One-Pot Four-Component Synthesis of N^2-Alkyl-N^3-[2-(1,3,4-oxadiazol-2-yl)aryl]benzofuran-2,3-diamines

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A simple synthesis of N^2-alkyl-N^3-[2-(1,3,4-oxadiazol-2-yl)aryl]benzofuran-2,3-diamines **5** *via* a one-pot four-component reaction is described (*Scheme 1*). A mixture of *N*-(isocyanoimino)triphenylphosphorane (**1**), a 2-aminobenzoic acid **2**, a 2-hydroxybenzaldehyde **3**, and an isocyanide **4** in absolute EtOH at room temperature undergoes a smooth reaction to afford **5** in excellent yields (*Table*).

Introduction. – Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry due to their valued features such as atom economy, straightforward reaction design, and the opportunity to construct target compounds by the introduction of several diversity elements in a single chemical event. Typically, purification of products resulting from MCRs is also simple since all the organic reagents employed are consumed and are incorporated into the target compound [1]. MCRs, leading to interesting heterocyclic scaffolds, are particularly useful for the construction of diverse chemical libraries of 'drug-like' molecules. The isocyanide-based MCRs are especially important in this area [1d][1e].

During recent years, there has been a broad investigation on different classes of oxadiazoles. In particular, compounds containing the 1,3,4-oxadiazole moiety have been shown to possess a wide range of pharmacological and therapeutic activities, *e.g.*, as active inhibitors of several enzymes [2][3]. Furthermore, differently substituted 1,3,4-oxadiazoles have potential applications as photosensitizers [4], liquid crystals [5], ionic liquids [6], and organic light-emitting devices [7]. Some examples have also photomechanic [8], photoluminescent, and electrochromic properties [9][10]. So far, the most common synthetic methods reported for the preparation of 1,3,4-oxadiazoles involve either transformation of an existing heterocycle or cyclizations [2][3][11].

Benzofurans, another important class of heterocyclic compounds, have attracted much attention because of their wide range of pharmaceutical activities [12]. Traditional synthetic routes for the preparation of benzofuran derivatives are often multistep reactions such as dehydrative cyclization of α-(phenoxy)alkyl ketones [13], cyclofragmentation of oxiranes [14], acidic dehydration of *o*-hydroxybenzyl ketones [15], base mediated decarboxylation of (*o*-acylphenoxy)acetic acids and esters [16], reaction of phenols with α-acyl sulfoxides [17], and Pd-catalyzed synthesis from *o*-ethynylphenol or from *o*-iodophenols and terminal arylacetylenes [18][19].

Results and Discussion. – There are several reports on the use of (isocyanoimino)-triphenylphosphorane (= *N*-(triphenylphosphoranylidene)isocyanamide; Ph_3PNNC, **1**; *Scheme 1*) in syntheses of metal complexes [20]. Recently, syntheses of 1,3,4-oxadiazepines [21a] and a variety of 1,3,4-oxadiazole derivatives [21] by using **1** in MCRs were reported. As part of our current studies on the design of new routes for the preparation of biologically active heterocyclic compounds from readily available building blocks [22], we have described the syntheses of 2-aryl-5-(hydroxyalkyl)-1,3,4-oxadiazoles [23a], 3-(1-hydroxyalkyl)[1,2,4]triazolo[4,3-*c*]quinazolines [23b], 3-(5-aryl/alkyl-1,3,4-oxadiazol-2-yl)-1,3-dihydro-3-hydroxy-2*H*-indol-2-ones [23c], 3-aryl-1-[(arylmethylidene)amino]pyrrolidine-2,5-diones [23d], and 3,4-disubstituted *N*-amino-pyrrolidine-2,5-diones [23e] by using **1** in MCRs.

We report herein a simple synthesis of N^3-[2-(1,3,4-oxadiazol-2-yl)aryl]benzofuran-2,3-diamines **5** *via* a four-component reaction (*Scheme 1*). Thus, a mixture of **1**, a 2-aminobenzoic acid **2**, a 2-hydroxybenzaldehyde **3**, and an isocyanide **4** in absolute EtOH underwent a smooth reaction to give the corresponding N^2-alkyl-N^3-[2-(1,3,4-oxadiazol-2-yl)aryl]benzofuran-2,3-diamines **5a**–**5g** in 90–96% yield (*Scheme 1*, *Table*). The reactions were carried out by first mixing **2**, **3**, and **4** in EtOH at room temperature. After 1 h and nearly complete conversion to the corresponding benzofuran-2,3-diamine intermediate (TLC monitoring), **1** was added to the mixture, which was stirred at room temperature for further 2 h. The ^{1}H-NMR spectra of the crude products clearly indicated the formation of compounds **5** in excellent yields (*Table*).

