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SIMPLE THREE STEPS SYNTHESIS OF POTENTIAL MEDICINE FOR METABOLIC SYNDROME

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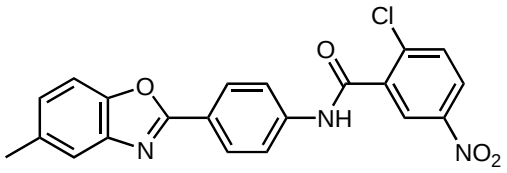
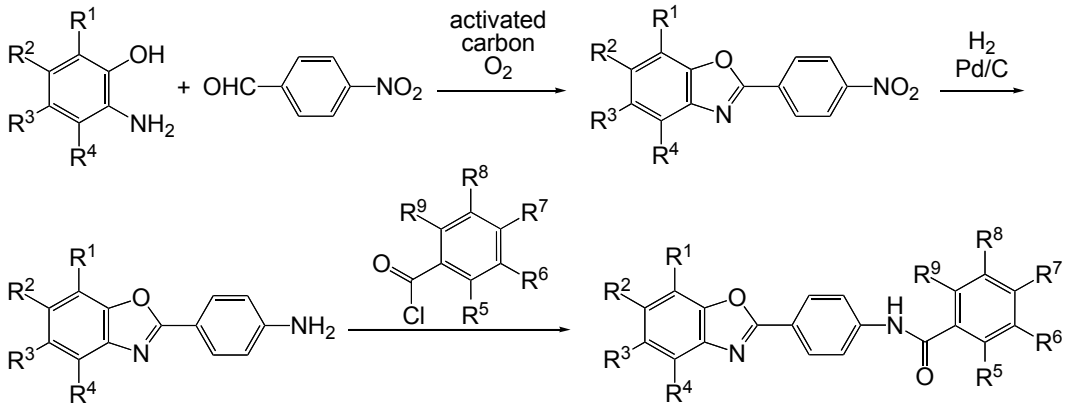
Abstract – Efficient synthesis of the derivatives of JTP-426467 was achieved by three steps including 1) oxidative aromatization promoted by activated carbon, 2) hydrogenation, 3) amidation to afford the desired amide compounds in high yield.

The compound, JTP-426467 is the potential candidate compound for metabolic syndrome developed by JT group.[1] This compound contains 2-phenylbenzoxazole moiety and amide bond.



JTP-426467

Recently, we have developed the method for direct preparation of 2-arylbenoxazoles under O_2 atmosphere by the aid of activated carbon.[2] Therefore, we made plan to synthesize some analogues of JTP-426467.



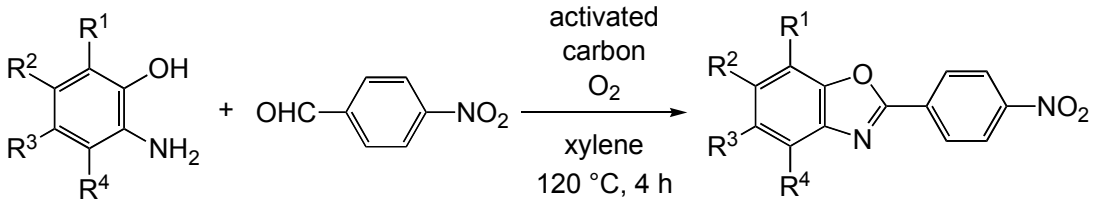
Scheme 1

This paper is dedicated to Prof. Dr. Albert Eschenmoser on the occasion of his 85th birthday.

In this paper, we would like to report general and simple three step synthesis of potential medicinal compounds for metabolic analogues of JYP-426567 based on the strategy of preparation of 2-(3-nitrophenyl)benoxazoles, followed by hydrogenation of nitro group to amine and final amidation step as shown Scheme 1.

