DOI 10.1007/s10593-014-1631-z
Chemistry of Heterocyclic Compounds, Vol. 50, No. 11, February, 2015 (Russian Original Vol. 50, No. 11, November, 2014)

SYNTHESIS AND AMINOMETHYLATION OF 3-SUBSTITUTED 6-HYDROXY-1,2-BENZISOXAZOLES

M. S. Frasinyuk[1]*

Oximes of 2,4-dihydroxybenzophenones, 1-(2,4-dihydroxyphenyl)-2-phenylethanones, and 1-(2,4-dihydroxyphenyl)-2-phenoxyethanones were dehydrated with 1,1'-carbonyldiimidazole, yielding 3-substituted 6-hydroxy-1,2-benzisoxazoles, aminomethylation reactions of which were studied with various reagents.

Keywords: 7-aminomethyl-1,2-benzisoxazole, 1,2-benzisoxazole, Mannich reaction.

The recent interest towards synthesis of 1,2-benzisoxazole derivatives has been motivated by the biological activity of these compounds. For example, *N*-alkyl derivatives of 6-fluoro-3-(piperidin-4-yl)-1,2-benzisoxazole exhibit strong neuroleptic activity. The best known atypical neuroleptic agents of this category are iloperidone [1], approved for clinical use in the USA, and abaperidone [2], currently undergoing clinical studies.

One of the most convenient methods for the synthesis of 1,2-benzisoxazoles is the cyclization of aldehyde or ketone oxime derivatives containing a 2-hydroxyphenyl fragment by employing various reagents. In the majority of cases, Beckmann rearrangement leading to 1,3-benzoxazole derivatives [3-5] was prevented by performing the reaction in two stages: formation of acyl derivatives of oximes followed by intramolecular substitution of acyl group at the nitrogen atom by phenol group in the presence of bases. This was achieved by using pyridine [6-9], sodium acetate [10-12], potassium carbonate [13-15], or potassium hydroxide [16], as well as sodium hydride [10, 13, 17-19]. Besides that, 1,2-benzisoxazole derivatives were obtained from 2-hydroxyphenyl ketoximes by the action of thionyl chloride, methanesulfonyl chloride, or toluenesulfonyl chloride in the presence of an organic base [20-22]. At the same time, direct dehydration of 2-hydroxyphenyl ketoximes (without isolation of acyl derivatives) has found only limited application. There are reports of using azodicarboxylic acid esters [5, 23, 24] or 5,6-dichloro-2,3-dicyano-1,4-benzoquinone [25, 26] in the presence of triphenylphosphine. In some cases, 3-hydroxy-1,2-benzisoxazole derivatives were prepared by dehydration of 2-hydroxyphenylhydroxamic acids [20, 27]. Synthesis of 3-amino-1,2-benzisoxazoles through intramolecular cyclization of *O*-(2-cyanophenyl)acetone oxime in the presence of aqueous alcohol solution of hydrochloric acid has been reported [28].

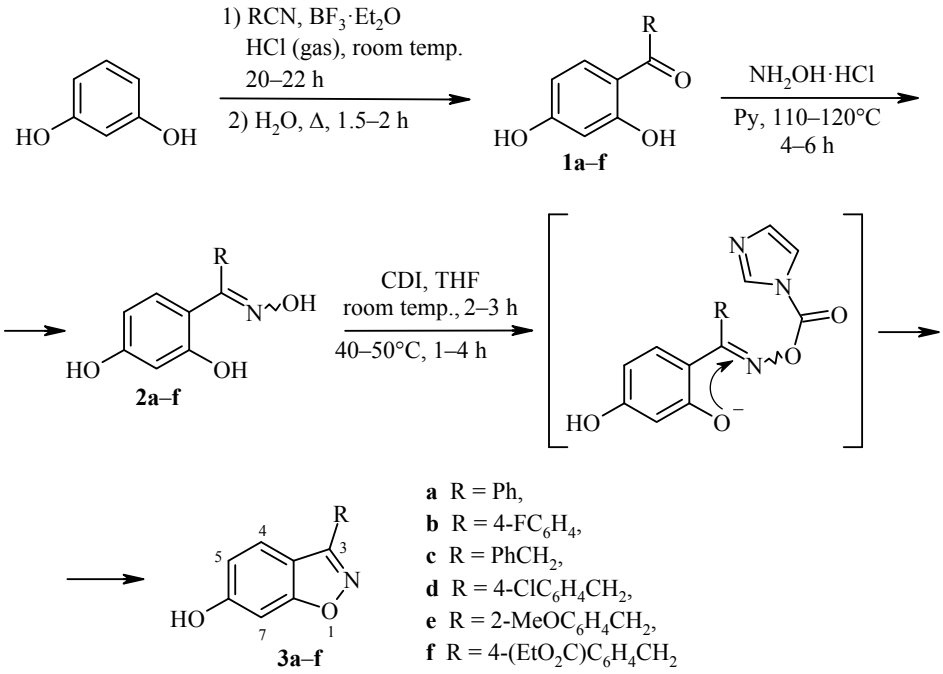
The goal of this study was development of a single-stage synthesis for the preparation of hydroxy derivatives of 1,2-benzisoxazole as well as synthesis of their aminomethyl derivatives, which are important synthons for obtaining various compounds [29].