Scheme 1. *One-Pot Four-Component Synthesis of* N^3*-[2-(1,3,4-Oxadiazol-2-yl)aryl]benzofuran-2,3-diamines* **5**. See *Table* for X, Y, Z, and R.

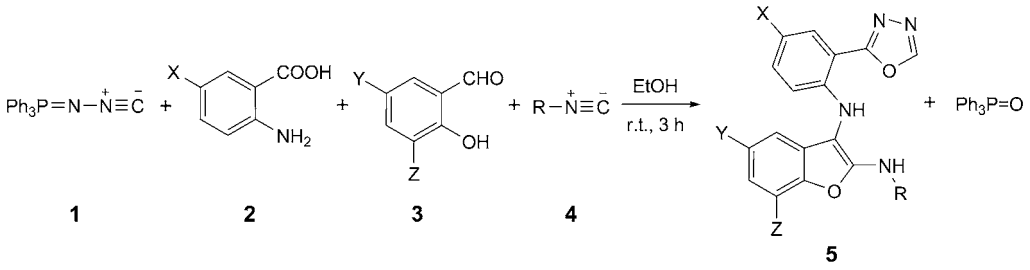

Table. *Synthesis of* N^2*-Alkyl-*N^3*-[2-(1,3,4-oxadiazol-2-yl)aryl]benzofuran-2,3-diamines* **5a**–**5g**

Product	X	Y	Z	R	Yield [%][a])
5a	H	NO_2	H	$Me_3CCH_2C(Me)_2$	90
5b	Cl	NO_2	H	$Me_3CCH_2C(Me)_2$	90
5c	H	Br	H	cyclohexyl	95
5d	H	H	MeO	^{t}Bu	91
5e	Cl	Br	H	cyclohexyl	93
5f	H	NO_2	H	cyclohexyl	95
5g	Cl	NO_2	H	cyclohexyl	96

[a]) Yields of isolated product.

The isolated products **5** were characterized by their IR, ^{1}H- and ^{13}C-NMR, and mass spectra and elemental analysis. The mass spectrum of **5b** displayed the molecular-ion (M^+) peaks at m/z 485 and 483, which was consistent with a product formed from 2-hydroxy-5-nitrobenzaldehyde, 2-amino-5-chlorobenzoic acid, 1,1,3,3-tetramethylbutyl isocyanide, and (isocyanoimino)triphenylphosphorane in a 1:1:1:1 ratio with the loss of H_2O and Ph_3PO. The IR spectrum of **5b** showed absorptions at 3246 and 3128 cm^{-1} indicative for NH of amine groups. The ^{1}H-NMR spectrum of **5b** exhibited four sharp *s* arising from the Me_3C (δ(H) 0.98), Me_2C (δ(H) 1.48), and CH_2 (δ(H) 1.75) groups and the oxadiazole-ring CH (δ(H) 8.49), along with characteristic signals with appropriate chemical shifts and coupling constants for the six aromatic H-atoms. Two fairly broad *s* (δ(H) 4.41 and 8.53) were observed for the two amine H-atoms. The ^{1}H-decoupled ^{13}C-NMR spectrum of **5b** showed characteristic signals for the 1,1,3,3-tetramethylbutyl group, two deshielded signals at δ(C) 151.34 and 163.70 for the oxadiazole CH group and C-atom, respectively, as well as 14 signals for the aromatic C atoms (6 CH and 8 C), in agreement with the adduct structure (see *Exper. Part*). The ^{1}H- and ^{13}C-NMR spectra of compounds **5a** and **5c**–**5g** were similar to those of **5b**, except for the signals of the N^2-alkyl and N^3-aryl substituents and of the benzofuran moiety, which exhibited characteristic signals with appropriate chemical shifts and coupling constants (see *Exper. Part*).

