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Efficient synthesis and characterization of novel isoxazole derivatives including dihdyropyrazole and methanoisoindole moieties

Meliha Burcu Gürdere [1] Fatih Ertürk [2] Yakup Budak [1*] and Mustafa Ceylan [1]

[1]*Department of Chemistry, Faculty of Arts and Sciences, Tokat Gaziosmanpasa University, 60250 Tokat, Türkiye*
[2]*Vocational School, Occupational Health and Safety Programme, Istanbul Arel University, Istanbul, Türkiye*

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Abstract: Isoxazole and pyrazole derivatives have a wide range of biological activity and they are of great interest to medicinal chemist. In this study, the synthesis and characterization of a series of novel hybrid molecules containing pyrazole and isoxazole rings ((3a*S*,4S,4a*R*,7a*S*,8*S*,8a*S*)-6-(4-(1-acetyl-5-(4-(aryl/heteroaryl))-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3a*H*-4,8-methanoisoxazolo [4,5-*f*] isoindole-5,7(6*H*,7a*H*)-dione derivatives) were reported.

Keywords: Isoxazole; synthesis; characterization; NMR.

1. Introduction

Five membered heterocycles such as thiazole,[1] diydropyrazol[2] and tetrahyroisoxazole derivatives[3] are very important compounds due to their biological activities. These compounds can be easily synthesized by addition hydrazine and nitrile oxides to α,β-unsaturated compounds such as chalcones.[4,5] Tetrahydroisoxazole derivatives are an important class of heterocyclic pharmaceuticals and bioactive natural products, which have been widely applied in medicinal chemistry, material science, natural products, and some other fileds.[6] Great efforts have been made on the synthesis of isoxazole and their derivatives[7] due to their biological activities, including exhibit analgesic,[8] antinociceptive,[9] anticancer,[10] antitubercular,[11] potent and selective antagonism of the NMDA receptor[12] and anti-HIV activity[13] may allow differing helical strands. Also, isoxazoline and tetrahydroisoxazoles are versatile intermediates for the synthesis of a variety of bioactive compounds. For the synthesis of five membered heterocycles, cycloaddition reactions is one of the most effective methods.[14,15] The 1,3-dipolar cycloaddition of nitrile oxides to alkenes is a widely used for the synthesis of tetradydroisoxazoline derivatives[3].

* Corresponding author: E-mail: yakup.budak@gop.edu.tr

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In addition, dihydropyrazole is an important heterocyclic compound that is of intense interest to medical chemists because of its wide spectrum of biological activity. Easily synthesized dihydropyrazoles have important activities such as antimicrobial,[16] anticancer,[17] antioxidant,[18] antiamoebic,[19] anti-inflammatory,[20] antidiabetic,[21] diuretic[22] and carbonic anhydrase inhibition.[23]

In this study, as a continuation of our previous work, the synthesis and characterization of a series of novel hybrid molecules containing dihydropyrazole and tetrahydroisoxazole rings ((3a*S*,4*S*,4a*R*,7a*S*,8*S*,8a*S*)-6-(4-(1-acetyl-5-(4-(aryl/heteroaryl))-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3a*H*-4,8-methanoisoxazolo[4,5-*f*]isoindole-5,7(6*H*,7a*H*)-dione derivatives were reported.

2. Experimental

2.1. Chemical Materials and Apparatus

All chemicals and solvents were obtained from Merck (Germany) and Fluka (Germany). Melting points were measured on an Electrothermal 9100 apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-400 instrument. IR spectra (KBr disc) were recorded on a Jasco FT/IR-430 spectrometer. Elemental analyses were obtained from a LECO CHNS 932 Elemental Analyzer.

2.2. General procedure for the synthesis of (3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(4-(aryl/heteroaryl))-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione derivatives

