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Unexpected Formation of *N*-(1-(2-Aryl-hydrazono)isoindolin-2-yl)benzamides and Their Conversion into 1,2-(Bis-1,3,4-oxadiazol-2-yl)benzenes

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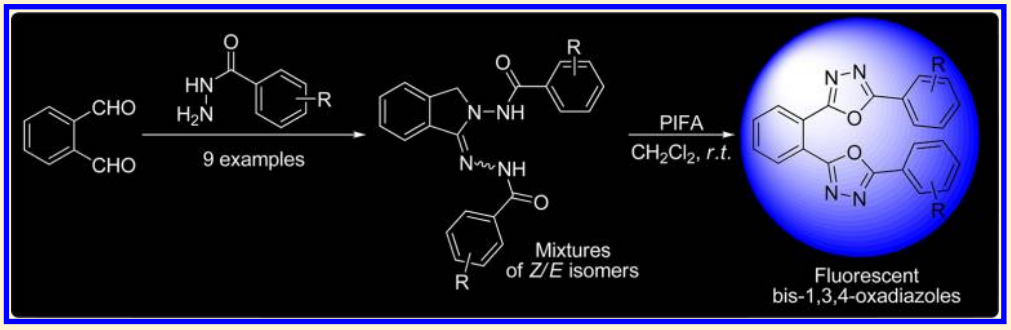
Supporting Information



ABSTRACT: Reaction between *ortho*-phthalaldehyde and various aroylhydrazines unexpectedly yields *N*-(1-(2-aryl-hydrazono)isoindolin-2-yl)benzamides as major products along with the predictable 1,2-bis-aroylhydrazones. NMR investigation of the major reaction products indicate the presence of a mixture of geometrical isomers, in various ratios. Single crystal X-ray diffraction confirms the proposed structure and indicates a *Z* configuration of the C=N double bond substitutents. Optimization of the condensation reaction conditions enabled quantitative isolation of the cyclic isomer. Oxidation of the isomers with bis(trifluoroacetoxy)iodobenzene (PIFA) leads to rapid formation of new highly fluorescent 1,2-bis(5-aryl-1,3,4-oxadiazol-2-yl)benzenes.

INTRODUCTION

The increasing interest in the synthesis of 2,5-substituted-1,3,4-oxadiazoles can be attributed to their remarkable photophysical properties[1,2] but also because they have been evaluated as promising antiviral,[3,4] antibacterial, anti-inflammatory/analgesic or antifungal agents, as well as inhibitors of various enzymes.[4] Bis-1,3,4-oxadiazoles have emerged as important targets for development of organic light emitting diodes (OLEDs)[5−10] as a consequence of their improved optoelectronic properties with an increasing number of the heterocyclic rings.

Generally, closure of the 1,3,4-oxadiazole ring has been described[4,11] either through intramolecular dehydration[1,12−17] of diacylhydrazines or oxidative cyclization[18−24] of *N*-acyl-*N*′-arylidene-hydrazines. Numerous dehydrating and oxidative reagents were reported to be very effective for this purpose including phosphorus oxychloride[1,12,15] and thionyl chloride.[13] Recently, triflic anhydride,[16] zirconium(IV) chloride,[14] or $[Et_2NSF_2]BF_4$[17] have been mostly used for dehydration, while cerium ammonium nitrate (CAN),[18] lead(IV) tetracetate,[19−21] or hypervalent iodine reagents[22−25] were reported for the oxidative cyclization. Mixtures of acetic anhydride and acetic acid were also used for the synthesis of dihydrooxadiazoles.[26]

Bis-1,3,4-oxadiazoles could be easily prepared using both synthetic strategies, starting from a wide variety of scaffolds. Most commonly, the heterocycles are generated on different aromatic rings such as in compounds **1**[27] and **2**[5] or as 1,3- or 1,4-subtituted compounds of type **3** or **4** (Scheme 1).[21,26] Early research[21] describes preparation of bis-1,3,4-oxadiazoles of type **3** (Scheme 1) by cyclization with lead(IV) acetate of the corresponding bis-aroylhydrazones derived from 1,3- and 1,4-

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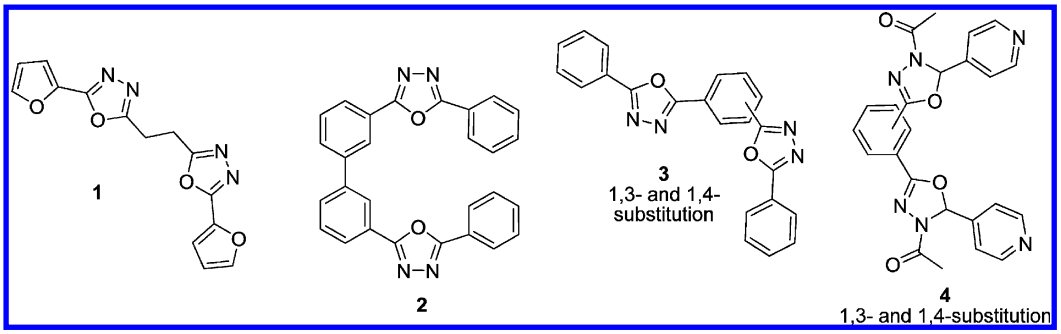
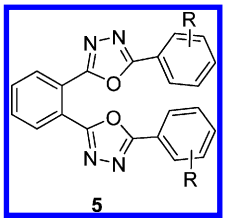
Scheme 1. Examples of Bis-(1,3,4-oxadiazoles) Grafted on Different Aromatic Rings or on the Same Ring As 1,3- or 1,4-Disubstituents



phthalaldehydes, respectively. The attempt to obtain the 1,2-(bis-oxadiazolyl)benzenes derived from *ortho*-bis-aroylhydrazones was reported to fail under the same conditions.[20] Later,[26] only preparation of 1,3- and 1,4-bis(dihydrooxadiazolyl)-benzenes **4** (Scheme 1) was successfully reported starting from the corresponding 1,3- and 1,4-bis-aroylhydrazones.