*To whom correspondence should be addressed, e-mail: mykhaylo.frasinyuk@ukr.net.

[1]Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Murmanska St., Kyiv 02094, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1758-1765, November, 2014. Original article submitted August 26, 2014.

The reaction of resorcin with benzonitrile or its 4-fluoro derivative in boron trifluoride etherate in the presence of anhydrous HCl, followed by hydrolysis of ketimines gave 2,4-dihydroxybenzophenones **1a**,**b**. Substituted phenylacetonitriles under analogous conditions were converted to 2',4'-dihydroxy-2-deoxybenzoins **1c**-**e**, while 4-ethoxycarbonylphenoxyacetonitrile was converted to α-phenoxyacetophenone **1f**. Heating of the synthesized ketones **1a-f** with hydroxylamine in pyridine gave their oximes **2a-f** (Table 1).



The most convenient dehydrating agent for the synthesis of 6-hydroxy-1,2-benzisoxazoles **3a-f** from oximes **2a-f** was 1,1'-carbonyldiimidazole (CDI) in tetrahydrofuran. The use of this reagent allowed to perform the synthesis of derivatives **3a-f** in a single stage, bypassing the preparation of acyl oximes and protection of phenolic hydroxyl group. Apparently, *O*-acyl derivative of oxime was formed in the first stage and was subsequently converted to 3-substituted 6-hydroxy-1,2-benzisoxazoles by intramolecular substitution at the nitrogen atom in the presence of imidazole as base, by analogy to the methods of 1,2-benzisoxazole synthesis described above.

In order to obtain Mannich bases from 6-hydroxy-1,2-benzisoxazoles **3a-f**, their aminomethylation was studied in the presence of amines and formaldehyde. The interaction of compounds **3a-f** with amine hydrochlorides or free amines and formalin in alcohol solution did not give the desired results. Opening of 1,2-benzisoxazole ring was observed in this case with the formation of starting oximes **2a-f**. The most convenient reagents for aminomethylation of 3-substituted 6-hydroxy-1,2-benzisoxazoles **3a-f** were aminals, also identified as intermediates of Mannich reaction in alkaline or neutral medium. The use of aminals allowed to synthesize Mannich bases **4a-h** in 54-75% yield (Table 1). In those cases when the synthesis of aminals from amines was difficult or impossible (high-boiling or solid amines, amino acids), the best results were obtained by using these amines in the presence of paraform, allowing to minimize the evolution of water during the reaction. The use of 3- and 4-piperidinecarboxylic acids in the aminomethylation reaction under the described conditions allowed to obtain not only 7-[4-(pyridin-2-yl)piperazin-1-yl]methyl derivatives **4i**,**j**, but also 1,2-benzisoxazole amino acid derivatives **4k**-**m**.

TABLE 1. Physicochemical Characteristics of the Obtained Compounds

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %
		C	H	N		
1b	$C_{13}H_9FO_3$	67.43 / 67.24	4.12 / 3.91	—	152-154	68
1f	$C_{17}H_{16}O_6$	64.37 / 64.55	5.29 / 5.10	—	162-164	82
2b	$C_{13}H_{10}FNO_3$	63.39 / 63.16	4.17 / 4.08	5.55 / 5.67	205-207	77
2e	$C_{15}H_{15}NO_4$	66.18 / 65.93	5.39 / 5.53	4.97 / 5.13	203-205 (decomp.)	63
2f	$C_{17}H_{17}NO_6$	61.49 / 61.63	5.22 / 5.17	4.34 / 4.23	152-154	81
3b	$C_{13}H_8FNO_2$	68.33 / 68.12	3.27 / 3.52	6.27 / 6.11	229-231	67
3c	$C_{14}H_{11}NO_2$	74.89 / 74.65	5.13 / 4.92	6.04 / 6.22	152-154	58
3d	$C_{14}H_{10}ClNO_2$	64.58 / 64.75	3.62 / 3.88	5.51 / 5.39	173-175	64
3e	$C_{15}H_{13}NO_3$	70.46 / 70.58	5.00 / 5.13	5.68 / 5.49	136-138 (decomp.)	51
3f	$C_{17}H_{15}NO_5$	65.46 / 65.17	5.15 / 4.83	4.73 / 4.47	167-169	47
4a	$C_{20}H_{22}N_2O_5$	65.03 / 64.85	6.17 / 5.99	7.38 / 7.56	115-117	54
4b	$C_{19}H_{19}FN_2O_2$	70.18 / 69.92	5.60 / 5.87	8.31 / 8.58	138-139	62
4c	$C_{20}H_{21}ClN_2O_2$	67.17 / 67.32	5.78 / 5.93	7.99 / 7.85	112-113	73
4d	$C_{21}H_{24}N_2O_3$	71.69 / 71.57	7.04 / 6.86	7.93 / 7.95	141-142	58
4e	$C_{18}H_{17}FN_2O_3$	65.66 / 65.85	5.05 / 5.22	8.68 / 8.53	185-187	75
4f	$C_{19}H_{19}ClN_2O_3$	63.82 / 63.60	5.12 / 5.34	8.02 / 7.81	170-172	66
4g	$C_{20}H_{22}N_2O_4$	67.92 / 67.78	6.01 / 6.26	8.12 / 7.90	125-127	57
4h	$C_{20}H_{22}ClN_3O_2$	64.35 / 64.60	6.01 / 5.96	11.22 / 11.30	152-153	71
4i	$C_{23}H_{22}N_4O_2$	71.22 / 71.48	5.58 / 5.74	14.26 / 14.50	194-196	63
4j	$C_{24}H_{24}N_4O_2$	72.12 / 71.98	6.23 / 6.04	13.71 / 13.99	128-130	57
4k	$C_{21}H_{21}ClN_2O_4$	62.83 / 62.92	5.04 / 5.28	7.14 / 6.99	233-235	63
4l	$C_{24}H_{26}N_2O_7$	63.18 / 63.43	5.49 / 5.77	6.37 / 6.16	182-184 (decomp.)	55
4m	$C_{24}H_{26}N_2O_7$	63.57 / 63.43	5.51 / 5.77	6.03 / 6.16	201-203	48