Compounds **1a-j** (1 equiv.) and acetaldehyde oxime (4 equiv.) were dissolved in CH_2Cl_2 and cooled in the ice bath. Then NaOCl (4 equiv.) was added to this solution as dropwise. The reaction mixture was stirred at room temperature for 6 hours. At the end of the reaction, the mixture was extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4, and the solvent was removed on the evaporator. The products were crystallized with CH_2Cl_2-Hexane.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl) phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3a**):* Yield, 75%; m.p. 123-127 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.86 (d, *J* = 6.4 Hz, 2H), 7.35 (d, *J* = 1.6 Hz, 2H), 7.18-7.14 (m, 2H), 6.87-6.84 (m, 2H), 5.60-5.54 (dd, *J* = 11.8 Hz, 4.2 Hz, 1H), 4.65 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.78-3.71 (m, 1H), 3.41-3.31 (m, 2H), 3.19 (s, 3H), 3.13-3.12 (d, *J* = 4.8 Hz, 1H), 2.41 (bs, 3H), 1.98 (bs, 3H), 1.88-1.85 (d, *J* = 11.2 Hz, 1H), 1.68-1.65 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5 (2C), 168.9, 159.1, 159.0, 154.5, 152.5, 134.6, 132.6, 127.3 (2C), 127.1 (2C), 126.9 (2C), 81.5, 59.6, 56.2, 52.3, 46.0, 45.8, 44.3, 42.1, 35.9, 29.6, 22.0, 11.7. IR (KBr, cm^{-1}): 3005, 2985, 2968, 1768, 1711, 1673, 1603, 1511, 1444, 1411, 1366, 1323, 1257, 1172, 1125, 1063, 1035, 1017. Elemental Analysis Anal. calcd for $C_{29}H_{28}N_4O_5$: C, 67.96; H, 5.51; N, 10.93; Found: C, 68.09; H, 5.48; N, 10.97.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(p-tolyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3b**):* Yield 65%; m.p. 133-138 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.79 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.11 (bs, 4H), 5.57-5.53 (dd, *J* = 11.6 Hz, 4.4 Hz, 1H), 3.73-3.66 (dd, *J* = 17.6 Hz, 11.6 Hz, 1H), 3.51 (bs, 1H), 3.45-3.44 (m, 3H), 3.14-3.08 (dd, *J* = 17.8 Hz, 4.6 Hz, 1H), 2.41 (bs, 3H), 2.30 (bs, 2H), 1.79 (d, *J* = 8.8 Hz, 1H), 1.62 (d, *J* = 8.8 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.6 (2C), 169.0, 154.5, 152.9, 138.8, 137.4, 134.6, 133.3 (2C), 131.5, 129.1, 127.1, 126.8 (2C), 125.5 (2C), 59.9, 52.3, 47.1, 45.8, 45.5, 42.2, 25.3, 22.0, 21.1, 11.7. IR (KBr, cm^{-1}): 2974, 2961, 1768, 1718, 1676, 15916, 1513, 1440, 1409, 1353, 1327, 1258, 1172, 1131, 1058, 1034, 1014. Elemental Analysis Anal. calcd for $C_{29}H_{28}N_4O_4$: C, 70.15; H, 5.68; N, 11.28; Found: C, 70.09; H, 5.62; N, 11.34.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(3-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3c**):* Yield 565; m.p. 132-135 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.82 (d, *J*= 7.6 Hz, 2H), 7.32 (d, *J*= 7.6 Hz, 2H), 7.28-7.17 (m, 3H), 7.10-7.08 (dd, *J* = 6.8 Hz, 1,2 Hz, 1H), 5.57-5.52 (dd, *J* = 12 Hz, 4.8 Hz, 1H), 4.61 (d, *J*= 7.6 Hz, 1H), 3.78-3.70 (dd, *J* = 17.6 Hz, 12 Hz, 1H), 3.36-3.28 (m, 2H), 3.19-3.08 (m, 3H), 3.09-2.96 (m, 1H), 2.42 (bs, 3H), 1.94 (bs, 3H), 1.79 (d, *J* = 11.2 Hz, 1H), 1.63 (d, *J*= 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5 (2C), 169.0, 154.5, 152.7, 143.6(2C), 134.8, 134.6, 133.4, 131.2, 130.2, 128.0, 127.2 126.8, 125.7 (2C), 81.5, 59.6, 56.2, 46.5, 44.3, 42.1, 41.2, 35.9, 25.3, 21.9, 11.7. IR (KBr, cm^{-1}): 2987, 2978, 1772, 1714, 1670, 1596, 1511, 1433, 1410, 1357, 1321, 1255, 1166, 1121, 1060, 1031, 1012. Elemental Analysis Anal. calcd for $C_{28}H_{25}ClN_4O_4$: C, 65.05; H, 4.87; N, 10.84; Found: C, 65.01; H, 4.83; N, 10.79.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3d**):* Yield 62%; m.p. 160-164 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 (d, *J*= 8.8 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 5.60-5.54 (m, 1H), 4.65 (d, *J* = 8 Hz, 1H), 3.78-3.74 (dd, *J* = 9.6; 6.0 Hz, 1H), 3.42-3.32 (m, 1H), 3.20 (d, *J*= 6.4 Hz, 3H), 3.16-3.08 (m,1H), 3.00 (d, *J* = 4.8 Hz, 1H), 2.42 (s, 3H), 1.97 (s, 3H), 1.85-1.82 (d, *J* = 11.2 Hz, 1H), 1.68-1.65 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5 (2C), 168.9, 154.5, 152.2, 140.1, 134.6, 133.5, 131.7, 129.1 (2C), 129.1 (2C), 126.8 (2C), 126.7 (2C), 81.5, 59.6, 56.2, 46.5, 44.3, 42.1, 41.2, 35.9, 25,3, 21.9, 11.7. IR (KBr, cm^{-1}): 2997, 2988, 1769, 1717, 1670, 1596, 1518, 1438, 1405, 1359, 1326, 1257, 1174, 1123, 1065, 1039, 1018. Elemental Analysis Anal. calcd for $C_{28}H_{25}ClN_4O_4$: C, 65.05; H, 4.87; N, 10.84; Found: C, 65.12; H, 4.83; N, 10.78.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(2-bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3e**):* Yield 74%; m.p. 175-180 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* =7.6 Hz, 1H), 7.33-7.26 (m, 3H), 7.15 (t, *J*= 7.0 Hz, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 5.97-5.92 (dd, *J* = 11.2, 7.2 Hz, 1H), 4.65 (d, *J* = 8 Hz, 1H), 3.92-3.84 (dd, *J* = 12.0, 5.6 Hz, 1H), 3.41-3.31 (m, 2H), 3.19 (brs, 3H), 3.08-3.01 (m, 1H), 2.51 (s, 3H), 1.98 (s, 3H), 1.84 (d, *J* = 10.8 Hz, 1H), 1.67 (d, *J* = 10.4 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.8 (2C), 168.9, 154.5, 152.2, 139.8, 133.2, 132.7, 131.8, 129.1, 127.9, 127.3(2C), 126.6 (2C), 121.5, 81.5, 60.1, 56.2, 46.0, 41.5, 41.2, 35.9, 29.7, 21.9, 11.7. IR (KBr, cm^{-1}): 2998, 2958, 1772, 1714, 1671, 1592, 1519, 1438, 1405, 1367, 1322, 1251, 1162, 1124, 1066, 1037, 1014. Elemental Analysis Anal. calcd for $C_{28}H_{25}BrN_4O_4$: C, 59.90; H, 4.49; N, 9.98; Found: C, 59.86; H, 5.51; N, 10.02.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(3-bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3f**):* Yield 58%; m.p. 141-145 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.41-7.38 (m, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 7.26-7.14 (m, 3H), 5.59-5.55 (dd, *J* = 12.2 Hz, 4.6 Hz, 1H), 4.65 (d, *J* = 8 Hz, 1H), 3.80-3.71 (m, 1H), 3.41-3.31 (m, 1H), 3.21-3.19 (m, 3H), 3.17-3.13 (m, 1H), 3.01-3.00 (d, *J* = 4.8 Hz, 1H), 2.43 (s, 3H), 1.97 (s, 3H), 1.85-1.82 (d, *J* = 11.2 Hz, 1H), 1.68-1.65 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 175.4 (2C), 168.9, 154.5, 152.7, 143.8, 134.6 (2C), 130.9, 130.5 (2C), 128.6 (2C), 127.4, 127.2, 126.8, 123.0, 81.5, 59.9, 56.2, 46.5, 45.5, 42.1, 41.2, 35.9, 29.7, 21.9, 11.7. IR (KBr, cm^{-1}): 3010, 2975, 2962, 1775, 1716, 1673, 1582, 1514, 1438, 1405, 1358, 1326, 12538, 1163, 1123, 1063, 1035, 1014. Elemental Analysis Anal. calcd for $C_{28}H_{25}BrN_4O_4$: C, 59.90; H, 4.49; N, 9.98; Found: C, 59.94; H, 4.45; N, 9.94.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(4-bromophenyl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3g**):* Yield 54%; m.p. 136-140 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm): δ = 7.83 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.*0* Hz, 2H), 5.55-5.49 (m, 1H), 4.62 (d, *J* = 8 Hz, 1H), 3.71-3.68 (m, 1H), 3.36-3.30 (m, 1H), 3.18 (d, *J* = 8.0 Hz, 3H), 3.09-3.05 (m, 1H), 2.97 (d, *J* = 4.8 Hz, 1H), 2.40 (s, 3H), 1.94 (s, 3H), 1.79 (d, *J* = 9.2 Hz, 1H), 1.61(d, *J* = 8.0 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 176.5 (2C), 168.9, 154.6, 152.6, 140.7, 134.6, 132.8, 131.6 (2C), 131.2

