SYNTHESIS OF SOME BENZOXAZOLYLETHOXYPIPERIDONES

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Abstract – 1-Hydroxy-2,6-diarylpiperidin-4-ones obtained from the corresponding 2,6-diarylpiperidin-4-ones upon cyanoethylation followed by condensation with *o*-aminophenol afforded 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones.

2,6-Disubstituted piperidines form a biologically important class of compounds due to their diverse pharmacological activities such as sedative, hypotensive, stimulant and depressant activities etc. and their presence in a variety of alkaloids(1-4). Benzoxazole and its derivatives have been reported to be antibacterial (5), analgesic (6), antifungal (7), activities etc. Antiinflammatory activity of benzoxazole nucleus was well established by the advent of a new antiinflammatory drug benzoxaprofen (8). Medicines derived from oxazole includes the antiepileptic drugs trimethadione and paramethadione (9), the sedative and muscle relaxant benzoxazolamine (9) and furazolidone (10), which is effective against wide range of enteric infections. These observations prompted us to synthesize a system, which combines both biolabile piperidines, and benzoxazole components together to give a compact structure like title compounds.

Cyclic ketones normally undergo Baeyer-Villiger oxidation (oxygen insertion reaction) to yield lactones by the treatment of peracids (11). When 2,6-diarylpiperidin-4-ones were subjected to Baeyer-Villiger type of reaction by using *m*-CPBA, 1-hydroxy-2,6-diarylpiperidin-4-ones (12) resulted instead of lactones. On treatment with acrylonitrile, substituted tetrahydrothiapyran-4-ones containing active hydrogen underwent cyanoethylation yielding 3-[2-cyanoethoxy]derivatives (13). In 1-hydroxy-2,6-diarylpiperidin-4-ones, there are active methylenic hydrogens at C_3 and C_5. Hence expectation of cyanoethylation to occur at these positions besides at 1-hydroxyl group is quite normal. However in all the cases, specifically the 1-hydroxy group alone underwent cyanoethylation in good yields (60-74%) upon treatment with acrylonitrile in the presence of triton B, which on further condensation with *o*-aminophenol in acid medium resulted 1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diarylpiperidin-4-ones in moderate yields. The schematic representation and the analytical data of compounds **34-42** are given in scheme 1 and table 1 respectively.

EXPERIMENTAL

TLC was performed to access the reactions and purity of products. Melting points were recorded in open capillaries and were uncorrected. IR spectra were recorded in Perkin - Elmer 297 spectrophotometer in KBr pellets and only noteworthy absorption levels (reciprocal centimeter) are listed. ^{1}H - NMR spectra were recorded at 400 MHz on Brucker amx 400 MHz spectrophotometer in $CDCl_3$ using TMS as internal standard and ^{13}C-NMR spectra were recorded at 125 MHz on Brucker amx 400 MHz spectrophotometer in $CDCl_3$. Mass spectra were recorded on a VG

