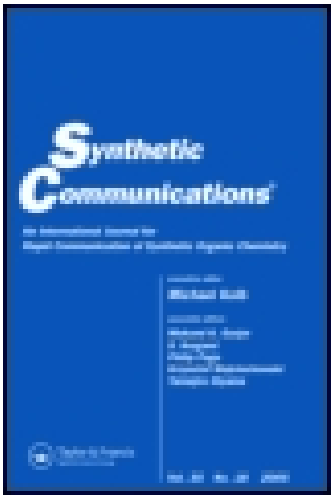

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Facile and Simple Synthesis of Novel 1-Methyl-2-(2-substituted-oxazol-4-yl)-1H-benzimidazole Derivatives

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FACILE AND SIMPLE SYNTHESIS OF NOVEL 1-METHYL-2-(2-SUBSTITUTED-OXAZOL-4-YL)-1*H*-BENZIMIDAZOLE DERIVATIVES

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Novel 1-methyl-2-(2-substituted-oxazol-4-yl)-1H-benzimidazole derivatives were obtained in good yields and purity by treating corresponding 2-benzimidazolyl esters with acetamide in the presence of BF_3-etherate, a Lewis acid.

Keywords: Acetamide; 2-benzimidazolyl ester; Lewis acid; oxazole

INTRODUCTION

Benzimidazoles are an important class of heterocyclic compounds with a wide spectrum of biological activity[1] and behave as antihypertensive, antiviral, antifungal, antitumor, and anthelmintic agents in veterinary medicine.[2] The oxazole heterocycle is a fundamental ring system found in natural products, pharmaceuticals, agrochemicals, peptidomimetics, and polymers.[3] Naturally occurring oxazoles are usually found with a 2,4-substitution pattern,[4] a consequence of their biosynthetic assembly from serine residues, although 2,5-substituted oxazole natural products are known.[5]

Synthesis and study of biological activities of compounds having both benzimiadazole and oxazole moieties have attracted our attention because both these moieties exhibit considerable biological activity independently, and when present together they may have synergistic affects leading to more potent molecules.

RESULTS AND DISCUSSION

Condensation of o-phenylenediamine (**1**) with lactic acid under the Philips condition[6] gave the known 2-(α-hydroxyethyl)benzimidazole (**2**). Compound **2** on oxidation with acid dichromate yielded the required 2-acetyl benzimidazole (**3**).[7]

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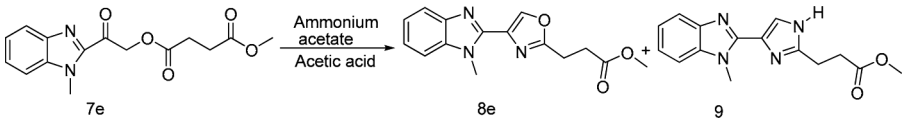


Scheme 1. Synthesis of oxazole.

The resulting **3** was subjected to N-methylation with dimethylsulfate in acetonitrile, potassium carbonate, and triethylbenzylammonium chloride (as a phase-transfer catalyst), giving the corresponding N-methylated compound (**4**),[8] which on bromination in acetic acid gave **5**[9] and its dibromoderivative. Compound **5** was converted into its ester (**7**) on reacting with carboxylic acid (**6**) in acetone medium.

Initially, we attempted to convert the ester (**7**) into an oxazole under Cornforth's condition,[10] which yielded a major by-product and, based on the literature,[11] was presumed to be **9** (Scheme 1).

Attempts to convert the compound **5** directly to **8** using amide derivatives[12] did not yield the required product. However, **7**, on reacting with acetamide in the presence of BF_3-Et_2O, led to the isolation of the corresponding oxazoles (**8**) in good yield and quality. Using this new protocol, different oxazoles were synthesized as shown in Table 1. (Scheme 2).

Based on the literature information, the mechanism proposed for the conversion of the ester to the corresponding oxazoles is shown in Scheme 3.

In summary, a facile synthetic process for 1-methyl-2-(2-substituted-oxazol-4-yl)-1*H*-benzimidazole derivatives was developed, and a plausible mechanism is proposed for the conversion of ester to the corresponding oxazole.