In this context, preparation of 1,2-bis(1,3,4-oxadiazol-2-yl)benzenes **5** (Scheme 2) looked challenging and therefore

Scheme 2. Structure of the Target 1,2-Bis(1,3,4-oxadiazol-2-yl)benzenes

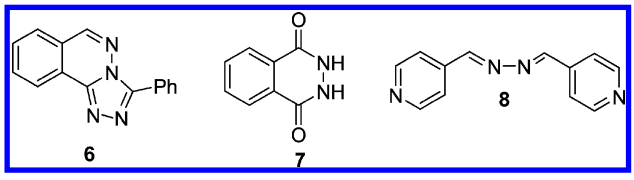


we focused on finding a new strategy to synthesize them. We describe here the synthesis of **5** via oxidative cyclization with bis(trifluoroacetoxy)iodobenzene (PIFA) of the condensation products between *ortho*-phthalaldehyde and various aroylhydrazines.

RESULTS AND DISCUSSION

To the best of our knowledge, except for the preparation of 1,2-bis(5-phenyl-1,3,4-oxadiazol-2-yl)benzene starting from 1,2-bis(5-tetrazolyl)benzene and acyl chlorides,[10,28] all previous results were negative in attempting to obtain aryl-substituted-bis-1,3,4-oxadiazoles from aroylhydrazones.[20,26] Oxidative cyclization of *ortho*-bis-aroylhydrazones with lead(IV) tetracetate was reported to yield phthalazine derivative **6**[20] (Scheme 3). In addition, in the attempt to prepare the *N*-acyl-*N*′-arylidene-hydrazines[26] precursors, the reaction between the

Scheme 3. Products Resulted from Oxidative Cyclization of *ortho*-Bis-aroylhydrazone Derived from Phthalaldehyde and Hydrazide of the Benzoic Acid (6) and Products Resulted from Condensation Reaction between *ortho*-Phthalic Acid and 4-Pyridylaldehyde (7 and 8)



hydrazide of *ortho*-phthalic acid and 4-pyridylaldehyde gave a mixture of phthalazine-1,4-dione **7** and pyridylmethylenehydrazine **8** (Scheme 3) instead of the expected aroylhydrazone. However, the reaction between *ortho*-phthalaldehyde and pyridin-4-yl-hydrazide was found to yield the corresponding bis-aroylhydrazone in such a low yield that the compound could not be isolated.[26]

It became clear that in order to prepare the target bis-1,3,4-oxadiazoles **5**, the synthesis of their precursors was the key step. Indeed, this proved to be the most challenging step. Between the two available methods for their synthesis,[4,11] the condensation of *ortho*-phthalaldehyde with various aroylhydrazines **9** (Scheme 4) was the most attractive and procedurally simple.

The condensation reactions were initially performed using a modified version of a previously reported procedure,[20] yielding, with no exception, a mixture of products, in which the target aroylhydrazones **10A** (Scheme 4) could be identified as minor products, along with a major compound **10C** that is different from all the structures previously described.[26]

Numerous attempts to separate these compounds always led to isolation of the major compounds **10C** as mixtures of *Z*/*E* isomers, while the minor aroylhydrazone **10A** could not be isolated in pure form.

Structural investigation of the isolated product by NMR (^{1}H, ^{13}C, ^{15}N, and 2D correlations), high-resolution-mass spectrometry (HR-MS), and X-ray diffraction in the particular case of compound **10a** led to identification of the cyclic compound **10Ca** (Scheme 4). This compound is present in solution as mixture of *Z*/*E* isomers in a 1:0.6 molar ratio, as inferred from the ^{1}H NMR integration of the corresponding signals of the CH_2 protons in *Z* and *E* diastereoisomers, respectively. Similar results were observed for all the condensation reactions. The isomeric ratios for all compounds **10C** were calculated from ^{1}H NMR (Scheme 4).

Structural Aspects in Solid State. The single crystal X-ray diffraction confirmed the structure of compound **10Ca**. It contains an isoindolinyl ring in which the nitrogen is provided by an aroylhydrazone group, while the second aroylhydrazone group yields an exocyclic double bond with *Z* configuration (Figure 1). The analysis of the bond lengths between the atoms of the five membered ring as well as of the exocyclic C−N and N−N bonds indicates a series of interesting features. Thus, the C2−N4 interatomic distance, which is equal to 1.379(4) Å, is an intermediary value between the length of a C−N bond in an aliphatic chain [usually between 1.472(5) and 1.479(5) Å] and in pyrrol [1.372(12) Å].[29] The length of the C2−N3 exocyclic bond, equal to 1.287(4) Å, is much smaller than the previous

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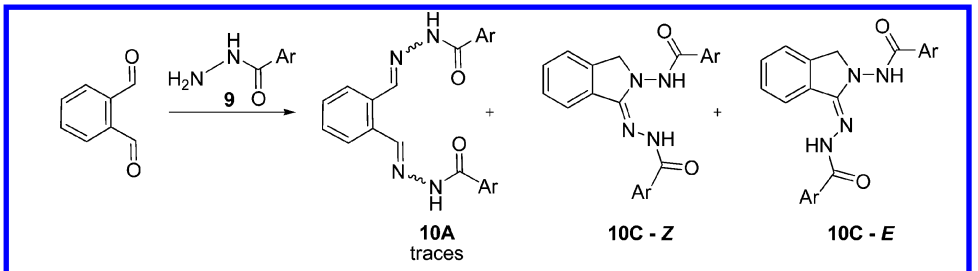
Scheme 4. Structure of the Products Resulted from the Condensation between *ortho*-Phthalaldehyde and the Aroylhydrazines 9 As Well As the Molar Ratio of *Z*/*E* of 10C Determined by ^{1}H NMR Spectroscopy through Integration of the CH_2 Resonances



Compound			Ar
9a	**10Aa**	**10Ca**	3,4,5-$(MeO)_3C_6H_2$
9b	**10Ab**	**10Cb**	4-Br-C_6H_4
9c	**10Ac**	**10Cc**	4-Cl-C_6H_4
9d	**10Ad**	**10Cd**	3-Cl-C_6H_4
9e	**10Ae**	**10Ce**	4-Me-C_6H_4
9f	**10Af**	**10Cf**	4-MeO-C_6H_4
9g	**10Ag**	**10Cg**	4-NO_2-C_6H_4
9h	**10Ah**	**10Ch**	C_6H_5
9i	**10Ai**	**10Ci**	4-Py