A mechanistic rationalization for this reaction is provided in *Scheme 2*. On the basis of the well-established chemistry of isocyanides [1d][1e][24–26], it is reasonable to assume that the imino intermediate **6**, generated from the condensation reaction between a 2-aminobenzoic acid **2** and an aldehyde **3**, could undergo nucleophilic addition of the isocyanide **4**, which is facilitated by protonation by the adjacent carboxylic acid function, leading to a nitrilium carboxylate intermediate **7**. The nitrilium may then undergo intramolecular attack by the adjacent phenol OH group to form 3-aminobenzofuran-2(3*H*)-imine derivative **8**, which could tautomerize to give benzofuran-2,3-diamine derivative **9** [27]. This COOH-substituted intermediate may protonate **1**, and the nitrilium intermediate **11** may be attacked by the conjugate base **10** to form the adduct **12**. This adduct may undergo an intramolecular aza-*Wittig* reaction of the iminophosphorane moiety with the ester C=O to form the 1,3,4-oxadiazole ring by removal of Ph_3P=O from zwitterion **13** and afford the isolated products **5** [21b–21h][23a–23c].

In summary, we have developed a one-pot four-component reaction between (isocyanoimino)triphenylphosphorane (**1**), a 2-aminobenzoic acid **2**, a 2-hydroxybenzaldehyde **3**, and an isocyanide **4** for the preparation of N^2-alkyl-N^3-(2-(1,3,4-oxadiazol-2-yl)aryl)benzofuran-2,3-diamines **5**, which are of potential synthetic and pharmacological interest. Mild reaction conditions and excellent yields of the products are the main advantages of this method. The reactions were performed under neutral conditions, and the starting materials were mixed without any activation or modification.

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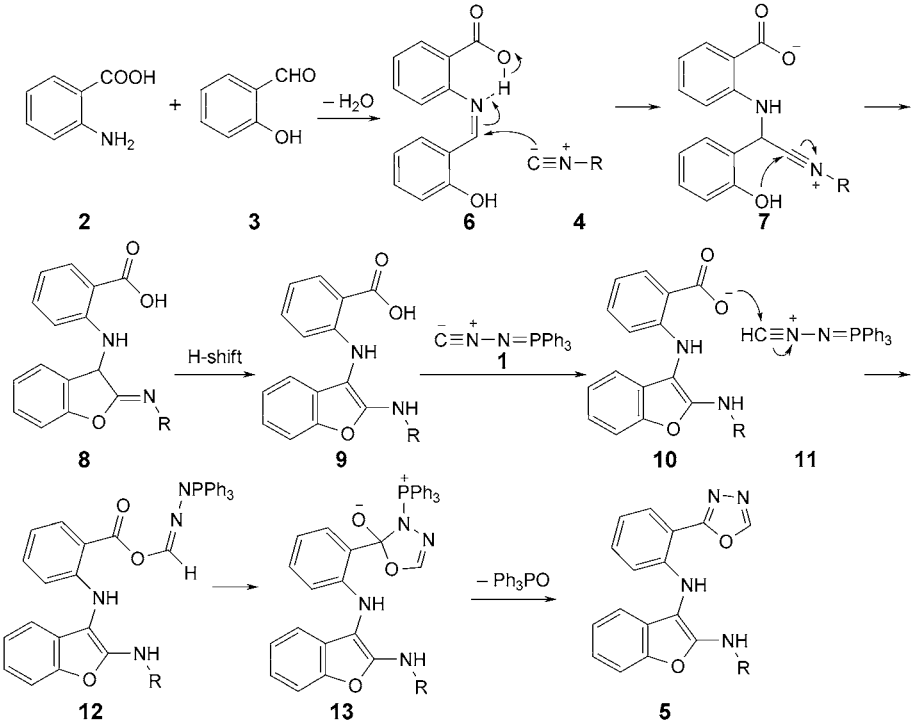
Scheme 2. *Proposed Mechanism for the MCR*



Experimental Part

General. All the chemicals were obtained from *Merck* (Germany) and used without further purification. Column chromatography (CC): silica gel *60* (SiO_2; *Merck*). M.p.: *Electrothermal-9100* apparatus; uncorrected. IR Spectra: *Shimadzu-IR-460* spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR Spectra: *Bruker-DRX-500-Avance* (at 500.1 and 125.8 MHz, resp.) and *Bruker-DRX-300* (at 300.1 and 75.5 MHz, resp.) instruments; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. EI-MS (20 eV): *Agilent-Technologies* (*HP*) *5973* mass spectrometer; in *m/z* (rel. %). Elemental analyses: *Heraeus-CHN-O-Rapid* analyzer.

