solid was filtered off, washed with water, and gave **10** as a colourless solid (1.46 g, 89%). This was recrystallised from methanol/chloroform (6:1) and had mp 154-155 ^{0}C; ir (potassium bromide): 700, 725, 735, 880, 1010, 1265, 1380, 1500, 1550, 1570, 1645 cm^{-1}; ms: m/z (%): 346 (M+2, 91), 344 (M^+, 100), 343 (M-1, 29), 316 (M-28, 11), 265 (M-Br, 20), 237 (19), 157 (27), 153 (40), 119 (49), 102 (54), 81 (30), 79 (76), 77 (94), 75 (52), 51 (41); ^{1}H NMR ($CDCl_3$): δ 1.89-1.96 (bm, 4H, H-6 and H-7), 2.71-2.74 (bm, 2H, H-5), 3.08-3.18 (bm, 2H, H-8), 7.63 (s, 4H, aromatic H), 9.72 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$): δ 21.9, 22.3, 22.4, 121.4, 121.9, 123.8, 130.6 (aromatic C), 131.9 (aromatic C), 147.6 (C-4a), 154.4 (C-8a), 156.8 (C-9a), 177.4 (CHO). Anal. Calcd. for $C_{16}H_{13}N_2O_2Br$: C, 55.67; H, 3.80; N, 8.11. Found: C, 55.42; H, 4.09; N, 7.82.

2-(4'-Bromophenyl)-3-nitro-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (11).

Nitric acid (70 %, 2 ml) was added dropwise to a stirred solution of 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (1.0 g, 3.15 mmol) in concentrated sulfuric acid (10 ml) at 0 ^{0}C. The mixture was stirred at room temperature for 30 minutes, poured into ice-water (30 ml), and neutralised with ammonium hydroxide (15 *M*, 20 ml). The precipitate was collected and crystallised from aqueous methanol. This gave **11** as colorless crystals (450 mg , 38 %) mp 189-191 ^{0}C ; ir (potassium bromide): 730, 815, 855, 1010, 1100, 1190, 1315, 1575, 1595, 1600 cm^{-1}; ms: m/z (%): 317 (M^+, 4), 316 (M-1, 10), 282 (M-Cl, 13), 206 (23), 182 (27), 127 (36), 100 (62), 94 (42), 79 (56), 77 (66), 67 (100), 55 (46), 41 (57); ^{1}H NMR ($CDCl_3$): δ 1.90-1.93 (bm, 4H, H-6 and H-7), 2.63-2.88 (bm, 4H, H-5 and H-8), 7.41-7.62 (m, 4H, aromatic H).

3-Bromo-2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (12).

A solution of bromine (510 mg, 3.15 mmol) in dry dichloromethane (10 ml) was added during 15 minutes to a stirred solution of 2-(4'-bromophenyl)-5,6,7,8-tetrahydroimidazo[2,1-*b*]benzoxazole (**6d**) (1.0 g, 3.15 mmol) in dry dichloromethane (15 ml) at 15-20 ^{0}C. After aqueous saturated sodium carbonate solution (15 ml) was added stirring was continued for further 15 minutes. Then, the layers were separated and the aqueous phase was further extracted with dichloromethane (2 x 30 ml). The extracts were combined, washed with brine (50 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was crystallised from diethyl ether to give **12** as colourless crystals (1.02 g, 82%) mp 184-186 ^{0}C; ir (potassium bromide): 720, 805, 840, 1000, 1090, 1180, 1390, 1570, 1590 cm^{-1}; ms: m/z (%): 398 (M+4, 51), 396 (M+2, 100), 394 (M$^+$, 52), 316 (9), 235 (13), 208 (23), 114 (19), 106 (23), 79 (53), 77 (35), 51 (9); ^{1}H NMR ($CDCl_3$): δ 1.89-1.91 (bm, 4H, H-6' and H-7'), 2.66 (b, 2H, H-5'), 2.85 (b, 2H, H-8'), 7.48-7.54 (m, 2H, aromatic H), 7.81-7.88 (m, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 19.8, 21.7, 21.9, 22.2, 84.2, 119.1, 121.1, 128.2 (aromatic C), 131.4 (aromatic C), 132.6, 137.9 (C-4a), 146.1 (C-8a), 154.3 (C-9a). Anal. Calcd. for $C_{15}H_{12}N_2OBr_2$: C, 45.49; H, 3.05; N, 7.07. Found: C, 45.70; H, 3.08; N, 6.82.

Acknowledgments

B.M. is grateful to the Australian Government for financial support.

REFERENCES AND NOTES

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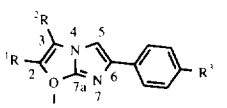
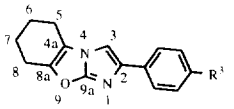
8. The numbering system used for imidazo[2,1-*b*]oxazole and tetrahydroimidazo[2,1-*b*]benzoxazole are as follows:



(**6 a,b**, R^1, R^2 = H or CH_3 and R^3 = Br or Cl)



(**6 c,d**, R^3 = Br or Cl)

(*Received in UK* 25 *February* 1997; *revised* 4 *April* 1997; *accepted* 7 *April* 1997)