(2C), 129.0 (2C), 127.3 (2C), 121.5, 81.5, 52,3, 45.5, 44.3, 42.0, 41.2, 35.8, 25.3, 21.9, 21,4, 11.7. IR (KBr, cm^{-1}): 3014, 2989, 2968, 1762, 1724, 1680, 1584, 1512, 1434, 1408, 1353, 1322, 1253, 1168, 1122, 1060, 1031, 1012. Elemental Analysis Anal. calcd for $C_{28}H_{25}BrN_4O_4$: C, 59.90; H, 4.49; N, 9.98; Found: C, 59.87; H, 5.54; N, 10.05.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(furan-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3h**):* Yield 60; m.p. 205-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$ ppm) δ: 7.89 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.32 (m, 1H), 6.36-6.33 (m, 2H), 5.73 (dd, *J* = 11.8; 4.6 Hz, 1H), 4.67 (d, *J* = 8.4 Hz, 1H), 3.63 (dd, *J* = 17.6, 11.6 Hz, 1H), 3.58 (d, *J* = 11.6 Hz, 1H), 3.48 (d, *J* = 4.8 Hz, 1H), 3.44-3.33 (m, 2H), 3.22 (d, *J* = 6.8 Hz, 2H), 3.02 (d, *J* = 4.8 Hz, 1H), 2.41 (s, 3H), 1.99 (s, 3H), 1.85 (d, *J* = 11.2 Hz, 1H), 1.68 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$ ppm) δ = 175.5, 174.9, 169.1, 154.6, 152.8, 151.9, 142.1, 132.7, 131.9, 127.4, 126.7, 110.6, 107.8, 81.5, 56.3, 53.6, 46.6, 46.1, 44.4, 41.3, 38.1, 35.9, 22.0, 11.8. IR (KBr, cm^{-1}): 3114, 2979, 2958, 1772, 1714, 1670, 1596, 1517, 1441, 1408, 1363, 1320, 1255, 1173, 1127, 1060, 1032, 1013. Elemental Analysis Anal. calcd for $C_{26}H_{24}N_4O_5$: C, 66.09; H, 5.12; N, 11.86; Found: C, 66.03; H, 5.08; N, 11.91.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(thiophen-2-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3i**):*Yield 70%; m.p. 174-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$ ppm) δ: 7.9 (brd, *J* = 8.4 Hz, 2H), 7.36 (brd, *J* = 8.4 Hz, 2H), 7.21 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 6.95 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.96 (dd, *J* = 11.4, 3.6 Hz, 1H), 4.67 (d, *J* = 8.4 Hz, 1H), 3.75 (dd, *J* = 17.6, 11.6 Hz, 1H), 3.43-3.33 (m, 3H), 3.22 (d, *J* = 7.2 Hz, 2H), 3.02 (d, *J* = 4.8 Hz, 1H), 2.42 (s, 3H), 1.99 (s, 3H), 1.86 (d, *J* = 11.2 Hz, 1H), 1.69 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$ ppm) δ = 175.5, 174.9, 169.0, 154.6, 152.6, 134.0 (2C), 132.7, 131.9, 127.4, 126.9, 126.7, 124.9, 124.7, 81.6, 56.3, 55.5, 46.6, 46.1, 44.4, 41.9, 41.3, 35.9, 22.0, 11.8. IR (KBr, cm^{-1}): 3127, 2971, 2960, 1772, 1760, 1666, 1519, 1409, 1376, 1326, 1172. Elemental Analysis Anal. calcd for $C_{26}H_{24}N_4O_4S$: C, 63.92; H, 4.95; N, 11.47; S, 6.56; Found: C, 63.87; H, 5.50; N, 11.51; S, 6.84.