Compounds **5**: *General Procedure.* Exemplified with **5a**. A mixture of 2-aminobenzoic acid (**2a**; 0.137 g, 1 mmol), 2-hydroxy-5-nitrobenzaldehyde (**3a**; 0.167 g, 1 mmol), and 1,1,3,3-tetramethylbutyl isocyanide (**4a**; 0.139 g, 1 mmol) in EtOH (2 ml) was stirred at 25° for 1 h. Next, (isocyanoimino)-triphenylphosphorane (**1**; 0.302 g, 1 mmol) was added to the mixture, which was stirred at 25° for further 2 h. Then, the solvent was evaporated, and the residue purified by CC (SiO_2, hexane/AcOEt 3 : 1) and recrystallization (hexane/AcOEt 1 : 1).

5-Nitro-N^3*-[2-(1,3,4-oxadiazol-2-yl)phenyl]-*N^2*-(1,1,3,3-tetramethylbutyl)benzofuran-2,3-diamine* (**5a**): Yield 90%. Orange crystals. M.p. 179–181°. IR (KBr): 3245 and 3135 (NH), 1618, 1512, 1455, 1339, 1277, 1218, 1141, 1079, 1006, 946, 877, 824, 724. ^1H-NMR (300.1 MHz): 1.00 (*s*, 9 H); 1.49 (*s*, 6 H); 1.75 (*s*, 2 H); 4.33 (br. *s*, 1 H); 6.64 (*d*, J = 8.3, 1 H); 6.88 (*dd*, J = 7.4, 7.7, 1 H); 7.29 (*t*, J = 8.2, 1 H); 7.39 (*d*, J = 8.8, 1 H); 7.88 (*d*, J = 1.9, 1 H); 7.93 (*d*, J = 7.9, 1 H); 7.97 (*dd*, J = 1.9, 9.0, 1 H); 8.50 (*s*, 1 H); 8.55 (*s*, 1 H). ^{13}C-NMR (75.5 MHz): 30.7; 31.5; 31.8; 54.1; 57.4; 95.2; 106.3; 110.2; 111.5; 113.3; 116.1; 117.7; 128.4; 129.0; 133.4; 144.5; 146.7; 151.1; 152.2; 157.7; 164.7. EI-MS: 449 (27, M^+), 371 (9), 354 (6), 337 (100), 320 (77), 293 (17), 283 (2), 263 (6), 161 (11), 97 (7), 57 (43), 41 (18). Anal. calc. for $C_{24}H_{27}N_5O_4$ (449.51): C 64.13, H 6.05, N 15.58; found: C 64.09, H 6.03, N 15.52.

N^3-*[4-Chloro-2-(1,3,4-oxadiazol-2-yl)phenyl]-5-nitro*-N^2-*(1,1,3,3-tetramethylbutyl)benzofuran-2,3-diamine* (**5b**): Yield 90%. Orange crystals. M.p. 195–197°. IR (KBr): 3246 and 3128 (NH), 1634, 1580, 1491, 1385, 1338, 1302, 1252, 1208, 1135, 1078, 1009, 949, 875, 821, 736, 697. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 0.98 (*s*, 9 H); 1.48 (*s*, 6 H); 1.75 (*s*, 2 H); 4.41 (*s*, 1 H); 6.59 (*d*, *J* = 9.0, 1 H); 7.22 (*dd*, *J* = 2.5, 9.0, 1 H); 7.38 (*d*, *J* = 8.9, 1 H); 7.83 (*d*, *J* = 2.4, 1 H); 7.85 (*d*, *J* = 2.4, 1 H); 7.95 (*dd*, *J* = 2.4, 8.8, 1 H); 8.49 (*s*, 1 H); 8.53 (*s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 30.7; 31.5; 31.8; 54.1; 57.5; 94.5; 107.2; 110.2; 111.3; 114.9; 116.2; 122.5; 127.6; 128.9; 133.2; 144.6; 145.3; 151.3; 152.1; 157.7; 163.7. EI-MS: 485 (3, M^+(^{37}Cl)), 483 (9, M^+(^{35}Cl)), 452 (4), 371 (63), 354 (46), 343 (24), 327 (12), 267 (27), 236 (8), 165 (8), 149 (15), 137 (9), 121 (11), 111 (13), 97 (24), 83 (27), 69 (34), 57 (100), 43 (53). Anal. calc. for $C_{24}H_{26}ClN_5O_4$ (483.95): C 59.56, H 5.42, N 14.47; found: C 59.47, H 5.44, N 14.36.