The formation of 7-aminomethyl derivatives **4a-m** was confirmed by the changes in ^{1}H NMR signal multiplicity of H-4,5 protons belonging to the 1,2-benzisoxazole ring. In contrast to the characteristic spin-spin coupling of 1,2,4-trisubstituted aromatic system in compounds **3a-f**, the signals of H-4,5 protons in 1,2-benzisoxazole fragment existed as doublets with spin-spin coupling constant equal to 7.9-8.9 Hz (Table 2).

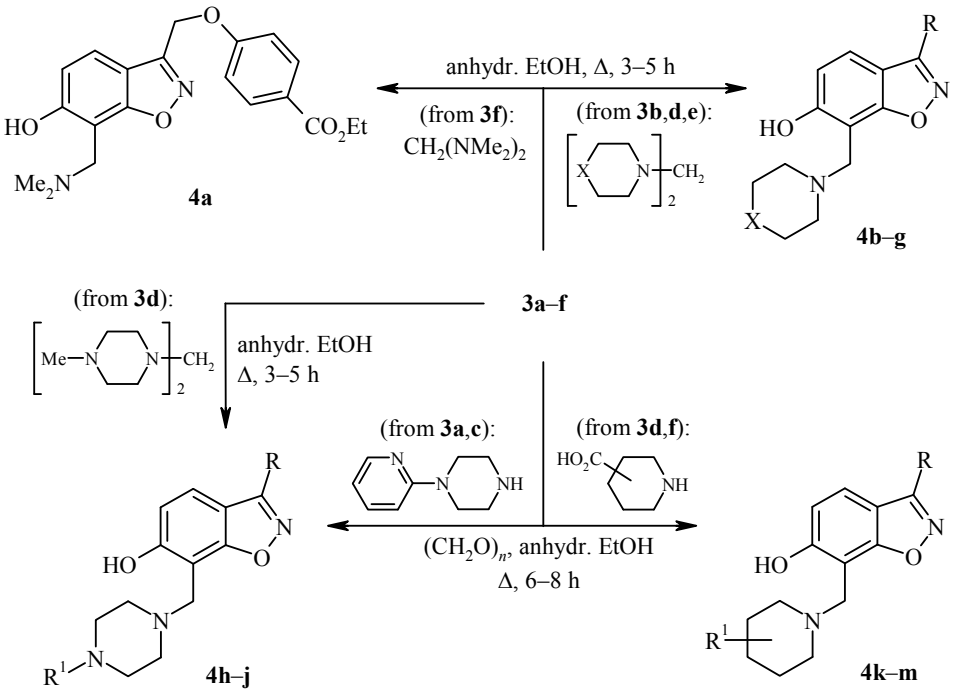
Thus, we have developed a method for the synthesis of 6-hydroxy-1,2-benzisoxazole derivatives, containing an aryl, benzyl, or phenoxymethyl substituent at position 3, and studied aminomethylation of these compounds with various reagents.