At first, we examined the reaction of 2-aminophenol with 4-nitrobenzaldehyde promoted by 100 weight% of activated carbon (Charcoal Activated, TOKYO CHEMICAL INDUSTRY CO., LTD (TCI)), in xylene under oxygen atmosphere. As summarized in Table 1, a variety of substituted 2-aminophenols (**1a**—**5a**) reacted with 4-nitrobenzaldehyde in xylene at 120 °C for 4 h to afford the corresponding 2-(4-nitrophenyl)benzoxazole (**1b**—**5b**) in satisfactory yield (80—88% yield). The present reactions will include imine formation, followed by cyclization affording dihydro-2-(4-nitrophenyl)benzoxazole and then oxidative aromatization. This first step, that is, direct synthesis of 2-(4-nitrophenyl)benzoxazoles promoted by activated carbon and molecular oxygen is environmentally friendly.[3]

Table 1. Direct synthesis of 2-(4-nitrophenyl)benzoxazoles[a]



1a—5a **1b—5b**

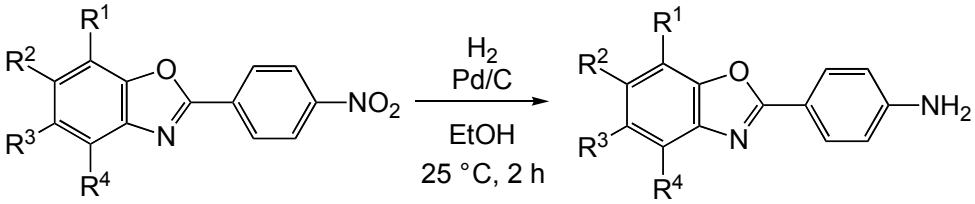
	substrate					product	
entry		R^1	R^2	R^3	R^4		yield/%[b]
1	**1a**	H	H	H	H	**1b**	88
2	**2a**	H	H	H	Me	**2b**	83
3	**3a**	H	H	Me	H	**3b**	84
4	**4a**	H	H	Cl	H	**4b**	80
5	**5a**	H	H			**5b**	87

[a] All reactions were carried out in xylene at 120 °C for 4 h.

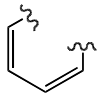
[b] Isolated yield by fractional recrystallizations.

The second step is transformation of nitro group to amine to give 2-(4-aminophenyl)benzoxazoles by usual hydrogenation with H_2 and Pd/C system in ethanol. This conversion also proceeded smoothly under mild conditions (at 25 °C for 2 h) as shown in Table 2.

Table 2. Hydrogenation of nitro group[a]



1b—5b **1c—5c**

entry	substrate					product	
		R^1	R^2	R^3	R^4		yield/%[b]
1	**1b**	H	H	H	H	**1c**	85
2	**2b**	H	H	H	Me	**2c**	86
3	**3b**	H	H	Me	H	**3c**	85
4	**4b**	H	H	Cl	H	**4c**	86
5	**5b**	H	H			**5c**	77

[a] All reactions were carried out in ethanol at 25 °C for 2 h.

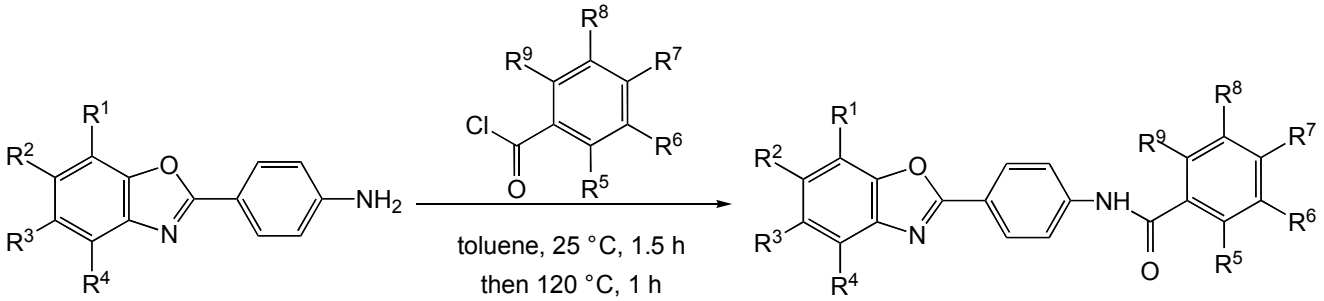
[b] Isolated yield by fractional recrystallizations.

The third step is amidation of various substituted benzoyl chlorides with amines (**1c—5c**). As shown in Table 3, all substituted benzoyl chlorides we examined reacted with amines smoothly to give the desired amide compounds (**1d—5d**) in high yield (82—96%). The present our method is the shortest and most convenient synthesis of analogues of JTP-426467 those have potential medicinal compounds for metabolic syndrome. It should be noted that all the compounds were obtained by recrystallization without using silica-gel column chromatography. Wide applicability of substrates and operational simplicity should be also mentioned.