SCHEME - 1

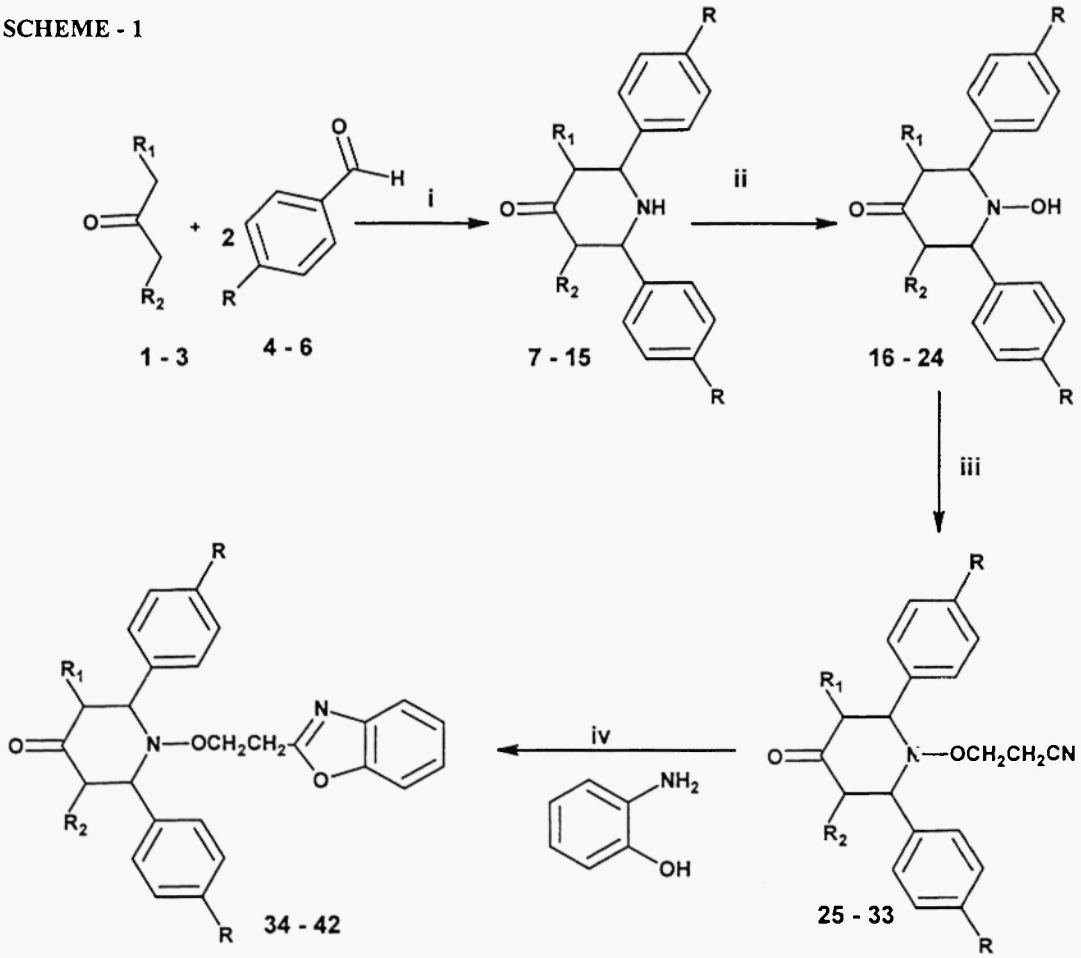

TABLE 1. Analytical data of compounds **34-42**.

Entry	R_1	R_2	R	Yield (%)	m.p (°C)	Elemental analysis		
						C(%)	H(%)	N(%)
34	H	H	H	54	139	75.69	5.80	6.84
35	H	CH_3	H	58	95	76.05	6.10	6.58
36	CH_3	CH_3	H	55	116	76.39	6.36	6.38
37	H	H	Cl	32	88-89	64.84	4.56	5.80
38	H	CH_3	Cl	27	75-76	65.45	4.84	5.65
39	CH_3	CH_3	Cl	40	106	66.01	5.10	5.50
40	H	H	OCH_3	58	100	71.16	5.92	5.91
41	H	CH_3	OCH_3	50	119-120	71.53	6.15	5.80
42	CH_3	CH_3	OCH_3	50	81	72.03	6.37	5.64

analytical 7070E instrument equipped with VG 11-250 data acquision system. Satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer models 240 CHN analyzer.

From the literature precedent (14), 2,6-diarylpiperidin-4-ones **7-15** were prepared by the condensation of appropriate ketones, aldehydes and ammonium acetate in 1:2:1 ratio.

1-Hydroxy-2,6-diphenylpiperidin-4-one 16 : A solution of 2,6-diphenylpiperidin-4-one **7** (0.005 mol) and *m*-CPBA (0.005 mol) in 40 ml of chloroform was stirred for 15 min. and kept aside for overnight at 20°C. Then the mixture was extracted with chloroform and washed with 10% sodium bicarbonate solution. The chloroform layer was dried over anhydrous sodium sulphate and distilled off under reduced pressure. Purifications with silicagel column chromatography with 8:2 benzene:pet-ether (bp40-60) mixture yielded the product **16**. The compounds **17-24** were prepared similarly.