TABLE 2. Spectral Characteristics of the Obtained Compounds

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm (*J*, Hz)	Mass spectrum, *m/z* $[M+H]^+$ (I_{rel}, %)
1	2	3	4
1b	3210, 2707, 1628, 1599, 1325, 1279	6.38 (1H, dd, ^3J = 8.5, ^4J = 2.4, H-5); 6.47 (1H, d, ^4J = 2.4, H-3); 6.56 (1H, d, ^3J = 8.5, H-6); 7.32-7.39 (2H, m, H-3',5'); 7.46-7.66 (2H, m, H-2',6'); 10.67 (1H, s, 4-OH); 11.95 (1H, s, 2-OH)	233 (100)
1f	3323, 2983, 1722, 1627, 1610, 1508, 1225	1.31 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 4.28 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 5.53 (2H, s, $COCH_2$); 6.39 (1H, d, ^4J = 2.4, H-3); 6.42 (1H, dd, ^3J = 8.8, ^4J = 2.4, H-5); 7.03 (2H, d, ^3J = 8.8, H-3',5'); 7.78 (1H, d, ^3J = 8.8, H-6); 7.90 (2H, d, ^3J = 8.8, H-2',6'); 10.65 (1H, s, 4-OH); 11.61 (1H, s, 2-OH)	317 (100)
2b	3320, 2870, 1641, 1606, 1512, 1252, 1225	6.22 (1H, dd, ^3J = 8.5, ^4J = 2.4, H-5); 6.32 (1H, d, ^4J = 2.4, H-3); 6.54 (1H, d, ^3J = 8.5, H-6); 7.26-7.38 (4H, m, C_6H_4F); 9.78 (1H, s, 4-OH); 11.27 (1H, s, 2-OH); 11.39 (1H, br. s, NOH)	248 (100)
2e	3367, 3223, 2837, 1649, 1603, 1441, 1248, 980	3.86 (3H, s, OCH_3); 4.05 (2H, s, CH_2); 6.21 (1H, dd, ^3J = 8.5, ^4J = 2.4, H-5); 6.26 (1H, d, ^4J = 2.4, H-3); 6.78-6.84 (1H, m, H-5'); 6.85-6.90 (1H, m, H-3'); 6.98-7.02 (1H, m, H-6'); 7.08 (1H, d, ^3J = 8.5, H-6); 7.15-7.21 (1H, m, H-4'); 9.70 (1H, s, 4-OH); 11.40 (1H, s, 2-OH); 11.79 (1H, br. s, NOH)	274 (100)
2f	3373, 2981, 1691, 1606, 1514, 1292, 1277	1.29 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 4.27 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 5.27 (2H, s, $C\underline{H}_2OAr$); 6.25-6.30 (2H, m, H-3,5); 7.07 (2H, d, ^3J = 8.8, H-3',5'); 7.20 (1H, d, ^3J = 8.5, H-6); 7.89 (2H, d, ^3J = 8.8, H-2',6'); 9.72 (1H, s, 4-OH); 10.81 (1H, s, 2-OH); 11.83 (1H, br. s, NOH)	332 (100)
3b	3140, 2850, 1632, 1618, 1500, 1481, 1227	6.86 (1H, dd, ^3J = 8.8, ^4J = 2.4, H-5); 7.09 (1H, d, ^4J = 2.4, H-7); 7.40 (2H, dd, ^3J = 8.8, $^3J_{H-F}$ = 8.8, H-3',5'); 7.56 (1H, d, ^3J = 8.8, H-4); 8.14 (2H, dd, ^3J = 8.8, $^4J_{H-F}$ = 5.6, H-2',6'); 9.89 (1H, s, 6-OH)	230 (100)
3c	3060, 2844, 1614, 1571, 1485, 1228, 1132	4.25 (2H, s, $C\underline{H}_2Ph$); 6.78 (1H, dd, ^3J = 8.6, ^4J = 2.4, H-5); 6.98 (1H, d, ^4J = 2.4, H-7); 7.23-7.39 (5H, m, H Ph); 7.45 (1H, d, ^3J = 8.6, H-4); 9.71 (1H, s, 6-OH)	226 (100)
3d	3160, 2960, 1612, 1579, 1482, 1225, 1136	4.27 (2H, s, CH_2); 6.78 (1H, dd, ^3J = 8.6, ^4J = 2.2, H-5); 6.98 (1H, d, ^4J = 2.2, H-7); 7.34-7.42 (4H, m, C_6H_4Cl); 7.44 (1H, d, ^3J = 8.6, H-4); 9.70 (1H, s, 6-OH)	260 (100), 262 (34)
3e	3188, 2940, 1618, 1562, 1498, 1255, 1136	3.75 (3H, s, OCH_3); 4.17 (2H, s, CH_2); 6.77 (1H, dd, ^3J = 8.5, ^4J = 2.0, H-5); 6.90-6.95 (1H, m, H-5'); 6.96 (1H, d, ^4J = 2.0, H-7); 6.98-7.03 (1H, m, H-3'); 7.22-7.31 (2H, m, H-4',6'); 7.42 (1H, d, ^3J = 8.5, H-4); 9.65 (1H, s, 6-OH)	256 (100)
3f	3312, 1687, 1605, 1490, 1252, 1177	1.31 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 4.27 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 5.49 (2H, s, $C\underline{H}_2OAr$); 6.85 (1H, dd, ^3J = 8.7, ^4J = 2.2, H-5); 7.07 (1H, d, ^4J = 2.2, H-7); 7.19 (2H, d, ^3J = 8.9, H-2',6'); 7.56 (1H, d, ^3J = 8.7, H-4); 7.94 (2H, d, ^3J = 8.9, H-3',5'); 9.90 (1H, s, 6-OH)	314 (100)
4a	3400, 2958, 1708, 1607, 1508, 1286, 1252	1.38 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 2.40 (6H, s, $N(CH_3)_2$); 3.94 (2H, s, $C\underline{H}_2NMe_2$); 4.34 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 5.30 (2H, s, $C\underline{H}_2OAr$); 6.86 (1H, d, ^3J = 8.7, H-5); 7.09 (2H, d, ^3J = 9.2, H-2',6'); 7.50 (1H, d, ^3J = 8.7, H-4); 8.03 (2H, d, ^3J = 9.2, H-3',5')	371 (100)
4b	3047, 2937, 1624, 1498, 1448, 1225, 1039	1.39-1.89 (6H, m, 3,4,5-CH_2 piperidine); 2.34-3.00 (4H, m, 2,6-CH_2 piperidine); 4.03 (2H, s, $ArC\underline{H}_2N$); 6.84 (1H, d, ^3J = 8.9, H-5); 7.18 (2H, dd, ^3J = 8.7, $^3J_{H-F}$ = 8.7, H-3',5'); 7.49 (1H, d, ^3J = 8.9, H-4); 8.17 (2H, dd, ^3J = 8.7, $^4J_{H-F}$ = 5.5, H-2',6')	327 (100)