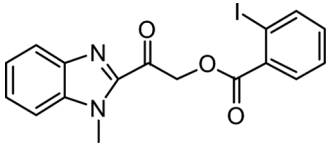
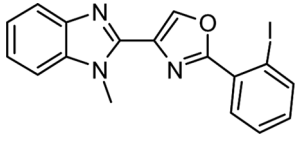
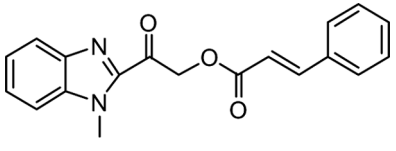
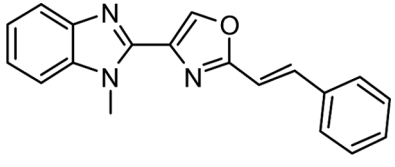
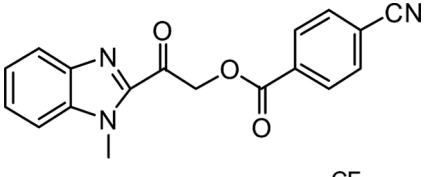
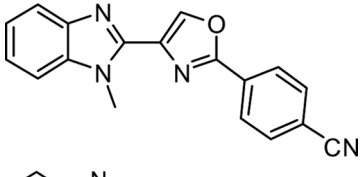
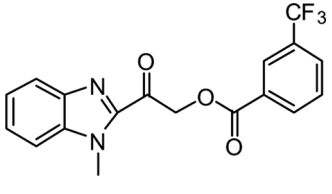
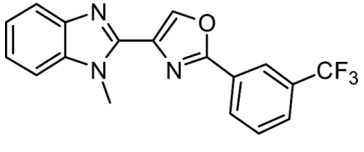
EXPERIMENTAL

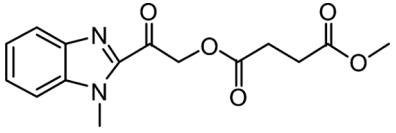
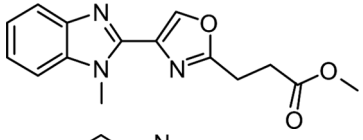
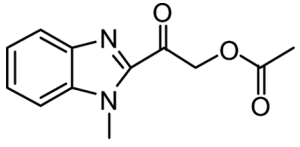
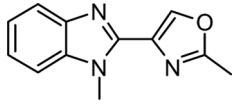
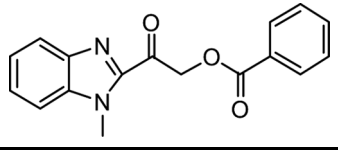
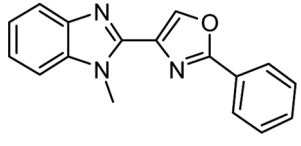
^{1}H NMR spectra were recorded in $CDCl_3$ and dimethyl sulfoxide (DMSO-d_6) on a Mercury Plus Varian 400-MHz spectrometer. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ 0.00) as internal standard and are expressed in parts per million (ppm). Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet). Coupling constants (*J*) are given in hertz. Melting points were determined using a scientific capillary melting-point apparatus and are uncorrected. Mass spectra were obtained on an HP-5989A mass spectrometer. Thin-layer chromatography (TLC) was performed on silica-gel plates (SRL 230–400 mesh). All the solvents used are commercially available and were distilled before use.