1-(2-Cyanoethoxy)-2,6-diphenylpiperidin-4-one 25 : A mixture of 1-hydroxy-2,6-diphenylpiperidin-4-one **16** (0.005 mol) and acrylonitrile (0.005 mol) in 50 ml of 1,4-dioxane was taken in 100 ml round bottom flask and cooled in an ice bath. A few crystals of resorcinol was added which was followed by dropwise addition of triton B (5 ml) with shaking. Then the content was stirred under warm for 9 h. at 65-75°C and was concentrated. After cooling, the resulting solution was poured over benzene:pet-ether 1:3 mixture. The solid thus obtained was recrystallised from methanol to afford **25**. The compounds **26-33** were prepared similarly.

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diphenylpiperidin-4-one 34. A mixture of 1-[2-cyanoethoxy]-2,6-diphenylpiperidin-4-one **13** (0.005 mole), *o*-aminophenol (0.005 mole) and dilute hydrochloric acid (10cc of Con. HCl in 100cc of water) was taken in a 250ml round bottom flask and was allowed to reflux in an oil bath for 18 hours. After cooling, the content in the flask was leached with 100cc of diethylether and the separated ether extract was washed with five 25cc portions of 4N sodium hydroxide solution. The ether layer was separated, dried with calcium chloride and freed of ether by distillation. The solid thus obtained was recrystallised twice from ethanol.

IR:cm^{-1}(KBr) 2924.1, 2850.6, 2767.2,(C-H Stretching), 1706.4(C=O Stretching). Other characteristic bands are 1600.3, 1456.7, 1429.3, 1392.3, 1374.7, 1347.6, 1287.1, 1255.3, 1237.8, 1155.4, 1104.9, 1076.2, 1035.4, 945.3, 904.7, 856.4, 788.2, 748.9, 689.1, 658.2, 604.8, 518.6, 500.7, 472.1. Mass:m/z 412(M^+) (M.F : $C_{26}H_{24}N_2O_3$), 280, 267, 250, 222, 208, 194, 167, 145, 132, 118, 103 (100%), 91.77, 65, 55, 51. ^{1}H NMR:δ 4.04(dd, ^{3}J=12.64Hz; 3.86Hz; 2H) H_2 and H_6, 2.60-2.85(m, 6H) H_3, H_5 and $-OCH_2-CH_2-$, 7.29-7.49(m, 14H) aryl protons, 3.93(t, J=6.50 Hz; 2H)–OCH_2-CH_2-. ^{13}C NMR:δ 69.262(C_2, C_4), 49.312(C_3, C_5), 206.050(C=O), 67.573($-OCH_2-CH_2-$), 27.647 ($-OCH_2-CH_2-$), 109.738, 114.284, 118.943, 119.058, 127.798, 129.773, 130.731, 133.105, 143.134(aryl carbons), 141.739(C_2' and C_6'), 162.605(C_2 of benzoxazole moiety).

The compounds **35-42** were synthesised similarly.

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diphenyl-3-methylpiperidin-4-one 35. IR:cm^{-1}(KBr) 2965.7, 2938.2, 2856.5, 2805.3(C-H Stretching), 1696.5(C=O Stretching). Other characteristic bands are 2352.8, 1952.1, 1813.2, 1589.3, 1488.2, 1449.7, 1368.2, 1335.1, 1269.3, 1251.7, 1229.4, 1198.2, 1131.9, 1089.8, 1024.2, 951.2, 930.7, 913.4, 871.8, 841.5, 834.6, 748.3, 686.9, 670.2, 635.0, 593.3, 551.8, 526.4. Mass:m/z 426(M^+), (M.F : $C_{27}H_{26}N_2O_3$), 294, 281, 264, 239, 172, 162, 145, 132, 118, 103(100%), 91, 77, 69, 65, 51. ^{1}H NMR:δ 4.02(dd, ^{3}J=13.03Hz; 3.36Hz, 2H) H_6, 3.60(d, ^{3}J=11.65Hz, 1H)H_2, 2.60-2.88(m, 5H) H_3, H_5 and $-OCH_2-CH_2-$, 7.28-7.48(m, 14H) aryl protons, 3.92(t, J=6.49 Hz, 2H)