TABLE 2 (continued)

1	2	3	4
4c	2936, 2852, 1639, 1614, 1495, 1413, 1254	1.37-1.89 (6H, m, 3,4,5-CH_2 piperidine); 2.34-3.00 (4H, m, 2,6-CH_2 piperidine); 3.93 (2H, s, $C\underline{H}_2C_6H_4Cl$); 4.18 (2H, s, $ArC\underline{H}_2N$); 6.82 (1H, d, ^3J = 8.5, H-5); 7.28-7.34 (4H, m, C_6H_4Cl); 7.43 (1H, d, ^3J = 8.5, H-4)	357 (100), 359 (35)
4d	2937, 2832, 1616, 1496, 1448, 1253, 760	1.41-1.75 (6H, m, 3,4,5-CH_2 piperidine); 2.43-3.00 (4H, m, 2,6-CH_2 piperidine); 3.83 (3H, s, OCH_3); 3.93 (2H, s, $C\underline{H}_2C_6H_4OMe$); 4.23 (2H, s, $ArC\underline{H}_2N$); 6.80 (1H, d, ^3J = 8.5, H-5); 6.88-6.97 (2H, m, H-3',5'); 7.22-7.31 (2H, m, H-4',6'); 7.41 (1H, d, ^3J = 8.5, H-4)	353 (100)
4e	3434, 2839, 1623, 1601, 1499, 1220, 1112	2.59-2.88 (4H, m, CH_2NCH_2); 3.76-3.94 (4H, m, CH_2OCH_2); 4.12 (2H, s, $ArC\underline{H}_2N$); 6.90 (1H, d, ^3J = 8.5, H-5); 7.21 (2H, dd, ^3J = 8.5, $^3J_{H-F}$ = 8.5, H-3',5'); 7.54 (1H, d, ^3J = 8.5, H-4); 8.20 (2H, dd, ^3J = 8.5, $^4J_{H-F}$ = 5.8, H-2',6')	329 (100)
4f	2981, 2827, 1616, 1495, 1444, 1414, 1115, 804	2.55-2.78 (4H, m, CH_2NCH_2); 3.74-3.88 (4H, m, CH_2OCH_2); 3.97 (3H, s, $C\underline{H}_2C_6H_4Cl$); 4.12 (2H, s, $ArC\underline{H}_2N$); 6.83 (1H, d, ^3J = 8.2, H-5); 7.28-7.35 (4H, m, C_6H_4Cl); 7.45 (1H, d, ^3J = 8.2, H-4)	359 (100), 361 (34)
4g	2931, 2836, 1614, 1498, 1552, 1117	2.61-2.81 (4H, m, CH_2NCH_2); 3.75-3.88 (7H, m, CH_2OCH_2, OCH_3); 4.02 (3H, s, $C\underline{H}_2C_6H_4OMe$); 4.24 (2H, s, $ArC\underline{H}_2N$); 6.85 (1H, d, ^3J = 7.9, H-5); 6.89-6.98 (2H, m, H-3',5'); 7.22-7.32 (2H, m, H-4',6'); 7.49 (1H, d, ^3J = 7.9, H-4)	355 (100)
4h	2945, 2800, 1614, 1493, 1444, 1155, 814	2.37 (3H, s, NCH_3); 2.43-2.95 (8H, m, 4CH_2 piperazine); 3.96 (3H, s, $C\underline{H}_2C_6H_4Cl$); 4.18 (2H, s, $ArC\underline{H}_2N$); 6.80 (1H, d, ^3J = 8.5, H-5); 7.28-7.35 (4H, m, C_6H_4Cl); 7.43 (1H, d, ^3J = 8.5, H-4)	372 (100), 374 (35)
4i	3432, 2836, 1624, 1598, 1480, 1440, 1254	2.56-2.96 (4H, m, 2,6-CH_2 piperazine); 3.38–3.81 (4H, m, 3,5-CH_2 piperazine); 4.13 (2H, s, $ArC\underline{H}_2N$); 6.63-6.70 (2H, m, H-3,5 Py); 6.88 (1H, d, ^3J = 8.5, H-5); 7.47-7.53 (5H, m, H Ph); 7.55 (1H, d, ^3J = 8.5, H-4); 8.15-8.22 (2H, m, H-4,6 Py)	387 (100)
4j	3438, 2840, 1612, 1597, 1436, 1254, 1138	2.58–2.90 (4H, m, 2,6-CH_2 piperazine); 3.33-3.87 (4H, m, 3,5-CH_2 piperazine); 4.00 (2H, s, $C\underline{H}_2Ph$); 4.22 (2H, s, $ArC\underline{H}_2N$); 6.62-6.70 (2H, m, H-3,5 Py); 6.83 (1H, d, ^3J = 8.5, H-5); 7.28-7.40 (5H, m, H Ph); 7.46 (1H, d, ^3J = 8.5, H-4); 7.48-7.54 (1H, m) and 8.19-8.22 (1H, m, H-4,6 Py)	401 (100)