Compound **10C**	**10C-Z/10C-E** isomers
10Ca	1:0.45
10Cb	1:0.60
10Cc	1:0.65
10Cd	1:0.70
10Ce	1:0.60
10Cf	1:0.60
10Cg	1:0.63
10Ch	1:0.60
10Ci	1:0.69

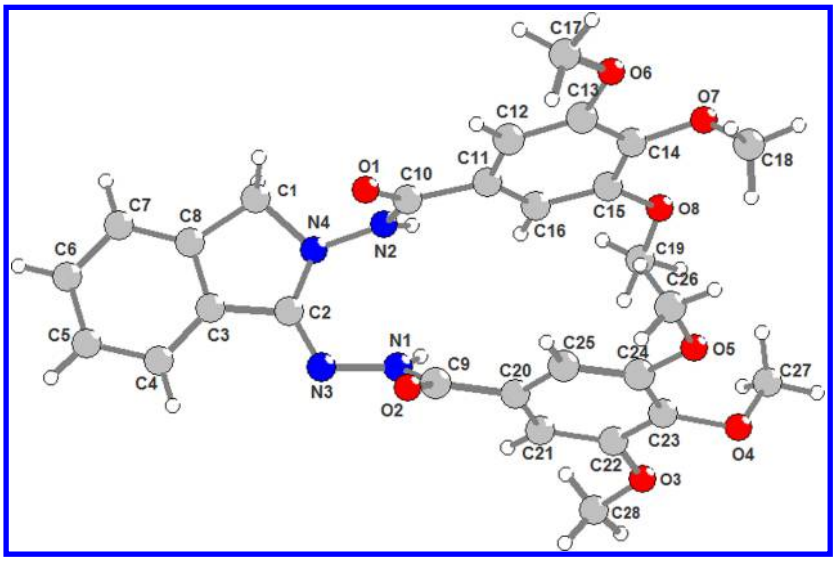


Figure 1. Molecular structure of compound **10Ca-*Z***, showing the atom numbering scheme. Selected bonds lengths (Å): C2−N4, 1.379(4); C2−N3, 1.287(4); C1−N4, 1.471(4); C1−C8, 1.497(5); N4−N2, 1.390(4); C10−O1, 1.213(4); N1−N3, 1.414(4); C9−O2, 1.245(4).

one and corresponds to a double bond length, comparable to a bond of azomethines[30−33] or oxadiazoles.[10] The C1−N4 [1.471(4) Å] and C1−C8 [1.497(5) Å] bonds have typical lengths for simple covalent bonds. In addition, it was noticed that the N4−N2 [1.390(4) Å] and C10−O1 [1.213(4) Å] bond lengths are slightly smaller than the N1−N3 [1.414(4)] and C9−O2 [1.245(4) Å)].

The crystal structure of **10C-*Z*** comprises supramolecular chains of molecules associated through hydrogen bonding (Figure 2). The molecules within the same chain adopt a zigzag arrangement. The dihedral angle between the isoindolinyl benzene rings of two neighboring molecules is 45.763°.

The supramolecular chains are built up by intermolecular association of molecules via four hydrogen bonds: two NH---O hydrogen bonds ($d_{H\cdots O}$ equal to 2.136 Å and 2.248 Å, with N−H−O angles equal to 167.704° and 125.449°, respectively) between the N−H groups of one molecule and the O2 oxygen of another molecule; two CH---O hydrogen bonds between (i) an aromatic CH group and the same O2 oxygen atom ($d_{H\cdots O}$ equal to 2.506 Å and C−H−O angle 159.382°) and (ii) a hydrogen atom of the CH_2 group with the O1 atom of a second molecule ($d_{H\cdots O}$ equal to 2.326 Å and C−H−O angle equal to 140.791°) as well as a CH−π interaction between a hydrogen atom of a methoxy group and the benzene ring of the isoindolinyl from the neighboring molecule (the distance of this hydrogen atom to the benzene ring centroid is 2.794 Å and the angle between the C−H bond axis and the plane of the benzene ring is 155.056°), (Figure 2). In addition, the supramolecular chains in the lattice of **10C-*Z*** are associated by hydrogen bonding between the H atoms of the methoxy groups belonging to molecules of one chain and the O atoms of methoxy groups from molecules of another chain ($d_{H\cdots O}$ equal

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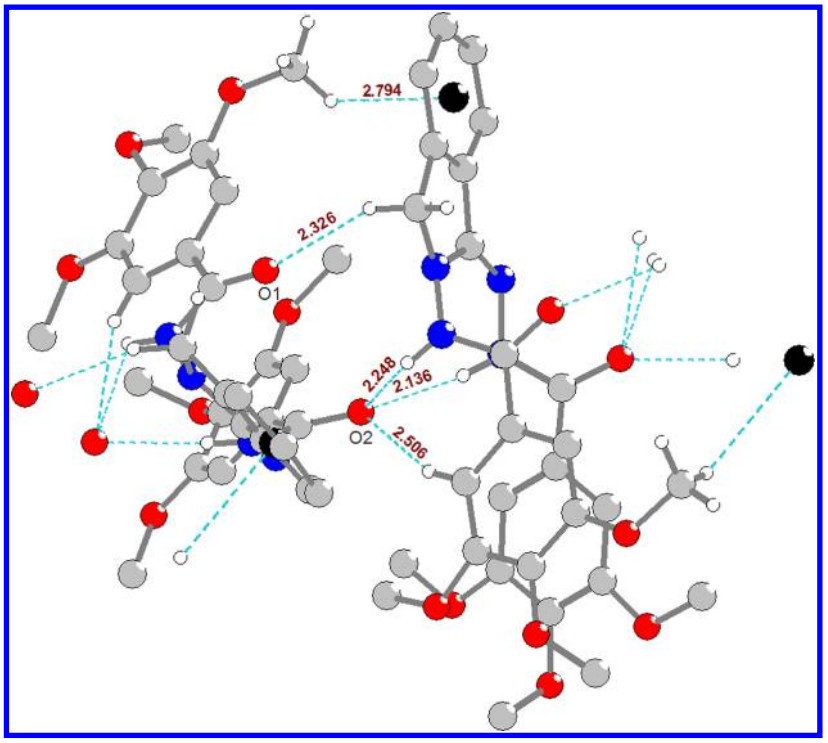

Figure 2. Fragment of the lattice of **10C-Z**: a perspective view (along the *a* axis) reveals the association of molecules through hydrogen bonds and CH−π interaction to form supramolecular chain associations. Hydrogen atoms (except the ones involved in different interactions) are omitted for clarity.

to 2.615, 2.784, 2.823, or 2.878 Å and C−H−O angles of 157.617°, 123.737°, 115.860°, and 115.881° respectively; see Figure S2 in the Supporting Information).