*(3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(pyridin-4-yl)-4,5-dihydro-1H-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3aH-4,8-methanoisoxazolo[4,5-f]isoindole-5,7(6H,7aH)-dione (**3j**):*Yield 55%; m.p. 260-63°C. ^{1}H NMR (400 MHz, $CDCl_3$ ppm) δ: 8.60 (brs, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 5.59 (dd, *J* = 12.0, 4.8, 1H), 3.80 (dd, *J* = 17.8, 12.0 Hz, 1H), 3.73 (dd, *J* = 14.0, 6.8 Hz, 1H), 3.42-3.32 (m, 3H), 3.20 (d, *J* = 8.4 Hz, 2H), 3.16 (d, *J* = 4.8 Hz, 1H), 3.11 (d, *J* = 4.8 Hz, 1H), 2.47 (s, 3H), 1.97 (s, 3H), 1.86 (d, *J* = 11.2 Hz, 1H), 1.67 (d, *J* = 11.2 Hz, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$ ppm) δ = 176.6, 175.6, 169.2, 153.0, 152.8, 150.3, 150.0 (2C), 140.9, 133.6, 130.8,127.3 127.0, 126.1 (2C), 81.4, 59.1, 52.2, 45.9, 45.8, 44.3, 41.7, 35.9, 21.7, 18.2,11.6. IR (KBr, cm^{-1}): 3114, 2979, 2958, 1772, 1714, 1670, 1596, 1517, 1438, 1405, 1363, 1322, 1253, 1168, 1122, 1060, 1031, 1012. Elemental Analysis Anal. calcd for $C_{27}H_{25}N_5O_4$: C, 67.07; H, 5.21; N, 14.48; Found: C, 67.13; H, 5.17; N, 14.52.