$-OCH_2-CH_2-$, 0.81(d, J=6.58Hz, 3H) CH_3. ^{13}C NMR:δ 75.767(C_2), 69.570(C_6), 49.140(C_3), 48.787(C_5), 207.498(C=O), 67.608($-OCH_2-CH_2-$), 27.718($-OCH_2-CH_2-$), 109.757, 114.194, 118.938, 119.101, 127.754, 129.712, 129.820, 130.601, 130.714, 133.110, 143.137(aryl carbons), 140.979(C_2'), 141.820(C_6'), 162.618(C_2 of benzoxazole moiety), 10.589(CH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-diphenyl-3,5-dimethylpiperidin-4-one 36 IR:cm^{-1}(KBr) 2965.2, 2923.3, 2876.4, 2847.4, 2813.3(C-H Stretching), 1697.7(C=O Stretching). Other characteristic bands are 2354.9, 1596.7, 1485.4, 1433.9, 1375.2, 1349.4, 1260.5, 1195.0, 1088.3, 1041.9, 1022.4, 980.0, 927.3, 882.1, 787.2, 760.7, 691.3, 673.2, 623.0, 554.3, 513.2. Mass: m/z 440(M^+), (M.F : $C_{28}H_{28}N_2O_3$), 322, 295, 266, 190, 177, 159, 146, 132, 118, 103(100%), 100, 77, 69, 56, 51. ^1H NMR:δ 3.62(d, ^3J=11.66Hz, 2H) H_2 and H_6, 2.83-2.88(m, 2H) H_3 and H_5, 2.71(t, J=6.52Hz, 2H) $-OCH_2-CH_2-$, 7.29-7.50(m, 14H) aryl protons, 3.92(t, J=6.50Hz, 2H) $-OCH_2-CH_2-$, 0.81(d, J=6.62Hz, 6H) CH_3. ^{13}C NMR:δ 76.025(C_2,C_6), 49.440(C_3 and C_5), 209.169(C=O), 67.609($-OCH_2-CH_2-$), 27.684($-OCH_2-CH_2-$), 109.746, 114.257, 118.940, 119.097, 127.854, 129.791, 130.676, 133.107, 143.140(aryl carbons), 141.120(C_2',C_6'), 162.620(C_2 of benzoxazole moiety), 10.968(CH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one 37 IR:cm^{-1}(KBr) 2927.1, 2841.7, 2796.2(C-H Stretching), 1704.8 (C=O Stretching). Other characteristic bands are 1628.7, 1492.2, 1409.3, 1371.3, 1323.4, 1280.8, 1265.3, 1237.7, 1129.1, 1116.9, 1044.5, 1005.3, 954.7, 895.2, 820.8, 740.3, 690.8, 518.1, 490.9, 475.9. Mass:m/z 480(M^+), (M.F : $C_{26}H_{22}N_2O_3Cl_2$), 348, 335, 318, 290, 276, 262, 194, 166, 146, 137, 132, 118, 111, 75, 53(100%), 50. ^1H NMR:δ 4.07(dd, ^3J=12.64Hz; 3.87Hz, 2H) H_2 and H_6, 2.60-2.86(m, 6H) H_3, H_5 and $-OCH_2-CH_2-$, 7.31-7.58(m, 12H) aryl protons, 3.92(t, J=6.50 Hz; 2H) $-OCH_2-CH_2-$.^{13}C NMR:δ 68.470(C_2, C_6), 48.986(C_3, C_5), 205.062(C=O), 67.576($-OCH_2-CH_2-$), 27.642 ($-OCH_2-CH_2-$), 109.750, 114.290, 118.984, 119.080, 129.130, 129.963, 133.124, 143.347(aryl carbons), 134.932(C_2'''' and C_6''''), 139.892 ($C_2'$and C_6'), 162.614(C_2 of benzoxazole moiety).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)–3-methylpiperidin-4-one 38. IR:cm^{-1}(KBr) 2964.7, 2931.7, 2852.4, 2726.9(C-H Stretching), 1694.9(C=O Stretching). Other characteristic bands are 2363.3, 1945.0, 1820.1, 1633.2, 1586.1, 1492.1, 1380.2, 1304.4, 1258.3, 1221.9, 1139.2, 1110.7, 1039.5, 1009.9, 948.2, 918.7, 898.1, 866.6, 773.1, 689.7, 633.4, 563.8, 499.9. Mass:m/z 494(M^+), (M.F : $C_{27}H_{24}N_2O_3Cl_2$), 362, 349, 332, 307, 262, 196, 180, 166, 155, 146, 137, 118, 111, 75, 69, 53(100%), 50. ^1H NMR:δ 4.06(dd, ^3J=13.02Hz; 3.36Hz, 1H) H_6, 3.69 (d, ^3J=11.64Hz, 1H) H_2, 2.61-2.90(m, 5H) H_3, H_5 and $-OCH_2-CH_2-$, 7.13-7.43(m, 12H) aryl protons, 3.93(t, J=6.50Hz, 2H) $-OCH_2-CH_2-$, 0.79(d, J=6.54Hz, 3H) CH_3. ^{13}C NMR:δ 74.970(C_2), 68.842(C_6), 48.856(C_3) 48.476(C_5), 206.211(C=O), 67.614($-OCH_2-CH_2-$), 27.702($-OCH_2-CH_2-$), 109.768, 114.202, 118.976, 119.154, 129.361, 129.373, 129.883, 130.004, 133.120, 143.354(aryl carbons), 139.094(C_2'), 139.953(C_6'), 134.753(C_2''''), 134.920(C_6''''), 162.627(C_2 of benzoxazole moiety), 10.681(CH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-chlorophenyl)–3,5-dimethylpiperidin-4-one 39 IR:cm^{-1}(KBr) 2957.7, 2929.9, 2844.1, 2796.7(C-H Stretching), 1696.5(C=O Stretching). Other characteristic bands are 2355.2, 1651.1, 1585.3, 1478.0, 1410.5, 1373.7, 1319.6, 1268.7, 1198.9, 1080.0, 1048.6, 1006.3, 975.3, 883.7, 824.9, 697.4, 645.2, 560.0. Mass:m/z 390(M 118), (M.F : $C_{28}H_{26}N_2O_3Cl_2$), 363, 334, 224, 211, 193, 180, 165, 152, 146, 132, 118, 111, 100,