Structural Aspects in Solution. The presence in solution of the two diastereomers could be due either to the existence of geometrical isomers at the exocyclic C═N double bond or as a result of the hindered rotation of the C−N amide bond, the latter situation having been previously reported for related *N*′,*N*″-1*H*-isoindole-1,3-diylidenedicarbohydrazides.[34] To establish the stereochemistry of the two detected diastereoisomers, nuclear Overhauser effects (NOE) have been used (see the Supporting Information). The results clearly indicated the geometrical isomerism at the exocyclic C═N bond. Thus, in the rotating frame Overhause effect spectroscopy (ROESY) spectrum (Figure 3), a correlation peak between the NH signal at 10.84 ppm (assigned to the NH-1′) and CH signal at 7.93 ppm (CH-4) could be observed, both signals corresponding to the minor isomer. For the major isomer no such correlation peak could be observed. This indicated that the major isomer has the *Z* configuration while the minor isomer has the *E* configuration, relative to the exocyclic C═N double bond. Moreover, in the ROESY spectrum correlation peaks between the NH signals with CH signals belonging to the aromatic rings (NH-1′ with CH-21/CH-25 and NH-2′ with CH-12/CH-16, respectively) could be observed, for both major and minor isomers.

Dynamic NMR studies conducted up to 393 K in DMSO-d_6 as solvent did not reveal any coalescence of resonances. This suggests a free rotation around the amide (C−N) bond at room temperature and above. This conclusion is also supported by the presence of a single set of signals (one for each *Z* or *E* diastereoisomer) in the ^{1}H and ^{13}C- NMR spectra. Around 373 K, the spectra indicate decomposition of the product (see the Supporting Information).

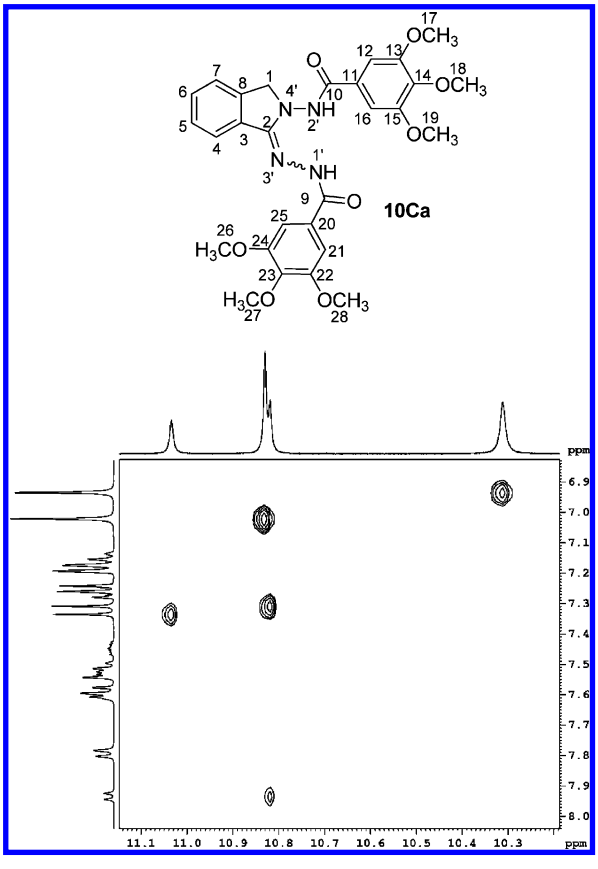

Figure 3. ROESY spectrum (selection) for compound **10Ca** in DMSO-d_6 (400 MHz).

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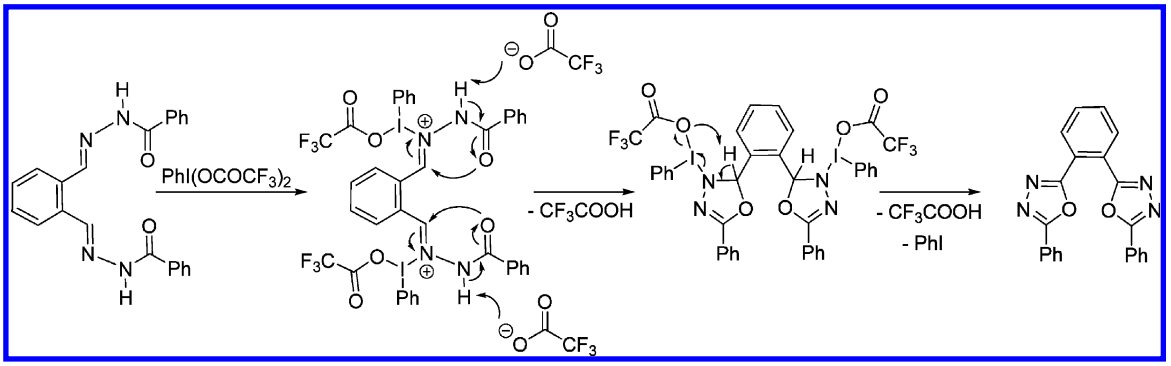
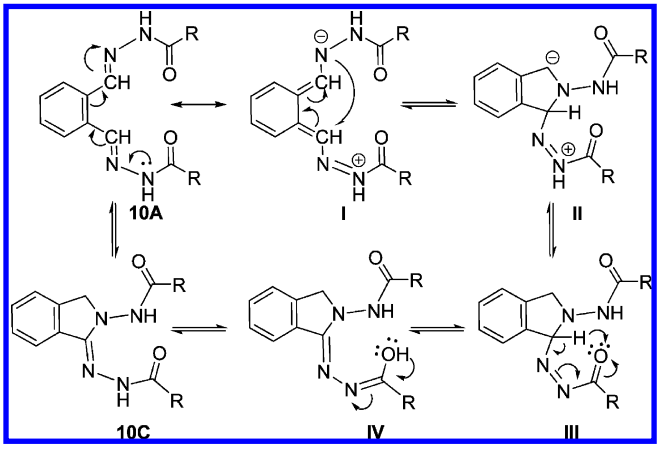
Scheme 5. Proposed Reaction Mechanism for the Oxadiazole Ring Closure