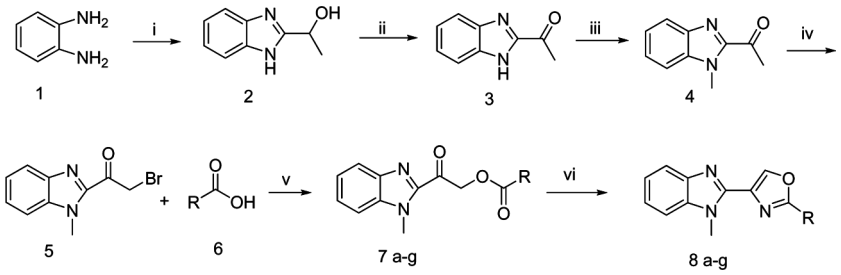
General Procedure for Synthesis of Ester 7a–g

A mixture of **5** (1.0 mol), **6** (1.0 mol), triethylamine (1.5 mol), and acetone (10 ml) were stirred at 25–30°C for 30–60 min. After completion of reaction, as monitored by thin-layer chromatography (TLC), triethylamine hydrobromide salt was filtered, and the mother liquor was distilled off under vacuum. The residue was stirred with water and filtered and, on recrystallization from methanol the wet cake afforded the corresponding ester. Please see Table 2 for details.

Table 1. Preparation of 1-methyl-2-(2-subtituted-oxazol-4-yl)-1*H*-benzimidazole derivatives using BF_3-Et_2O

Entry	Ester (**7**)	Product (**8**)	Yield (%)	Time (h)	Mp (°C)
a			76	48	260–262
b			50	48	217–218
c			75	48	306–309
d			68	40	243–245

e			65	24	148–150
f			55	48	217–218
g			45	48	—



Scheme 2. R=Methyl, pheny, 4-cyano phenyl, etc. Reagent and conditions: (i) 4 N HCl, lactic acid, 100°C, 3 h; (ii) $K_2Cr_2O_7$, H_2SO_4, rt, 2 h; (iii) K_2CO_3, dimethyl sulfate, TEBAC, CH_3CN, rt, 3 h; (iv) Br_2, acetic acid, 100°C, (v) TEA, acetone, rt; and (vi) acetamide, BF_3-etherate, ethylacetate, reflux, 48 h.

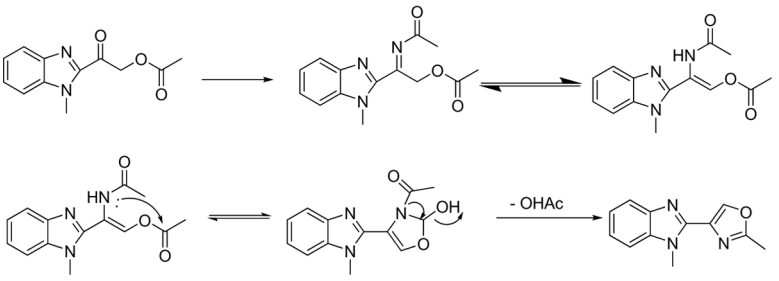
General Procedure for Synthesis of Oxazole Derivatives 8a–g

To a mixture of **7** (1.0 mol) and acetamide (5.0 mol) in ethyl acetate (10 mol), 47% BF_3-Et_2O (10 mmol) dropwise was added. The resulting mixture was refluxed for 48 h. After completion of the reaction, as monitored by TLC, the solution was quenched with water, and the resulting solid was filtered, washed with water, and dried. Please see Table 1 for details.