3. Results and Discussions

The starting compounds **1a-j** were synthesized by our previously published procedure.[24,25] Then the reaction of compounds **1a-j** with acetaldoxime **(2)** (4 equiv.) in the presence of NaOCl (4 equiv.) in CH_2Cl_2 at 0-5°C for 6 hours gave the isoxazole derivatives **(3a-j)** in moderate to good yields (54-75%) (Scheme 1, Table 1). The products **3a-j** were purified by crystallization in CH_2Cl_2-Hexane. It was observed that electron donating groups in the phenyl ring increased the yield (Table 1, Entry 1) while the electron withdrawing groups decreased the yield (Table 1, Entry 10).

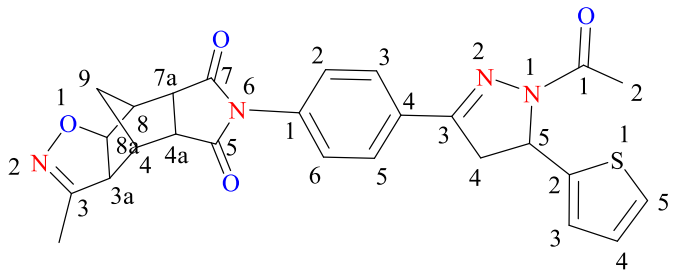
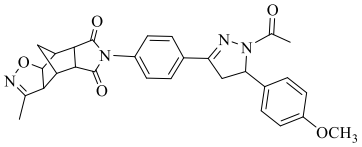
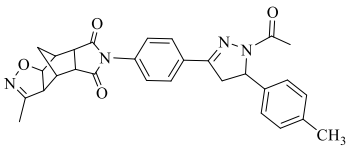
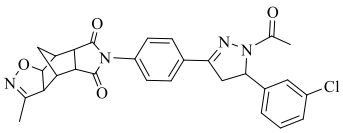
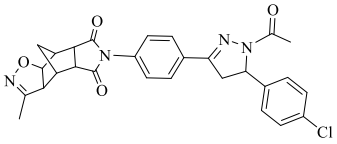
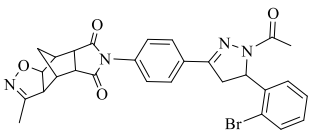
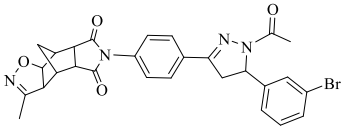
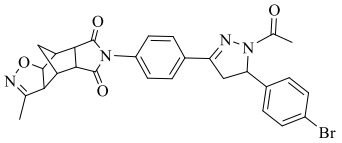
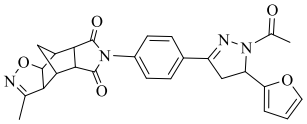
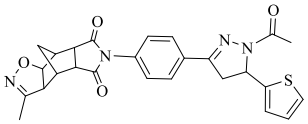
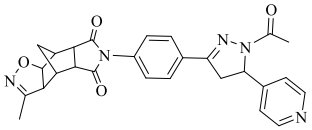
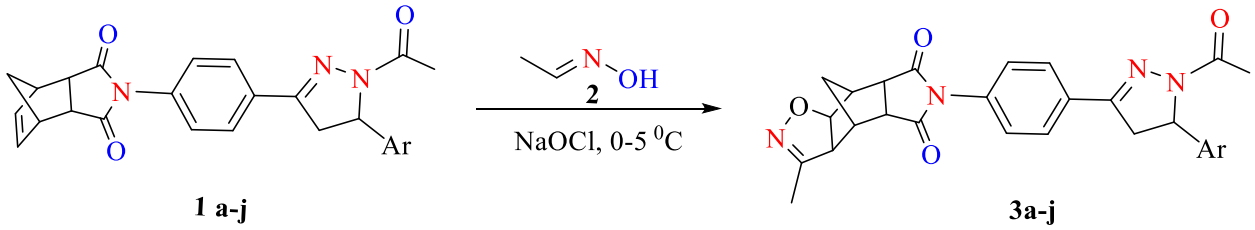