Optimization of the Condensation Reaction. As already stated, under reaction conditions previously reported, we obtained mixtures of aroylhydrazones **10A** and the isoindolin derivatives **10C** that cannot be separated without complete loss of the acyclic hydrazones. However, we performed a series of preliminary tests which showed that both the crude reaction (containing cyclic isomers **10C**-*Z*, **10C**-*E* and aroylhydrazones **10A**) and the isolated cyclic isomers **10C** conveniently convert into the target oxadiazole when subjected to an oxidizing agent such as bis(trifluoroacetoxi)iodobenzene, as it will be further described. This suggests that the two compounds are present in solution in equilibrium and the cyclization reaction probably occurs through an identical intermediate. A proposed reaction mechanism involving the acyclic isomer is depicted in Scheme 5, following the suggested mechanism of oxadiazoles formation by Shang.[24]

The presumed reaction mechanism for the reversible transformation of the acyclic forms **10A** to cyclic isomers **10C** is presented in Scheme 6. Thus, we presume that the

Scheme 6. Proposed Reaction Mechanism for the Transformation 10A to 10C



formation of the five member ring takes place in the canonical form **I** of the acyclic isomer **10A** by the nucleophilic attack of a negatively charged nitrogen to the electrophilic double bonded CH. Next, the azo form **III** undergoes an azo-hydrazone tautomerism[35] reaction with the formation of the isolated cyclic isomer **10C**.

Since the cyclization reaction is presumed to occur through the same intermediate species, it follows that the reaction performed on the mixture of **10A** and **10C** isomers should occur better than the reaction performed on the pure cyclic forms **10C**. Therefore, on the basis of this hypothesis, we focused on optimizing the reaction conditions to provide a mixture of the two forms, so that we obtain the greatest amount of the acyclic compound. We used as a model compound the corresponding hydrazide of 3,4,5-trimethoxybenzoic acid **9a**.

Various conditions were assessed, including previously reported ones[20,36] in terms of solvent, reaction time, temperature, and catalyst (see the Supporting Information). As expected, each of the reactions yielded a different ratio of acyclic/cyclic form, as the ^{1}H NMR spectra of the crude products indicated. The reactions that were performed in ethanol displayed either a very complex mixture of products or the cyclic isomers accompanied by considerable amounts of unreacted raw materials. When chloroform was used for the condensation reaction, the resulting products ratio varied according to the presence of the acid catalyst. Thus, if the condensation was run without any acid catalyst, at room temperature, the ^{1}H NMR spectrum of the crude reaction indicated the formation of the cyclic isomers as major products. In the presence of acetic acid as a catalyst and a reflux temperature for a certain time, the ^{1}H NMR spectra indicated the presence of both cyclic and acyclic isomers, the former being the major ones. Finally, when the reaction was run in toluene, the ^{1}H NMR spectrum of the crude reaction indicated the formation almost exclusively of the cyclic forms with a very high degree of purity, after minimum workup (see the Supporting Information).

Taking into account that (i) the greatest amount of the acyclic compound was provided from the reaction run in chloroform, in the presence of acetic acid, at reflux for a few hours, then at room temperature, (ii) the condensation in toluene provided almost exclusively the cyclic isomers, and (iii) the cyclization reactions for the preparation of the target 1,3,4-oxadiazoles occurred similarly when performed on mixture of compounds and on the cyclic isomers (see the Supporting Information), it follows that the cyclization reaction occurs efficiently no matter the resulting ratio of the cyclic and acyclic isomers, probably through the same intermediate species. In this context, we decided to use the following reaction conditions for all condensation reactions: chloroform and catalytic amounts of acetic acid, 4 h at reflux and then stirred overnight at room temperature.

Synthesis of Bis-1,3,4-oxadiazoles. Among the multitude of possible oxidative agents, we have chosen the hypervalent iodine reagents[37] since their use is very efficient in preparation of such compounds.[25] Bis(trifluoroacetoxy)iodobenzene (PIFA) requires very mild reaction conditions and is commercially available, inexpensive, stable to air and humidity,

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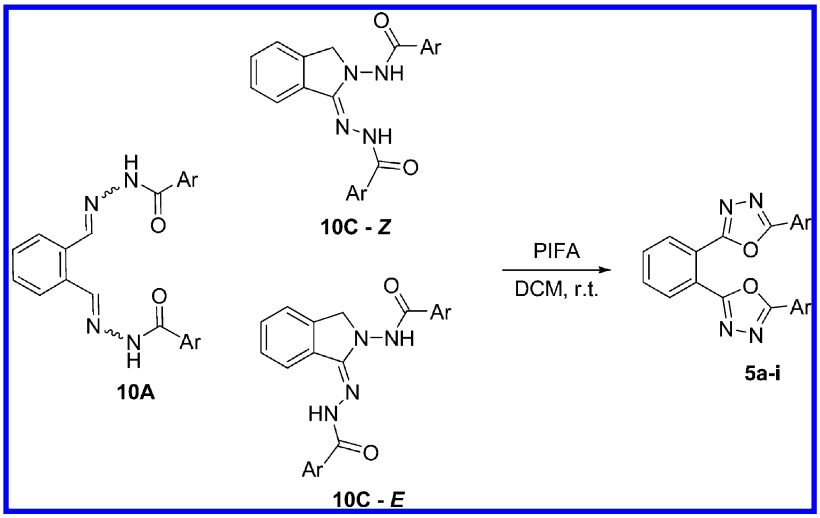
Table 1. Formation of the Target Oxadiazoles 5 through Oxidation with PIFA of the Acyclic and Cyclic Isomers 10 and the Overall Isolated Yields