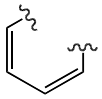
EXPERIMENTAL

General: All melting points were measured on a Yanaco MP-500D and uncorrected. IR spectra were measured on a PERKIN ELMER FT-IR Spectrometer SPECTRUM 1000. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were recorded on a JEOL JNM-LA 400 using Me_4Si as the internal standard in $CDCl_3$ or DMSO-d_6. Elemental analyses were performed with a Yanaco CHN Corder MT-5. Filtrations were carried out using nacalai tesque Celite®500 (grain size 1.5 μm) or nacalai tesque Hyflo Super-Cel® (grain size 7 μm). Thin-layer chromatography (TLC) was carried out on Merck 25 TLC aluminum Sheets silica gel 60 F_{254} (layer thickness 0.2 mm).

Table 3. Reaction of amines **(1c)**—**(5c)** with various substituted benzoyl chlorides[a]



1c—5c **1d—5d**

		product						
entry	substrate		R^5	R^6	R^7	R^8	R^9	yield/%[b]
1	**1c**	**1d**	H	H	H	H	H	93
2[c]	**2c**	**2d (1)**	Cl	H	H	Me	H	87
3	**2c**	**2d (2)**	Cl	H	H	NO_2	H	82
4	**3c**	**3d**	Cl	H	H	NO_2	H	95
5	**4c**	**4d**	Me	H	Me	H	Me	82
6	**5c**	**5d (1)**	H	H	OMe	H	H	96
7	**5c**	**5d (2)**	H	H	H			87

[a] All reactions were carried out in toluene at 25 °C for 1.5 h then 120 °C for 1 h.
[b] Isolated yield by fractional recrystallizations. [c] In benzene.

General procedure for direct synthesis of 2-(4-nitrophenyl)benzazoles (Table 1): A mixture of substituted 2-aminophenol (10 mmol), 4-nitrobenzaldehyde (10 mmol) and 100 wt% of activated carbon (Charcoal Activated, TOKYO CHEMICAL INDUSTRY CO., LTD (TCI)), in xylene (22 mL) was placed in a 100 mL three-necked flask under an oxygen atmosphere and stirred at 120 °C for 4 h. The reaction mixture was then filtered using Celite. After the filtrate was concentrated, the product was isolated by recrystallization from toluene to give 2-(4-nitrophenyl)benzazoles (**1b**—**5b**).

2-(4-Nitrophenyl)benzoxazole (1b). pale brown needle. mp 266.0−266.4 °C (lit.,[4] 266−268 °C). IR (KBr): 3108,1597, 1554, 1521, 1484, 1450, 1338, 1104, 1057, 851, 766, 751, 706 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.8 Hz, 2H), 8.40 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 6.8 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.5−7.4 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 151.0, 141.9, 132.8, 128.4, 126.3, 125.2, 124.2, 120.7, 111.0, 97.4. Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 64.73; H, 3.36; N, 11.52.

4-Methyl-2-(4-nitrophenyl)benzoxazole (2b). pale yellow needle. mp 207.5−208.3 °C. IR (KBr): 3100, 1596, 1555, 1534, 1484, 1351, 1306, 1237, 1066, 863, 852, 781, 757, 709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 8.8 Hz, 2H), 8.38 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.32 (dd, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 2.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 150.8, 149.2, 141.3, 133.1, 131.4, 128.3, 126.0, 125.6, 124.1, 108.1, 16.5. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N,11.02. Found: C, 65.93; H, 4.03; N, 10.71.

5-Methyl-2-(4-nitrophenyl)benzoxazole (3b). pale yellow solid. mp 211.1−212.1 °C (lit.,[5] 220−221 °C). IR (KBr): 3103, 1602, 1555, 1521, 1482, 1343, 1289, 1105, 1061, 853, 801, 706 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.5−8.4 (m, 4H), 7.61 (s, 1H), 7.50 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 149.2, 149.2, 142.1, 135.2, 132.9, 128.2, 127.5, 124.1, 120.4, 110.3, 21.5. Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 65.94; H, 3.99; N, 11.06.

5-Chloro-2-(4-nitrophenyl)benzoxazole (4b). pale orange flake. mp 245.4−246.8 °C (lit.,[5] 248−250 °C). IR (KBr): 3091, 1552, 1519, 1452, 1349, 1331, 1285, 1065, 861, 853, 814, 707 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 9.0 Hz, 2H), 8.40 (d, *J* = 9.0 Hz, 2H), 7.81 (d, *J* = 2.0 Hz, 1H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.41 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 143.0, 132.3, 130.8, 128.6, 127.8, 126.7, 124.3, 120.6, 111.7, 97.4. Anal. Calcd for $C_{13}H_7ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.81; H, 2.69; N, 10.27.