Spectral Data

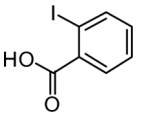
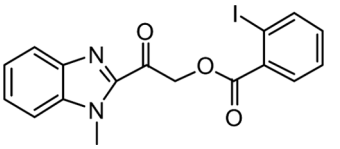
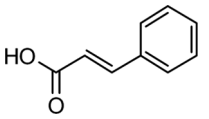
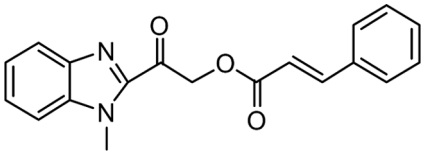
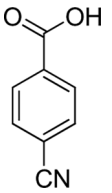
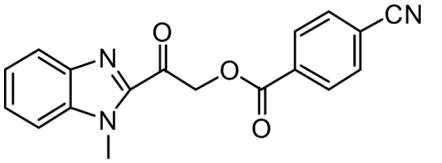
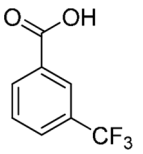
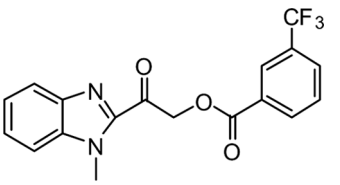
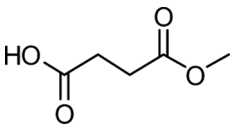
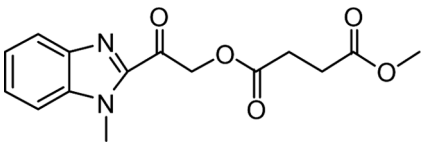
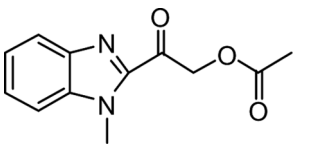
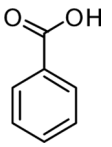
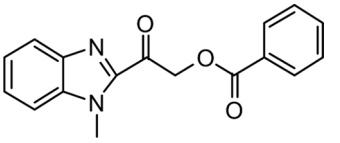
2-Iodo-benzoic acid 2-(1-methyl-1*H*-benzimidazol-2-yl)-2-oxo-ethyl ester (7a). Solid, mp 128–129°C; IR (KBr, cm^{-1}): 3664, 3061, 2948, 2551, 1931, 1744, 1702, 1613, 1582, 1562, 1488, 1463, 1428, 1407, 1362, 1346, 1282, 1269, 1247, 1200, 1124, 1105, 1026, 1014, 1002, 965, 898; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.09 (dd, $J = 7.8$ Hz, 1H), 7.96 (dd, $J = 7.8$ Hz, 1H), 7.88 (dd, $J = 8.0$ Hz, 1H), 7.78 (dd, $J = 8.3$ Hz, 1H), 7.60 (dt, $J = 7.5$ Hz, 1H), 7.57–7–59 (m, 1H), 7.33–7.53 (m, 2H), 5.84 (s, 2H), 4.11 (s, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): ppm, δ 186.6, 165.4, 143.5, 141.0, 136.4, 134.1, 133.4, 130.8, 128.3, 125.9, 123.7, 121.1, 111.66, 94.8, 67.2, 31.8; ESI-MS (m/z): 421.1 (M + 1), 231.0.

2-[2-(2-Iodo-phenyl)-oxazol-4-yl]-1-methyl-1*H*-benzimidazole (8a). Solid, mp 243–245°C; IR (KBr, cm^{-1}): 3674, 3486, 3102, 3039, 2884, 1956, 1751, 1628,



Scheme 3. Proposed mechanism.

Table 2. Preparation of ester upon reaction with carboxylic acid in acetone medium

Entry	Acid (**6**)	Ester (**7**)	Yield (%)	Time (h)	Mp (°C)
a			72	0.5	128–129
b			75	0.5	155–156
c			68	0.5	193–194
d			89	0.5	132–133
e			72	0.5	88–90
f			75	0.5	117–119
g			89	0.5	153–154

1610, 1578, 1560, 1491, 1476, 1466, 1420, 1334, 1312, 1279, 1259, 1246, 1225, 1162, 1143, 1090, 1061, 1029, 1002, 984, 880; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.16–8.22 (m, 2H), 7.82–7.91 (m, 2H), 7.65–7.74 (m, 2H), 7.50–7.55 (m, 2H), 7.42–7.46 (m, 1H), 3.90 (s, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): ppm, δ 165.1, 152.6, 143.5, 141.5, 134.5, 133.27, 131.9, 130.9, 128.5, 125.4, 124.9, 118.7, 114.2, 111.7,96.1, 31.4.