4k	3048, 2955, 1628, 1618, 1563, 1432, 1392, 820, 793	1.46-1.68 (2H, m) and 1.73-1.88 (2H, m, 3,5-CH_2 piperidine); 2.13-2.31 (3H, m) and 2.76-2.92 (2H, m, 2,6-CH_2, 4-CH piperidine); 3.85 (3H, s, $C\underline{H}_2C_6H_4Cl$); 4.25 (2H, s, $ArC\underline{H}_2N$); 6.75 (1H, d, ^3J = 8.5, H-5); 7.34 (1H, d, ^3J = 8.5, H-4); 7.36-7.43 (4H, m, C_6H_4Cl)	401 (100), 403 (35)
4l	3446, 2960, 1710, 1606, 1436, 1280	1.29 (3H, t, ^3J = 7.1, $OCH_2C\underline{H}_3$); 1.46-1.60 (2H, m) and 1.74-1.86 (2H, m, 3,5-CH_2 piperidine); 2.09-2.27 (3H, m) and 2.76-2.89 (2H, m, 2,6-CH_2, 4-CH piperidine); 3.85 (3H, s, $ArC\underline{H}_2N$); 4.27 (2H, q, ^3J = 7.1, $OC\underline{H}_2CH_3$); 5.47 (2H, s, $C\underline{H}_2OAr$); 6.82 (1H, d, ^3J = 8.5, H-5); 7.19 (2H, d, ^3J = 8.9, H-2',6'); 7.47 (1H, d, ^3J = 8.5, H-4); 7.92 (2H, d, ^3J = 8.9, H-3',5')	455 (100)
4m	1706, 1605, 1597, 1362, 1245, 1174, 772	1.29 (3H, t, ^3J = 7.0, $OCH_2C\underline{H}_3$); 1.34-1.50 (2H, m, 5-CH_2 piperidine); 1.56-1.67 (1H, m) and 1.72-1.84 (1H, m, 4-CH_2 piperidine); 2.10-2.21 (1H, m), 2.28-2.38 (1H, m) and 2.40-2.50 (1H, m, 2-CH_A, 6-CH_A, 3-CH piperidine); 2.59-2.71 (1H, m) and 2.86-2.97 (1H, m, 2-CH_B, 6-CH_B piperidine); 3.80-3.93 (3H, m, $ArC\underline{H}_2N$); 4.27 (2H, q, ^3J = 7.0, $OC\underline{H}_2CH_3$); 5.47 (2H, s, $C\underline{H}_2OAr$); 6.82 (1H, d, ^3J = 8.5, H-5); 7.19 (2H, d, ^3J = 8.7, H-2',6'); 7.47 (1H, d, ^3J = 8.5, H-4); 7.92 (2H, d, ^3J = 8.7, H-3',5')	455 (100)



Compound	R	X	Compound	R	R^1
4b	4-FC_6H_4	CH_2	**4h**	4-$ClC_6H_4CH_2$	Me
4c	4-$ClC_6H_4CH_2$	CH_2	**4i**	Ph	2-Py
4d	2-$MeOC_6H_4CH_2$	CH_2	**4j**	$PhCH_2$	2-Py
4e	4-FC_6H_4	O	**4k**	4-$ClC_6H_4CH_2$	4-COOH
4f	4-$ClC_6H_4CH_2$	O	**4l**	4-$(EtO_2C)C_6H_4OCH_2$	4-COOH
4g	2-$MeOC_6H_4CH_2$	O	**4m**	4-$(EtO_2C)C_6H_4OCH_2$	3-COOH

EXPERIMENTAL

IR spectra were recorded on a Nicolet 380 FT-IR spectrometer in KBr pellets. ^{1}H NMR spectra were acquired on a Varian M 400 spectrometer (400 MHz) in $CDCl_3$ (compounds **4a-j**) and in DMSO-d_6 (the rest of compounds), with TMS as internal standard. Mass spectra were recorded on an Agilent 1100 instrument (chemical ionization). Elemental analysis was performed on a vario Micro cube automated CHNS-analyzer. Melting points were determined with a Buchi B-535 apparatus. The reaction progress and purity of the obtained compounds were controlled by TLC on Merck silica gel 60 F_{254} plates, compounds **1-3 a-f** were eluted with 9:1 and 19:1 mixtures of $CHCl_3$–MeOH, while Mannich bases **4a-m** – with EtOAc.