2-(4-Nitrophenyl)naphth[1,2-*d*]oxazole (5b). pale yellow solid. mp 242.5−243.7 °C (lit.,[6] 240 °C). IR (KBr): 3073, 1606, 1550, 1534, 1482, 1378, 1346, 1288, 1053, 1008, 862, 854, 816, 713 cm^{-1}. ^1H NMR (400 MHz, CDCl): δ 8.60 (d, *J* = 8.0, 1H), 8.50 (d, *J* = 7.8 Hz, 2H), 8.41 (d, *J* = 7.8 Hz, 2H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.73 (dd, *J* = 7.7 Hz, 7.7 Hz, 1H), 7.60 (dd, *J* = 8.0 Hz, 7.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 148.6, 137.9, 137.8, 133.1, 131.4, 128.8, 128.0, 127.5, 126.6, 125.9, 124.3, 122.2, 110.8. Anal. Calcd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 70.48; H, 3.50; N, 9.99.

General procedure for hydrogenation nitro group of 1b—5b to 1c—5c (Table 2). A mixture of various 2-(4-nitrophenyl)benzazoles (3 mmol), 50 wt% of 5% Pd/C, and ethanol (8 mL) was placed in a flask under an hydrogen atmosphere using a balloon. The whole was stirred at 25 °C for 2 h at this

temperature. After confirmation of the completion of the reaction by TLC analysis (hexane : EtOAc = 3 : 1), Pd/C was filtered off using celite. The filtrate was evaporated then recrystallized from a mixture of ethyl acetate and hexane to give amines **1c—5c**.

2-(4-Aminophenyl)benzoxazole (1c). pale yellow solid. mp 180.3−181.0 °C (lit.,[7] 172−174 °C). IR (KBr): 3470, 3290, 3183, 1607, 1497, 1455, 1441, 1311, 1247, 1056, 830, 759, 744, 511 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.06 (dt, *J* = 8.8 Hz, 2.4 Hz, 2H), 7.7 (m, 1H), 7.5 (m, 1H), 7.4−7.3 (m, 2H), 6.76 (dt, *J* = 8.8 Hz, 2.8 Hz, 2H), 4.05 (br s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.8, 150.5, 149.7, 142.4, 129.4, 124.2, 124.2, 119.3, 116.8, 114.6, 110.2. Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33. Found: C, 74.08; H, 4.86; N, 13.14.

4-Methyl-2-(4-aminophenyl)benzoxazole (2c). colorless solid. mp 147.5−148.6 °C. IR (KBr): 3480, 3386, 3324, 3215, 1607, 1502, 1440, 1310, 1245, 1179, 1039, 864, 830, 754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (dt, *J* = 8.8 Hz, 1.9 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.18 (dd, *J* = 7.9 Hz, 7.4 Hz, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 6.76 (dt, *J* = 8.8 Hz, 2.3 Hz, 2H), 4.04 (br s, 2H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 150.3, 149.5, 141.6, 129.8, 129.3, 124.8, 123.8, 117.2, 114.6, 107.5, 16.6. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.80; H, 5.45; N, 12.31.

5-Methyl-2-(4-aminophenyl)benzoxazole (3c). yellow crystal. mp 196.5−197.0 °C (lit.,[8] 191−193 °C). IR (KBr): 3473, 3303, 1620, 1499, 1427, 1306, 1263, 1178, 1057, 927, 835, 792, 699, 513 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (dt, *J* = 8.8 Hz, 1.2 Hz, 2H), 7.49 (d, *J* = 0.8 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.09 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 6.76 (dt, *J* = 8.8 Hz, 1.2 Hz, 2H), 4.04 (br s, 2H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 152.5, 148.1, 142.3, 133.6, 128.9, 124.9, 118.7, 113.6, 112.9, 109.7, 21.1. Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.85; H, 5.41; N, 12.30.

5-Chloro-2-(4-aminophenyl)benzoxazole (4c). pale yellow solid. mp 205.1−206.6 °C (lit.,[9] 197 °C). IR (KBr): 3424, 3319, 3215, 1639, 1611, 1502, 1443, 1312, 1258, 1179, 1061, 918, 832, 802, 517 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 1.8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.34 (dd, *J* = 8.8 Hz, 1.8Hz, 1H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.09 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.3, 152.9, 148.8, 143.6, 129.3, 128.6, 123.9, 118.4, 113.5, 112.1, 111.6. Anal. Calcd for $C_{13}H_9ClN_2O$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.87; H, 3.84; N, 11.44.