5-Bromo-N^2-*cyclohexyl*-N^3-*[2-(1,3,4-oxadiazol-2-yl)phenyl]benzofuran-2,3-diamine* (**5c**): Yield 95%. Yellow crystals. M.p. 184–186°. IR (KBr): 3323 and 3130 (NH), 1648, 1604, 1508, 1440, 1321, 1272, 1186, 1098, 1042, 996, 946, 852, 790, 739. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.13–2.05 (*m*, 10 H); 3.59–3.63 (*m*, 1 H); 4.10 (br. *s*, 1 H); 6.70 (*d*, *J* = 8.4, 1 H); 6.84 (*t*, *J* = 8.1, 1 H); 7.09 (*dd*, *J* = 2.0, 8.4, 1 H); 7.11 (*d*, *J* = 1.9, 1 H); 7.15 (*d*, *J* = 8.4, 1 H); 7.29 (*dt*, *J* = 1.3, 8.4, 1 H); 7.88 (*dd*, *J* = 1.3, 7.9, 1 H); 8.44 (*s*, 1 H); 8.46 (br. *s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 25.0; 25.5; 34.4; 52.6; 92.2; 105.9; 111.3; 113.6; 116.3; 117.2; 118.3; 122.4; 128.3; 131.2; 133.4; 147.1; 147.7; 151.0; 155.5; 164.8. EI-MS: 454 (66, M^+(^{81}Br)), 452 (65, M^+(^{79}Br)), 371 (42), 344 (23), 326 (28), 301 (18), 263 (9), 199 (49), 178 (12), 161 (48), 149 (40), 120 (26), 93 (18), 83 (93), 69 (44), 55 (100), 41 (77). Anal. calc. for $C_{22}H_{21}BrN_4O_2$ (453.34): C 58.29, H 4.67, N 12.36; found: C 58.21, H 4.57, N 12.14.

N^2-*(*tert*-Butyl)-7-methoxy*-N^3-*[2-(1,3,4-oxadiazol-2-yl)phenyl]benzofuran-2,3-diamine* (**5d**): Yield 91%. Yellow crystals. M.p. 223°. IR (KBr): 3315 and 3167 (NH), 1629, 1574, 1507, 1445, 1379, 1333, 1273, 1168, 1068, 950, 813, 717. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.40 (*s*, 9 H); 3.88 (*s*, 1 H); 4.04 (*s*, 3 H); 6.67 (*d*, *J* = 8.1, 1 H); 6.71 (*d*, *J* = 7.7, 1 H); 6.75 (*d*, *J* = 8.5, 1 H); 6.83 (*t*, *J* = 7.7, 1 H); 7.02 (*t*, *J* = 7.9, 1 H); 7.27 (*t*, *J* = 7.7, 1 H); 7.89 (*dd*, *J* = 1.3, 7.9, 1 H); 8.47 (*s*, 1 H); 8.58 (br. *s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 30.5; 53.8; 56.4; 99.5; 105.3; 105.9; 109.7; 113.9; 117.1; 123.4; 128.2; 129.6; 133.2; 138.4; 144.6; 147.1; 151.0; 154.5; 164.8. EI-MS: 378 (< 1, M^+), 277 (100), 236 (8), 199 (15), 183 (10), 151 (17), 109 (12), 91 (8), 77 (14), 65 (5), 51 (11). Anal. calc. for $C_{21}H_{22}N_4O_3$ (378.43): C 66.65, H 5.86, N 14.81; found: C 66.60, H 5.78, N 14.74.

5-Bromo-N^3-*[4-chloro-2-(1,3,4-oxadiazol-2-yl)phenyl]*-N^2-*cyclohexylbenzofuran-2,3-diamine* (**5e**): Yield 93%. Yellow crystals. M.p. 194–196°. IR (KBr): 3353 and 3142 (NH), 1640, 1611, 1579, 1501, 1476, 1444, 1396, 1308, 1264, 1229, 1193, 1170, 1108, 1042, 994, 950, 875, 851, 823, 783, 749, 728. ^{1}H-NMR (300.1 MHz, $CDCl_3$): 1.13–2.06 (*m*, 10 H); 3.58–3.62 (*m*, 1 H); 4.07 (*d*, *J* = 8.6, 1 H); 6.65 (*d*, *J* = 9.0, 1 H); 7.07–7.15 (*m*, 2 H); 7.24 (*dd*, *J* = 1.7, 9.1, 1 H); 7.27 (*s*, 1 H); 7.87 (*d*, *J* = 1.9, 1 H); 8.46 (br. *s*, 1 H); 8.51 (*s*, 1 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): 24.9; 25.4; 34.4; 52.5; 91.6; 106.7; 111.4; 115.1; 116.3; 118.1; 121.9; 122.5; 127.4; 130.8; 133.2; 145.6; 147.5; 151.2; 155.4; 163.8. EI-MS: 490 (< 1, M^+(^{81}Br^{37}Cl)), 488 (3, M^+(^{81}Br^{35}Cl)/(^{79}Br^{37}Cl)), 486 (2, M^+(^{79}Br^{35}Cl)), 405 (4), 390 (5), 335 (45), 317 (3), 195 (5), 180 (4), 171 (6), 111 (5), 69 (55), 57 (42), 43 (100). Anal. calc. for $C_{22}H_{20}BrClN_4O_2$ (487.78): C 54.17, H 4.13, N 11.49; found: C 54.09, H 4.14, N 11.43.