Figure 1. Numbering scheme for compound 2h

Table 1. Synthesized compounds **3a-j**

Entry	Compound	Compound No	Yield (%)	M.p. (℃)
1		**3a**	75	124-127
2		**3b**	65	135-138
3		**3c**	56	132-135
4		**3d**	62	160-164
5		**3e**	74	177-180
6		**3f**	58	141-145
7		**3g**	54	136-140
8		**3h**	60	205-208
9		**3i**	70	174-176
10		**3j**	55	260-263



Scheme 1. Synthesis of **3a-j**

When acetaldoxime is added to the double bond, it is expected that the endo and exo products will be formed, but only endo addition was observed in this reaction. In the literature, in the 1,3-dipolar cycloaddition of nitrile oxides to bicyclo[2.2.1]heptene systems, it is reported the only endo product was formed.[3, 26, 27]

The structures of compounds **3a-j** were explained by spectral data (IR, ^{1}H-NMR and ^{13}C-NMR) and Elemental analysis. The **3h** was chosen as an example to explain the structures of the compounds. In the ^{1}H-NMR spectrum of compound **3h**, the protons of phenyl ring gave the AA'BB' systems as expected at 7.87 ppm (d, J = 8.4 Hz) and at 7.35 ppm (d, J = 8.8 Hz), respectively. Moreover, the proton H5 of the thiophene ring resonates as doublet of doublet (J = 5.2, 1.2 Hz) at 7.21 ppm, the H4 proton gave the doublet of doublet at 6.95 ppm (J = 5.2, 3.6 Hz), and the H3 proton gave the doublet at 7.05 ppm (J = 3.6 Hz), respectively. In addition, the protons of pyrazole ring gave the ABX system in the regions of 3.34 ppm (1H, HA, dd, J_{AX} = 3.8 Hz, dd, J_{AB} = 17.6 Hz), 3.75 ppm (1H, HB, dd, J_{AB} = 17.6 Hz, dd, J_{BX} = 11.4 Hz) and 5.96 ppm (1H(H5), HX, dd, J_{AX} = 3.8 Hz, dd, J_{BX} = 11. 4 Hz), respectively. Furthermore, while the H8a proton of the isoxazole ring gave the doublet at 4.76 ppm (J = 8.5 Hz), the proton H3a gave the doublet at 3.02 ppm (J = 8.8 Hz). The H9 protons gave the AX system at 1.85 and 1.68 ppm (J = 11.2 Hz), respectively. Moreover, disappearance of double bond protons in the starting compounds in the ^{1}H-NMR spectrum and appearance of a signal at 81.5 ppm (C-O) in the ^{13}C-NMR spectrum is evidence that the isoxazole ring is formed. All spectral data were in good agreement with the proposed structures.

4. Conclusion

In summary, a series of novel hybrid compounds ((3aS,4S,4aR,7aS,8S,8aS)-6-(4-(1-acetyl-5-(4-(aryl/heteroaryl))-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl)-3-methyl-4,4a,8,8a-tetrahydro-3a*H*-4,8-methanoisoxazolo [4,5-f] isoindole-5,7(6*H*,7a*H*)-dione derivatives) were synthesized by addition of acetaldoxime in the presence of NaOCl to starting compounds **1a-j** in moderate to good yields (54-75%). The structures of synthesized compounds **3a-j** were explained by spectral data (IR, ^{1}H-NMR and ^{13}C-NMR) and Elemental analysis.

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Supporting Information

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ORCID
Meliha Burcu Gürdere: 0000-0003-4285-5528
Fatih Ertürk: 0000-0003-3696-7558
Yakup Budak: 0000-0001-7108-5548
Mustafa Ceylan: 0000-0002-9184-4385

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