2-(4-Aminophenyl)naphth[1,2-*d*]oxazole (5c). pale yellow solid. mp 242.4−244.3 °C. IR (KBr): 3482, 3317, 3189, 1617, 1495, 1378, 1308, 1243, 1179, 1007, 799, 735, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.65 (dd, *J* = 8.0 Hz, 7.4 Hz, 1H), 7.53 (dd, *J* = 7.8 Hz, 7.4 Hz, 1H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.1 (br s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 152.2, 146.9, 137.1, 130.8, 128.7, 128.7, 126.8, 125.4, 125.2, 124.6, 121.6, 113.6, 113.2, 110.9. Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.22; H, 4.73; N, 10.29.

General procedure for amidation: synthesis of 1d—5d (Table 3).

A mixture of substitute benzoic acid, thionyl chloride and toluene was refluxed overnight to prepare substituted benzoyl chloride. Then, in a three-necked flask, to a mixture of K_2CO_3, amines (**1c**—**5c**) and toluene (9 mL), substituted benzoyl chloride was added drop wise for 1.5 h at room temperature (25 °C). After that, the whole was stirred at 110 °C for 1 h. After evaporation, $CHCl_3$ and H_2O were added, then extracted and recrystallized from toluene to give the amide **1d—5d**.

***N*-[4-(2-Benzoxazolyl)phenyl]benzamide (1d).** yellow solid. mp 235.7−236.7 °C (lit.,[10] 225−227 °C). IR (KBr): 3373, 3055, 1653, 1601, 1528, 1502, 1455, 1410, 1327, 1249, 835, 743, 704, 517 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.8, 2H), 8.0 (s, 1H), 7.90 (d, *J* = 7.2 Hz, 2H), 7.86 (d, *J* = 8.8, 2H), 7.8−7.7 (m, 1H), 7.6−7.5 (m, 2H), 7.5−7.4 (m, 2H), 7.4−7.3 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.0, 162.3, 150.2, 142.6, 141.7, 134.7, 131.9, 128.5, 128.1, 127.9, 125.2, 124.8, 121.2, 120.3, 119.6, 110.8. Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.18; H, 4.53; N, 8.86.

2-Chloro-5-methyl-*N*-[4-(6-methyl-2-benzoxazolyl)phenyl]benzamide (**2d(1)**). colorless solid. mp 194.9−196.2 °C. IR (KBr): 3285, 3116, 1664, 1595, 1526, 1503, 1410, 1326, 1243, 1178, 1067, 1037, 826, 753, 526 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.87 (s, 1H), 8.20 (d, *J* = 8.8 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.32 (dd, *J* = 8.0 Hz, 7.4 Hz, 1H), 7.22 (d, *J* = 7.4, 1H), 2.59 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.4, 161.4, 149.9, 142.0, 140.8, 137.0, 136.3, 131.8, 129.6, 129.5, 129.3, 128.2, 126.9, 125.2, 124.9, 121.6, 119.7, 108.0, 20.2, 16.3. Anal. Calcd for $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55; N, 7.43. Found: C, 70.39; H, 4.65; N, 7.73.

2-Chloro-*N*-[4-(6-methyl-2-benzoxazolyl)phenyl]-5-nitrobenzamide (**2d(2)**). Colorless needle. mp

255.7−257.5 °C. IR (KBr): 3253, 3097, 1669, 1608, 1517, 1412, 1352, 1324, 1268, 1243, 1180, 1064, 881, 837, 752, 707 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 11.10 (s, 1H), 8.56 (d, J = 3.2 Hz, 1H), 8.37 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 8.24 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.31 (dd, J = 8.3 Hz, 7.7 Hz, 1H), 7.23 (d, J = 7.7 Hz, 1H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 161.3, 149.9, 146.2, 141.5, 140.8, 137.4, 137.1, 131.4, 129.7, 128.2, 125.9, 125.2, 125.0, 124.0, 122.0, 120.0, 108.1, 16.3. Anal. Calcd for $C_{21}H_{14}ClN_3O_4$: C, 61.85; H, 3.46; N, 10.30. Found: C, 62.00; H, 3.51; N, 10.05.