entry	compound	Ar	overall isolated yield (%)
1	**5a**	3,4,5-triMeO−C_6H_2	43
2	**5b**	4-Br−C_6H_4	39
3	**5c**	4-Cl−C_6H_4	47
4	**5d**	3-Cl−C_6H_4	37
5	**5e**	4-Me−C_6H_4	42
6	**5f**	4-OMe−C_6H_4	43
7	**5g**	4-NO_2−C_6H_4	32
8	**5h**	Ph	46
9	**5i**	4-Py	36

and well-known as an effective oxidative agent for preparation of 1,3,4-oxadiazoles.[22,23,38]

Therefore, the products of condensation were treated with PIFA in dichloromethane and left to react overnight at room temperature. The successful formation of the bis-1,3,4-oxadiazoles (Table 1) could be monitored by TLC and visualization under UV irradiation since the resulting compounds were displayed as fluorescent spots. Unlike their precursors, the heterocyclic compounds are very soluble in organic solvents and can be easily purified by column chromatography. The ^{1}H NMR spectra display fewer signals, in agreement with the symmetrical structures, which can be easily assigned to each structure.

Preliminary investigation of the photophysical properties of the newly synthesized 2,5-substituted bis-1,3,4-oxadiazoles indicated a strong absorption between 262 and 301 nm, when UV−vis spectra were recorded as well as fluorescence emission between 360 and 384 nm (see Supporting Information).[10]

CONCLUSIONS

In this work, we described the unexpected formation of *N*-(1-(2-aryl-hydrazono)isoindolin-2-yl)benzamides **10C** from *ortho*-phthalaldehyde and carboxylic acid hydrazides, as mixtures of geometrical isomers due to the exocyclic C=N double bond (as inferred from the X-ray molecular structure and NMR studies), along with their acyclic isomeric aroylhydrazones **10A** as nonseparable minor products. The single crystal X-ray analysis of **10Ca** indicates a *Z* configuration of the C=N double bond substituents. Variation of the conditions for the condensation reaction led to preparation of pure cyclic isomers. Synthesis of 1,2-(1,3,4-oxadiazol-2-yl)benzenes was conveniently performed both starting from mixtures of isomers and pure cyclic forms, under the action of the hypervalent iodine reagent bis(trifluoroacetoxy)iodobenzene. This indicates that the cyclization reaction occurs through the acyclic form, which is in equilibrium with and is less stable than the cyclic isomer. Current efforts are focused on the study of the photophysical properties of the oxadiazoles, especially their fluorescent properties.

EXPERIMENTAL SECTION

General Experimental Information. The air and water sensitive reactions were performed in anhydrous solvents and under a positive pressure of argon. Dry dichloromethane was distilled over CaH_2. All other solvents and reagents were purchased from commercial suppliers and used without further purification.

The NMR spectra have been fully assigned based on spectra recorded on a spectrometer equipped with a 5 mm multinuclear inverse detection probe, operating at 400.1, 100.6, and 40.6 MHz for ^{1}H, ^{13}C, and ^{15}N nuclei, respectively. The 1D and 2D experiments (H−H correlation spectroscopy (COSY), ROESY, H−C heteronuclear multiple bond correlation (HMBC), H−C heteronuclear single quantum correlation (HSQC), H−N heteronuclear multiple-quantum correlation (HMQC), and H−N HMBC) were recorded using standard pulse sequences in the version with z-gradients, as delivered by the spectrometer manufacturer operating software. The ^{15}N chemical shifts were indirectly detected as projections from the 2D H−N HMBC spectra and are referred to external liquid ammonia (0.0 ppm) using nitromethane (380.2 ppm) as an external standard. For the major isomers (*Z* configuration) all ^{15}N signals have been detected, whereas for minor isomers, due to the smaller concentration in the mixture, often two out of the four ^{15}N signals have not been detected. For reaction control, various NMR spectrometers operating at 400, 500, 360, 300, and 250 MHz have been used. Chemical shifts (δ) are reported in parts per million (ppm) using the residual solvent peak as

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an internal reference. High-resolution mass spectra were recorded using the positive mode atmospheric pressure chemical ionization (APCI) technique on a spectrometer equipped with an Orbital Ion Trap mass analyzer. Thin layer chromatography (TLC) was performed on silica gel coated aluminum F_{254} plates. All plates were visualized by UV irradiation at 254 nm. Preparative column chromatography was performed on silica. Melting points were determined in open capillary tubes using an electric melting point apparatus and are uncorrected.

Single Crystal X-ray Diffraction. X-ray diffraction measurements were performed using an Ag−Kα (λ = 0.5608 Å) X-ray tube with a graphite monochromator. The hydrogen atoms were introduced at calculated positions and not refined (riding model).[39] The structure was solved by direct methods and refined with full-matrix least-squares technique on F^2 using the SHELXS-97 and SHELXL-97 programs within the WINGX interface. The CCDC number is 912069. A summary of the crystallographic data is listed in the Supporting Information (Table S1).

Hydrazides **9c** and **9i** were commercially available and used as purchased, while the rest of them were synthesized from the corresponding carboxylic acids, as previously described.[15] NMR signal assignments for compounds **5** and **10C** were made according to the numbering schemes shown in the Supporting Information for each of them, which do not correspond to IUPAC numbering rules.

General Experimental Procedure for the Synthesis of the Compounds 10: *ortho*-Phthalaldehyde (1.5 mmol, 0.201 g) and the corresponding hydrazide **9** (3 mmol) were dissolved in chloroform (50 mL). Acetic acid (a few drops) was added into the resulted solution and heated to reflux for 4 h. The mixture was stirred overnight at room temperature, then the solvent was removed under vacuum, and the residue was washed with cold diethyl ether. The product was further used without any other purification, except for the NMR spectra recording, when it was recrystallized from methanol.