91, 75, 53(100%), 50. ^{1}H NMR:δ 3.65 (d, ^{3}J=11.66Hz, 2H) H_2 and H_6, 2.83-2.89(m, 2H) H_3 and H_5, 2.71(t, J=6.53Hz, 2H) $-OCH_2-\underline{C}H_2-$, 7.31-7.52(m, 12H) aryl protons, 3.92(t, J=6.49Hz, 2H) $-\underline{O}CH_2-CH_2-$, 0.80(d, J=6.57Hz, 6H) CH_3. ^{13}C NMR:δ 75.283(C_2,C_6), 49.201(C_3,C_5), 208.176(C=O), 67.628($-OCH_2-CH_2-$), 27.699($-OCH_2-\underline{C}H_2-$), 109.784, 114.222, 118.943, 119.162, 129.290, 129.820, 133.018, 143.359(aryl carbons), 134.841(C_2'''',C_6''''), 139.130(C_2',C_6'), 162.648(C_2 of benzoxazole moiety), 10.865(CH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)piperidin-4-one 40. IR:cm^{-1}(KBr) 2926.7, 2853.2, 2786.9(C-H Stretching), 1706.8(C=O Stretching). Other characteristic bands are 1639.2, 1465.7, 1378.9, 1366.5, 1259.1, 1236.4, 1189.3, 1137.9, 1040.4, 1025.3, 925.0, 856.4, 800.9, 744.7, 652.1, 602.9, 524.3, 510.7. Mass: m/z 472(M^+), (M.F : $C_{28}H_{28}N_2O_5$), 354, 327, 310, 282, 268, 254, 194, 162, 147, 145, 132, 118, 107, 75, 65, 55, 53(100%), 50. ^{1}H NMR:δ 4.06(dd, ^{3}J=12.65Hz; 3.85Hz, 2H) H_2 and H_6, 2.59-2.84(m, 6H) H_3, H_5 and $-OCH_2-CH_2-$, 6.90(d, 4H) and 7.34-7.55(m, 8H) aryl protons, 3.92(t, J=6.52Hz, 2H) $-\underline{O}CH_2-CH_2-$, 3.81(s, 6H) OCH_3. ^{13}C NMR:δ 68.612(C_2, C_6), 49.401(C_3, C_5), 206.164(C=O), 67.614($-\underline{O}CH_2-$ CH_2-), 27.674($-OCH_2-\underline{C}H_2-$), 109.785, 114.342, 114.490, 118.974, 119.005, 133.019, 133.148, 143.358(aryl carbons), 158.800(C_2'''' and C_6''''), 135.571 (C_2' and C_6'), 162.598(C_2 of benzoxazole moiety), 55.107(OCH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3-methylpiperidin-4-one 41 IR:cm^{-1}(KBr) 2937.9, 2837.7(C-H Stretching), 1698.7(C=O Stretching). Other characteristic bands are 2360.4, 2340.3, 1580.4, 1451.7, 1376.8, 1349.9, 1256.3, 1242.7, 1177.6, 1035.7, 1020.0, 932.6, 890.2, 842.2, 791.7, 656.5, 640.7, 535.1, 450.9. Mass:m/z 486(M^+), (M.F : $C_{29}H_{30}N_2O_5$), 354, 341, 324, 299, 254, 192, 176, 162, 148, 145, 133, 118, 107, 75, 69, 65, 53(100%), 50. ^{1}H NMR:δ 4.05(dd, ^{3}J=12.99Hz; 3.33Hz, 1H) H_6, 3.66(d, ^{3}J=11.67Hz, 1H) H_2, 2.59-2.87(m, 5H) H_3, H_5 and $-OCH_2-\underline{C}H_2-$, 6.89(4H) and 7.27-7.50(m, 8H) aryl protons, 3.92(t, J=6.52Hz, 2H) $-OCH_2-CH_2-$, 3.80(s, 6H) OCH_3, 0.80(d, J=6.58Hz, 3H) CH_3. ^{13}C NMR:δ 75.169(C_2), 68.985(C_6), 49.229(C_3) 48.892(C_5), 207.387(C=O), 67.768 ($-OCH_2-CH_2-$), 27.654($-OCH_2-CH_2-$), 109.742, 114.102, 114.648, 114.879, 118.768, 118.980, 132.999, 133.121, 143.380(aryl carbons), 135.132(C_2'), 135.847(C_6'), 158.569(C_2''''), 158.940(C_6''''), 162.504(C_2 of benzoxazole moiety) 55.188(OCH_3), 10.598(CH_3).