3-Phenyl-acrylic acid 2-(1-methyl-1*H*-benzimidazol-2-yl)-2-oxo-ethyl ester (7b). Solid, mp 155–156°C; IR (KBr, cm^{-1}): 3790, 3574, 3031, 1791, 1718, 1704, 1631, 1575, 1484, 1464, 1448, 1407, 1348, 1331, 1314, 1281, 1244, 1206, 1164, 1119, 1011, 983, 942, 896; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.87 (d, $J = 8.31$ Hz, 1H), 7.75–7.79 (m, 4H), 7.40–7.50 (m, 5H), 6.81 (d, $J = 16.1$ Hz, 1H), 5.7 (s, 2H), 4.10 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): ppm, δ 187.0, 165.6, 145.5, 143.5, 141.0, 136.4, 133.8, 130.6, 128.9, 128.4, 125.9, 123.7, 121.1, 117.1, 111.6, 66.5, 31.76; ESI-MS (m/z): 321.2 (M + 1), 131.1.

1-Methyl-2-(2-styryl-oxazol-4-yl)-1*H*-benzimidazole (8b). Solid, mp 217–218°C; IR (KBr, cm^{-1}): 3650, 3036, 2925, 2854, 1836, 1742, 1629, 1556, 1476, 1448, 1335, 1306, 1260, 1242, 1162, 1117, 1071, 1031, 1004, 959, 870; ^{1}H NMR (400 MHz, DMSO-d_6), δ_H 7.99 (d, $J = 15.9$ Hz, 1H), 7.70–7.88 (m, 5H), 7.47–7.69 (m, 5H), 7.02 (d, $J = 16.1$ Hz, 1H), 3.93 (s, 3H).

2-(1-Methyl-1*H*-benzimidazol-2-yl)-2-oxoethyl 4-cyanobenzoate (7c). Solid, mp 193–194°C; IR (KBr, cm^{-1}): 3637, 3381, 2951, 2231, 1945, 1792, 1732, 1698, 1607, 1579, 1487, 1463, 1409, 1358, 1307, 1278, 1250, 1196, 1118, 1036, 1016, 1003, 969, 751; ^{1}H NMR (400 MHz, DMSO-d_6); δ_H 8.19–8.22 (m, 2H), 8.06–8.08 (m, 2H), 7.87–7.89 (m, 1H), 7.76–7.79 (m,1H), 7.39–7.53 (m, 2H), 5.89 (s, 2H), 4.1 (s, 3H); ESI-MS (m/z): 320.1 (M + 1).

4-(4-(1-Methyl-1*H*-benzimidazol-2-yl)oxazol-2-yl)benzonitrile (8c). Solid, mp 306–309°C; IR (KBr, cm^{-1}): 3673, 3491, 3109, 2813, 2231, 1949, 1859, 1754, 1603, 1621, 1560, 1490, 1474, 1421, 1409, 1274, 1255, 1231, 1180, 1163, 1136, 1055, 1025, 984; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.35 (dd, $J = 6.8$ Hz, 2H), 8.14 (dd, $J = 6.6$ Hz, 2H), 7.82–7.87 (m, 2H), 7.70–7.73 (m, 1H), 7.50–7.54 (m, 2H), 3.88 (s, 3H).

3-Trifluoromethyl-benzoic acid 2-(1-methyl-1*H*-benzimidazol-2-yl)-2-oxo-ethyl ester (7d). Solid, mp 132–133°C; IR (KBr, cm^{-1}): 3635, 3072, 2939, 1935, 1836, 1738, 1706, 1616, 1593, 1585, 1541, 1488, 1460, 1434, 1407, 1358, 1340, 1333, 1291, 1252, 1200, 1173, 1155, 1116, 1093, 1070, 1040, 999, 919; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.36 (d, $J = 7.8$ Hz 1H), 8.30 (s, 1H), 8.13 (d, $J = 7.8$ Hz, 1H), 7.88 (dd, $J = 8.3$ Hz, 2H), 7.78 (d, $J = 8.3$ Hz, 1H), 7.41–7.53 (m, 2H), 5.90 (s, 2H), 4.10 (s, 3H); ESI-MS (m/z): 363.1(M + 1).