3,4,5-Trimethoxy-N-(1-(2-(3,4,5-trimethoxybenzoyl)hydrazono)-isoindolin-2-yl)benzamide ***10Ca.*** White solid, mp 162−164 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 3.58 (12H, s, OCH_3-17, 19, 26, 28), 3.66 (3H, s, OCH_3-27), 3.67 (3H, s, OCH_3-18), 4.73 (2H, s, H-1), 6.93 (2H, s, H-21, 25), 7.02 (2H, s, H-12, 16), 7.51 (1H, t, 8.0 Hz, H-5), 7.54 (1H, d, 7.5 Hz, H-7), 7.59 (1H, t, 8.0 Hz, H-6), 7.79 (1H, d, 7.5 Hz, H-4), 10.32 (1H, br, N*H*-1), 10.84 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 55.5 (OCH_3-17, 19 or OCH_3-26, 28), 55.6 (OCH_3-17, 19 or OCH_3-26, 28), 57.4 (C-1), 59.8 (OCH_3-27), 59.9 (OCH_3-18), 104.7 (C-21, 25), 105.1 (C-12, 16), 121.9 (C-4), 122.9 (C-7), 126.3 (C-11), 127.9 (C-5), 128.9 (C-20), 130.6 (C-6), 133.0 (C-3), 138.7 (C-10), 139.5 (C-23), 140.5 (C-14), 152.2 (C-22, 24), 152.4 (C-13, 15), 152.4 (C-2), 161.1 (C-9), 164.3 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 111.60 (N-4′), 134.12 (N-2′), 146.98 (N-1′), 223.97 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 3.73 (3H, s, OCH_3-27), 3.75 (3H, s, OCH_3-18), 3.84 (6H, s, OCH_3-17, 19 or OCH_3-26, 28), 3.86 (6H, s, OCH_3-17, 19 or OCH_3-26, 28), 4.78 (2H, s, H-1), 7.31 (2H, s, H-21, 25), 7.33 (2H, s, H-12, 16), 7.40−7.50 (1H, m, H-5), 7.60 (1H, t, 7.6 Hz, H-6), 7.62 (1H, d, 8.1 Hz, H-7), 7.93 (1H, d, 7.8 Hz, H-4), 10.84 (1H, br, N*H*-1), 11.04 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 55.9 (OCH_3-17, 19 or OCH_3-26, 28), 56.0 (OCH_3-17, 19 or OCH_3-26, 28), 53.6 (C-1), 60.0 (OCH_3-27), 60.1 (OCH_3-17), 104.6 (C-21, 25), 105.1 (C-12, 16), 123.4 (C-7), 126.3 (C-4), 127.1 (C-11), 127.8 (C-5), 128.9 (C-20), 131.1 (C-6), 133.0 (C-3), 139.7 (C-23), 140.2 (C-8), 140.6 (C-14), 152.6 (C-22, 24), 152.7 (C-13, 15), 160.8 (C-2), 162.6 (C-9), 164.7 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 132.15 (N-2′), 147.71 (N-1′). HRMS (APCI-Orbit trap) m/z calcd for $C_{28}H_{31}N_4O_8$ $[M + H]^+$, 551.2136; found, 551.2143.

4-Bromo-N-(1-(2-(4-bromobenzoyl)hydrazono)isoindolin-2-yl)-benzamide ***10Cb.*** White solid, mp 211−212 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.76 (2H, s, H-1), 7.47 (2H, d, 9.0 Hz, H-19, 21), 7.49 (2H, d, 8.6 Hz, H-18, 22), 7.51 (1H, t, 7.6 Hz, H-5), 7.53 (1H, d, 8.1 Hz, H-7), 7.59 (1H, t, 7.4 Hz, H-6), 7.61 (2H, d, 9.6 Hz, H-13, 15), 7.68 (2H, d, 8.4 Hz, H-12, 16), 7.78 (1H, d, 7.4 Hz, H-4), 10.43 (1H, br, N*H*-1), 10.94 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.2 (C-1), 121.9 (C-4), 122.9 (C-7), 124.4 (C-20), 126.1 (C-14), 127.9 (C-5), 128.9 (C-18, 22), 129.4 (C-12, 16), 130.3 (C-11), 130.7 (C-6), 130.9 (C-19, 21), 131.4 (C-13,15), 132.7 (C-3), 132.9 (C-17), 138.71 (C-8), 152.0 (C-2), 160.9 (C-9), 164.1 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 134.50 (N-2′), 147.40 (N-1′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.78 (2H, s, H-1), 7.40−7.50 (1H, m, H-5), 7.60 (1H, d, 7.9 Hz, H-7), 7.60 (1H, t, 7.8 Hz, H-6), 7.72 (2H, d, 8.1 Hz, H-19, 21), 7.77 (2H, d, 8.4 Hz, H-13, 15), 7.90 (2H, d, 8.0 Hz, H-18, 22), 7.92 (2H, d, 8.6 Hz, H-12, 16), 7.93 (1H, d, 8.5 Hz, H-4), 10.98 (1H, br, N*H*-1), 11.14 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.6 (C-1), 123.4 (C-7), 123.4 (C-20), 125.9 (C-14), 125.9 (C-4), 127.8 (C-5), 128.9 (C-3), 129.0 (C-18, 22), 129.6 (C-12, 16), 131.1 (C-6), 131.4 (C-11), 131.4 (C-19, 21), 131.6 (C-13, 15), 132.9 (C-17), 140.1 (C-8), 160.6 (C-2), 162.4 (C-9), 164.6 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 132.70 (N-2′), 148.00 (N-1′). HRMS (APCI-Orbit trap) m/z calcd for $C_{22}H_{17}Br_2N_4O_2$ $[M + H]^+$, 528.9692; found, 528.9695.