N^2-*Cyclohexyl-5-nitro*-N^3-*[2-(1,3,4-oxadiazol-2-yl)phenyl]benzofuran-2,3-diamine* (**5f**): Yield 95%. Orange crystals. M.p. 184–186°. IR (KBr): 3317 and 3139 (NH), 1652, 1582, 1512, 1442, 1333, 1276, 1196, 1157, 1099, 999, 948, 879, 820, 736. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.14–2.06 (*m*, 10 H); 3.61–3.68 (*m*, 1 H); 3.69 (br. *s*, 1 H); 6.67 (*d*, *J* = 8.5, 1 H); 6.86 (*t*, *J* = 7.5, 1 H); 7.27 (*t*, *J* = 7.3, 1 H); 7.33 (*d*, *J* = 8.8, 1 H); 7.84 (*d*, *J* = 2.0, 1 H); 7.90 (*d*, *J* = 8.0, 1 H); 7.93 (*dd*, *J* = 1.9, 8.8, 1 H); 8.47 (*s*, 1 H); 8.50 (br. *s*, 1 H). ^{13}C-NMR (125.8 MHz, $CDCl_3$): 24.9; 25.4; 34.4; 52.6; 92.4; 106.2; 109.9; 111.2; 113.3; 116.0; 117.6; 128.4; 130.1; 133.4; 144.6; 146.8; 151.1; 151.8; 157.0; 164.7. EI-MS: 419 (9, M^+), 320 (9), 309 (4), 300 (100), 270 (4), 254 (32), 210 (5), 182 (12), 167 (10), 57 (11), 43 (11). Anal. calc. for $C_{22}H_{21}N_5O_4$ (419.44): C 63.00, H 5.05, N 16.70; found: C 62.81, H 5.24, N 16.58.

N^3-*[4-Chloro-2-(1,3,4-oxadiazol-2-yl)phenyl]*-N^2-*cyclohexyl-5-nitrobenzofuran-2,3-diamine* (**5g**): Yield 96%. Orange crystals. M.p. 174–176°. IR (KBr): 3368 and 3136 (NH), 1651, 1590, 1512, 1474, 1390, 1336, 1232, 1164, 1097, 1044, 1000, 952, 876, 808, 742. ^{1}H-NMR (500.1 MHz, $CDCl_3$): 1.14–2.05 (*m*, 10 H); 3.62–3.67 (*m*, 1 H); 3.98 (br. *s*, 1 H); 6.61 (*d*, *J* = 9.0, 1 H); 7.23 (*dd*, *J* = 2.0, 8.9, 1 H); 7.33 (*d*, *J* = 8.8, 1 H); 7.82 (*s*, 1 H); 7.87 (*s*, 1 H); 7.94 (*dd*, *J* = 2.0, 8.8, 1 H); 8.50 (*s*, 1 H); 8.52 (br. *s*, 1 H). ^{13}C-NMR

(125.8 MHz, $CDCl_3$): 24.9; 25.4; 34.4; 52.6; 91.9; 107.1; 110.0; 111.1; 114.9; 116.1; 122.4; 127.7; 129.9; 133.3; 144.7; 145.4; 151.3; 151.8; 156.9; 164.7. EI-MS: 455 (5, $M^+(^{37}Cl)$), 453 (11, $M^+(^{35}Cl)$), 370 (5), 354 (7), 337 (6), 279 (8), 167 (19), 149 (57), 97 (17), 81 (33), 69 (74), 57 (61), 43 (100). Anal. calc. for $C_{22}H_{20}ClN_5O_4$ (453.88): C 58.22, H 4.44, N 15.43; found: C 58.31, H 4.51, N 15.37.

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