1-Methyl-2-[2-(3-trifluoromethyl-phenyl)-oxazol-4-yl]-1*H*-benzimidazole (8d). Solid, mp 132–133°C; IR (KBr, cm^{-1}): 3679, 3093, 1915, 1831, 1755, 1625, 1562, 1490, 1476, 1467, 1449, 1420, 1336, 1286, 1226, 1165, 1133, 1087, 1071, 1030, 1014, 1002, 988; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 8.50 (d, $J = 7.8$ Hz, 1H), 8.45 (s, 1H), 8.20 (d, $J = 7.8$ Hz, 1H), 7.80–7.95 (m, 3H), 7.70–7.73 (m, 1H), 7.50–7.54 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): ppm, δ 164.0, 152.9, 134.0, 133.2, 130.9, 130.6, 130.1, 129.5, 128.8, 128.4, 127.9, 126.4, 125.3, 124.8, 118.5, 114.1, 117.7, 31.3.

Succinic acid methyl ester 2-(1-methyl-1*H*-benzimidazol-2-yl)-2-oxo-ethyl ester (7e). Solid, mp 88–90°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.85–7.87 (m, 1H), 7.40–7.46 (m, 2H), 7.26–7.39 (m, 1H), 5.66 (s, 2H), 4.13 (s, 3H), 3.72 (s, 3H), 2.86 (t, $J = 6.9$ MHz, 2H), 2.71–2.75 (t, $J = 6.7$ Hz, 2H); ^{13}C

NMR (200 MHz, $CDCl_3$): ppm δ 186.8, 172.4, 171.7, 143.3, 141.6, 136.5, 126.3, 124.0, 121.8, 110.4, 66.8, 51.82, 31.8, 28.8, 28.7; ESI-MS (m/z): 305.0 (M + 1).

3-[4-(1-Methyl-1*H*-benzimidazol-2-yl)-oxazol-2-yl]-propionic acid methyl ester (8e). Solid, mp 148–150°C; ^{1}H NMR (400 MHz, DMSO-d_6); δ_H 7.71 (s, 1H), 7.51–7.57 (m, 2H), 7.16–7.23 (m, 2H), 4.12 (s, 3H), 3.6, (s, 3H), 2.99 (t, $J = 7.22$ Hz, 2H), 2.49–2.50 (t, $J = 6.9$ Hz, 2H).

2-(1-Methyl-1*H*-benzimidazol-2-yl)-2-oxoethyl acetate (7f). Solid, mp 117–119°C; IR (KBr, cm^{-1}): 3664, 3053, 3020, 2940, 2854, 1905, 1755, 1704, 1611, 1580, 1488, 1463, 1407, 1336, 1291, 1227, 1193, 995, 975; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H 7.85–7.88 (m, 1H), 7.36–7.48 (m, 3H), 5.6 (s, 2H), 4.13 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): ppm δ 187.2, 170.2, 143.4, 141.7, 136.6, 126.3, 124.0, 121.9, 110.5, 66.0, 31.9, 20.4; ESI-MS (m/z): 233.1 (M + 1), 211.1.

2-Methyl-4-(1-methyl-1*H*-benzimidazol-2-yl)oxazole (8f). Solid, mp 217–218°C; IR (KBr, cm^{-1}): 3632, 3079, 3051, 2881, 2508, 2240, 1975, 1975, 1856, 1782, 1708, 1628, 1611, 1557, 1492, 1476, 1417, 1372, 1334, 1316, 1270, 1245, 1203, 1195, 1119, 1033; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.83–7.86 (m, 1H), 7.50–7.69 (m, 2H), 7.48–7.49 (m, 2H), 3.92 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (200 MHz, $CDCl_3$): ppm δ 170.0, 152.3, 133.2, 130.9, 125.2, 124.7, 118.3, 114.1, 111.7, 31.3, 20.3.

2-(1-Methyl-1*H*-benzimidazol-2-yl)-2-oxoethyl benzoate (7g). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.06–809 (m, 2H), 7.88 (dd, $J = 8.05$ Hz, 1H), 7.78 (d, $J = 8.29$ Hz, 1H), 7.71–7.75 (m, 1H), 7.58–7.62 (m, 2H), 7.49–7.53 (m, 1H), 7.39–7.43 (m, 1H). ESI-MS (m/z): 295 (M + 1).

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