The physicochemical constants and spectral characteristics of the obtained compounds **1a** [30], **1c** [31], **1d**, **2c**,**d** [32], **1e** [33], **2a** [34] and **3a** [10] matched the literature values.

Synthesis of 2,4-Dihydroxyphenyl Ketones 1a-f (General Method). Gaseous HCl stream was passed for 4-6 h through a stirred mixture of resorcin (11.0 g, 0.1 mol) and the corresponding nitrile (0.1 mol) in $BF_3 \cdot Et_2O$ (50 ml). The reaction mixture was left overnight at room temperature, then poured while stirring into hot (80°C) water (500 ml), refluxed for 1.5-2 h, and cooled. The precipitate formed was filtered off, washed with cold water, and recrystallized from MeOH.

Synthesis of Oximes 2a-f (General Method). A solution of 2,4-dihydroxyphenyl ketone **1a-f** (10 mmol) and $NH_2OH \cdot HCl$ (2.08 g, 30 mmol) in pyridine (25 ml) was stirred for 4-6 h at 110-120°C, the solvent was removed by evaporation under vacuum, the residue was transferred into cold water (100 ml), the precipitate that formed was filtered off and recrystallized from MeOH.

Synthesis of 6-Hydroxy-1,2-benzisoxazoles 3a-f (General Method). A stirred solution of oxime **2a-f** (10 mmol) in anhydrous THF (20 ml) was cooled (20-25°C) and treated by addition of 1,1'-carbonyldiimidazole (3.24 g, 20 mmol). The reaction mixture was stirred for 2-3 h at room temperature, then for 1-4 h at 40-50°C, the solvent was evaporated under vacuum; the residue was transferred into cold water (100 ml), the precipitate formed was filtered off and recrystallized from MeOH.

6-Hydroxy-3-phenyl-1,2-benzisoxazole (3a). Yield 1.50 g (71%). Colorless crystals, mp 217-219°C (mp 218-219°C [10]).

Synthesis of 7-(Aminomethyl)-6-hydroxy-1,2-benzisoxazoles 4a-h (General Method). A hot solution of 6-hydroxy-1,2-benzisoxazole **3b**,**d-f** (1.0 mmol) in anhydrous EtOH (10 ml) was treated by addition of the corresponding aminal (1.2 mmol); the mixture was refluxed for 3-5 h, then cooled. The solvent was removed by evaporation under vacuum, the residue was recrystallized from hexane.

Synthesis of 7-(Aminomethyl)-6-hydroxy-1,2-benzisoxazoles 4i-m (General Method). A hot solution of 6-hydroxy-1,2-benzisoxazole **3a**,**c**,**d**,**f** (1.0 mmol) in anhydrous EtOH (10 ml) was treated by addition of paraform (36 mg, 1.2 mmol) and 1-(2-pyridyl)piperazine (1.1 mmol) or the corresponding piperidinecarboxylic acid. The reaction mixture was refluxed for 6-8 h, then cooled, solvent was evaporated under vacuum, the residue was recrystallized from hexane or 1:2 mixture of 2-PrOH–hexane.