1-[2-(benzoxazol-2-yl)ethoxy]-2,6-*bis*(*p*-methoxyphenyl)-3,5-dimethylpiperidin-4-one 42. IR:cm^{-1}(KBr) 2930.4, 2839.2(C-H Stretching), 1698.6(C=O Stretching). Other characteristic bands are 2351.7, 2337.4, 1580.2, 1504.8, 1344.3, 1301.5, 1257.8, 1234.7, 1076.1, 1040.8, 1033.6, 827.9, 791.4, 660.2, 537.6, 473.1. Mass:m/z 500(M^+), (M.F : $C_{30}H_{32}N_2O_5$), 382, 355, 326, 220, 207, 189, 176, 161, 146, 132, 118, 107, 100, 75, 69, 53(100%), 50. ^{1}H NMR:δ 3.64(d, ^{3}J=11.69Hz, 2H) H_2 and H_6, 2.81-2.86(m, 2H) H_3 and H_5 2.70(t, J=6.50Hz, 2H) $-OCH_2-\underline{C}H_2-$, 6.88(4H) and 7.36-7.49(m, 8H) aryl protons, 3.92(t, J=6.50Hz, 2H) $-OCH_2-CH_2-$, 3.80(s, 6H) OCH_3, 0.81d, J=6.53Hz, 6H) CH_3. ^{13}C NMR:δ 75.476(C_2,C_6), 49.548(C_3,C_5), 209.399(C=O), 67.704($-OCH_2-CH_2-$), 27.689($-OCH_2-\underline{C}H_2-$), 109.788, 114.235, 114.528, 118.864, 119.005, 133.002, 133.226, 143.347(aryl carbons), 158.880(C_2'''',C_6''''), 135.127(C_2',C_6'), 162.602(C_2 of benzoxazole moiety), 55.201(OCH_3), 10.960(CH_3).

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