2-Chloro-*N*-[4-(5-methyl-2-benzoxazolyl)phenyl]-5-nitrobenzamide (**3d**). colorless solid. mp 234.3−235.7 °C. IR (KBr): 3277, 3098, 1667, 1608, 1573, 1518, 1412, 1347, 1324, 1262, 1179, 1052, 837, 802, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.65 (d, J = 3.2 Hz, 1H), 8.29 (dd, J = 8.8 Hz, 3.2 Hz, 1H), 8.28 (d, J = 8.4 Hz, 2H), 8.09 (s, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.68 (d, J = 8.6 Hz, 1H), 7.55 (s, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.2, 162.1, 148.4, 146.2, 141.8, 141.6, 137.4, 137.1, 134.2, 131.4, 128.2, 126.3, 126.0, 124.0, 122.0, 119.9, 119.5, 110.2, 21.0. Anal. Calcd for $C_{21}H_{14}ClN_4O_3$: C, 61.85; H, 3.46; N, 10.30. Found: C, 62.04; H, 3.74; N, 10.22.

***N*-[4-(5-Chloro-2-benzoxazolyl)phenyl]-2,4,6-trimethylbenzamide** (**4d**). yellow solid. mp 262.2−263.7 °C. IR (KBr): 3282, 3110, 1653, 1599, 1560, 1539, 1496, 1459, 1411, 1324, 1255, 1177, 1061, 918, 847, 800, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, J = 8.6, 2H), 7.81 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 1.8 Hz, 1H), 7.54 (br s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.32 (dd, J = 8.6 Hz, 1.8 Hz, 1H), 6.91 (s, 2H), 2.37 (s, 6H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.7, 163.7, 149.0, 143.0, 142.8, 138.0, 135.4, 133.7, 129.0, 128.5, 127.9, 125.2, 120.7, 119.6, 119.3, 112.2, 20.7, 18.9. Anal. Calcd for $C_{23}H_{19}ClN_2O_2$: C, 70.68; H, 4.90; N, 7.17. Found: C, 70.28; H, 4.95; N, 7.47.

4-Methoxy-*N*-(4-naphth[1,2-d]oxazol-2-ylphenyl)benzamide (**5d(1)**). pale yellow solid. mp 213.0−214.5 °C. IR (KBr): 3329, 1653, 1606, 1509, 1411, 1325, 1256, 1182, 1028, 1006, 841, 806, 761, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.46 (s, 1H), 8.46 (d, J = 7.8 Hz, 1H), 8.27 (d, J = 8.8 Hz, 2H), 8.14 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 8.8 Hz, 2H), 8.02 (d, J = 9.0 Hz, 2H), 7.99 (s, 2H), 7.74 (dd, J = 7.8 Hz, 7.6 Hz, 1H), 7.62 (dd, J = 7.8 Hz, 7.6 Hz, 1H), 7.10 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ165.2, 162.1, 161.8, 147.5, 142.5, 136.8, 130.9, 129.8, 128.8, 127.7, 127.2, 126.6, 125.9, 125.6, 125.5, 121.6, 121.2, 120.3, 113.7, 111.2, 55.4. Anal. Calcd for $C_{25}H_{18}N_2O_3$: C, 76.13; H,

4.60; N, 7.10. Found: C, 75.72; H, 4.71; N, 6.88.

***N*-[4-(4-Naphth[1,2-*d*]oxazol)phenyl]-1-naphthalenecarboxamide** (**5d(2)**). pale yellow solid. mp 260.0 −261.6 °C. IR (KBr): 3219, 3046, 1653, 1598, 1539, 1499, 1414, 1372, 1330, 1260, 1006, 837, 804, 739, 706 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.46 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 6.8 Hz, 1H), 8.2−8.1 (m, 4H), 8.1−8.0 (m, 3H), 7.82 (d, J = 6.4 Hz, 1H), 7.73 (dd, J = 7.6 Hz, 7.6 Hz, 1H), 7.7−7.6 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.6, 161.7, 147.5, 142.3, 136.8, 134.3, 133.2, 130.9, 130.4, 129.6, 128.8, 128.4, 127.9, 127.2, 127.1, 126.4, 126.0, 125.7, 125.6, 125.5, 125.0, 125.0, 121.6, 120.0, 111.1. Anal. Calcd for $C_{28}H_{18}N_2O_2$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.00; H, 4.46; N, 6.67.

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