REFERENCES

1. L. J. Scott, *CNS Drugs*, **23**, 867 (2009).
2. J. Bolós, L. Anglada, S. Gubert, J. M. Planas, J. Agut, M. Príncep, N. De la Fuente, A. Sacristán, and J. A. Ortiz, *J. Med. Chem.*, **41**, 5402 (1998).
3. S. Fujita, K. Koyama, and Y. Inagaki, *Synthesis*, 68 (1982).
4. H. Sato, K. Kuromaru, T. Ishizawa, B. Aoki, and H. Koga, *Chem. Pharm. Bull.*, **40**, 2597 (1992).
5. G. Poissonnet, *Synth. Commun.*, **27**, 3839 (1997).
6. M. Jain and C.-H. Kwon, *J. Med. Chem.*, **46**, 5428 (2003).
7. A. D. Adams, Z. Hu, D. von Langen, A. Dadiz, A. Elbrecht, K. L. MacNaul, J. P. Berger, G. Zhou, T. W. Doebber, R. Meurer, M. J. Forrest, D. E. Moller, and A. B. Jones, *Bioorg. Med. Chem. Lett.*, **13**, 3185 (2003).
8. C. Santini, G. D. Berger, W. Han, R. Mosley, K. MacNaul, J. Berger, T. Doebber, M. Wu, D. E. Moller, R. L. Tolman, and S. P. Sahoo, *Bioorg. Med. Chem. Lett.*, **13**, 1277 (2003).
9. A. D. Adams, W. Yuen, Z. Hu, C. Santini, A. B. Jones, K. L. MacNaul, J. P. Berger, T. W. Doebber, and D. E. Moller, *Bioorg. Med. Chem. Lett.*, **13**, 931 (2003).
10. H. Sato, T. Dan, E. Onuma, H. Tanaka, B. Aoki, and H. Koga, *Chem. Pharm. Bull.*, **39**, 1760 (1991).
11. H. Sato, T. Dan, E. Onuma, H. Tanaka, B. Aoki, and H. Koga, *Chem. Pharm. Bull.*, **40**, 109 (1992).
12. K. Liu, R. M. Black, J. J. Acton III, R. Mosley, S. Debenham, R. Abola, M. Yang, R. Tschirret-Guth, L. Colwell, C. Liu, M. Wu, C. F. Wang, K. L. MacNaul, M. E. McCann, D. E. Moller, J. P. Berger, P. T. Meinke, A. B. Jones, and H. B. Wood, *Bioorg. Med. Chem. Lett.*, **15**, 2437 (2005).
13. J. T. Strupczewski, R. C. Allen, B. A. Gardner, B. L. Schmid, U. Stache, E. J. Glamkowski, M. C. Jones, D. B. Ellis, F. P. Huger, and R. W. Dunn, *J. Med. Chem.*, **28**, 761 (1985).
14. G. Roman, E. Comanita, and B. Comanita, *Tetrahedron*, **58**, 1617 (2002).
15. E. Comanita, I. Popovici, G. Roman, G. Robertson, and B. Comanita, *Heterocycles*, **51**, 2139 (1999).
16. J. J. Plattner, A. K. L. Fung, J. A. Parks, R. J. Pariza, S. R. Crowley, A. G. Pernet, P. R. Bunnell, and P. W. Dodge, *J. Med. Chem.*, **27**, 1016 (1984).
17. A. Nuhrich, M. Varache-Lembege, P. Renard, and G. Devaux, *Eur. J. Med. Chem.*, **29**, 75 (1994).
18. G. Jagath Reddy, D. Latha, C. Thirupathaiah, and K. Srinivasa Rao, *Heterocycl. Commun.*, **9**, 391 (2003).

19. G. M. Shutske, L. L. Setescak, R. C. Allen, L. Davis, R. C. Effland, K. Ranbom, J. M. Kitzen, J. C. Wilker, and W. J. Novick, Jr., *J. Med. Chem.*, **25**, 36 (1982).
20. D. Ferraris, B. Duvall, Y.-S. Ko, A. G. Thomas, C. Rojas, P. Majer, T. Tsukamoto, and K. Hashimoto, *J. Med. Chem.*, **51**, 3357 (2008).
21. Y. Luo, Y. Xu, L. Chen, J. Hu, C. Peng, D. Xie, J. Shi, W. Huang, G. Xu, M. Peng, J. Han, R. Li, S. Yang, and Y. Wei, *Bioorg. Med. Chem. Lett.*, **19**, 4702 (2009).
22. T. J. Dale, A. C. Sather, and J. Rebek, Jr., *Tetrahedron Lett.*, **50**, 6173 (2009).
23. M. S. Malamas, E. S. Manas, R. E. McDevitt, I. Gunawan, Z. B. Xu, M. D. Collini, C. P. Miller, T. Dinh, R. A. Henderson, J. C. Keith, and H. A. Harris, *J. Med. Chem.*, **47**, 5021 (2004).
24. M. D. Cullen, B.-L. Deng, T. L. Hartman, K. M. Watson, R. W. Buckheit, Jr., C. Pannecouque, E. De Clercq, and M. Cushman, *J. Med. Chem.*, **50**, 4854 (2007).
25. N. Iranpoor, H. Firouzabadi, and N. Nowrouzi, *Tetrahedron Lett.*, **47**, 8247 (2006).
26. L. Karadeniz, G. Koz, K. Aydin, and S. T. Astley, *Turk. J. Chem.*, **34**, 711 (2010).
27. R. Friary and B. R. Sunday, *J. Heterocycl. Chem.*, **16**, 1277 (1979).
28. G. M. Shutske and K. J. Kapples, *J. Heterocycl. Chem.*, **26**, 1293 (1989).
29. M. Tramontini and L. Angiolini, *Mannich Bases: Chemistry and Uses*, CRC Press, Boca Raton, 1994, p. 77-120.
30. P. Price and S. S. Israelstam, *J. Org.Chem.*, **29**, 2800 (1964).
31. T.-M. Lu, D.-H. Kuo, H.-H. Ko, and L.-T. Ng, *J. Agric. Food Chem.*, **58**, 10027 (2010).
32. E. Chapman and H. Stephen, *J. Chem. Soc.*, *Trans.*, **123**, 404 (1923).
33. Y. Kawase, K. Ogawa, S. Miyoshi, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **33**, 1240 (1960).
34. H. Lund, *Acta Chem. Scand.*, **18**, 563 (1964).