4-Chloro-N-(1-(2-(4-chlorobenzoyl)hydrazono)isoindolin-2-yl)-benzamide ***10Cc.*** White solid, mp 182−185 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.76 (2H, s, H-1), 7.34 (2H, d, 8.4 Hz, H-19, 21), 7.46 (2H, t, 8.4 Hz, H-13, 15), 7.52 (1H, t, 7.6 Hz, H-5), 7.54 (1H, d, 7.9 Hz, H-7), 7.59 (2H, d, 8.8 Hz, H-18, 22), 7.60 (1H, t, 8.0 Hz, H-6), 7.78 (2H, d, 8.2 Hz, H-12, 16), 7.80 (1H, d, 7.5 Hz, H-4), 10.44 (1H, br, N*H*-1), 10.96 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.3 (C-1), 121.9 (C-4), 122.9 (C-7), 127.9 (C-5), 127.9 (C-19, 21), 128.4 (C-13, 15), 128.5 (C-18, 22), 129.3 (C-12, 16), 129.9 (C-11), 130.7 (C-6), 132.6 (C-17), 132.7 (C-3), 135.6 (C-20), 137.1 (C-14), 138.7 (C-8), 152.1 (C-2), 160.9 (C-9), 163.9 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 135.42 (N-2′), 148.58 (N-1′), 224.30 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.79 (2H, s, H-1), 7.44−7.50 (1H, m, H-5), 7.60 (2H, d, 8.2 Hz, H-19, 21), 7.61 (1H, t, 8.1 Hz, H-6), 7.62 (1H, d, 7.8 Hz, H-7), 7.64 (2H, d, 8.6 Hz, H-13, 15), 7.94 (1H, d, 8.0 Hz, H-4), 7.97 (2H, d, 8.4 Hz, H-18, 22), 8.00 (2H, d, 8.4 Hz, H-12, 16), 10.99 (1H, br, N*H*-1), 11.16 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.6 (C-1), 123.4 (C-7), 126.1 (C-4), 127.8 (C-5), 128.6 (C-13, 15), 128.8 (C-19, 21), 128.9 (C-3), 129.1 (C-18, 22), 129.5 (C-12, 16), 130.9 (C-11), 131.1 (C-6), 132.6 (C-17), 135.8 (C-20), 136.9 (C-14), 140.1 (C-8), 160.6 (C-2), 162.3 (C-9), 164.5 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 133.41 (N-2′), 149.15 (N-1′), 228.0 (N-3′). HR-MS (APCI-Orbit trap) m/z calcd for $C_{22}H_{17}Cl_2N_4O_2$ $[M + H]^+$, 439.0723; found, 439.0728.

3-Chloro-N-(1-(2-(3-chlorobenzoyl)hydrazono)isoindolin-2-yl)-benzamide ***10Cd:*** White solid, mp 193−197 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.76 (2H, s, H-1), 7.33 (1H, t, 8.0 Hz, H-21), 7.42 (1H, t, 8.0 Hz, H-15), 7.50 (1H, d, 7.6 Hz, H-20), 7.53 (1H, t, 7.7 Hz, H-5), 7.55 (1H, d, 8.0 Hz, H-7), 7.55 (1H, s, H-18), 7.60 (2H, m, H-14 and H-22), 7.61 (1H, t, 8.2 Hz, H-6), 7.75 (1H, d, 8.1 Hz, H-16), 7.76 (1H, s, H-12), 7.80 (1H, d, 7.3 Hz, H-4), 10.51 (1H, br, N*H*-1), 11.01 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.2 (C-1), 121.9 (C-4), 122.9 (C-7), 125.7 (C-22), 126.2 (C-16), 126.8 (C-18), 127.2 (C-12), 127.9 (C-5), 129.9 (C-21), 130.3 (C-15), 130.6 (C-20), 130.7 (C-6), 131.9 (C-14), 132.7 (C-3), 132.9 (C-17), 133.3 (C-11 and C-13), 135.8 (C-19), 138.7 (C-8), 152.4 (C-2), 160.6 (C-9), 163.6 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 111.01 (N-4′), 135.73 (N-2′), 148.79 (N-1′), 224.43 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.80 (2H, s, H-1), 7.50−7.60 (1H, m, H-5), 7.56 (1H, t, 8.3 Hz, H-21), 7.61 (1H, t, 7.8 Hz, H-15), 7.62 (1H, t, 7.5 Hz, H-6), 7.63 (1H, d, 8.0 Hz, H-7), 7.64 (1H, d, 9.1 Hz, H-20), 7.72 (1H, d, 8.1 Hz, H-14), 7.55 (1H, s, H-18), 7.94 (1H, d, 7.7 Hz, H-22), 7.95 (1H, d, 6.1 Hz, H-4), 7.96 (1H, d, 7.8 Hz, H-16), 8.04 (1H, s, H-12), 11.05 (1H, br, N*H*-1), 11.21 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.7 (C-1), 126.1 (C-4), 123.5 (C-7), 125.8 (C-22), 126.3 (C-16), 127.0 (C-18), 127.4 (C-12), 127.9 (C-5), 128.7 (C-3), 130.4 (C-21), 130.7 (C-15), 130.9 (C-20), 131.2 (C-6), 131.9 (C-14), 133.2 (C-17), 133.3 (C-11), 134.1 (C-13), 135.8 (C-19), 140.1 (C-8), 160.6 (C-2), 161.1 (C-9), 164.1 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 149.39 (N-1′). HR-MS (APCI-Orbit trap) m/z calcd for $C_{22}H_{17}Cl_2N_4O_2$ $[M + H]^+$, 439.0723; found, 439.0728.

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4-Methyl-N-(1-(2-(4-methylbenzoyl)hydrazono)isoindolin-2-yl)-benzamide ***10Ce***. White solid, mp 225−228 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 2.31 (3H, s, H-24), 2.37 (3H, s, H-17), 4.76 (2H, s, H-1), 7.07 (2H, d, 7.6 Hz, H-20, 22), 7.25 (2H, d, 7.6 Hz, H-13, 15), 7.44 (2H, d, 7.6 Hz, H-19, 23), 7.52 (1H, t, 7.3 Hz, H-5), 7.53 (1H, d, 7.6 Hz, H-7), 7.59 (1H, t, 8.1 Hz, H-6), 7.73 (2H, d, 8.8 Hz, H-12, 16), 7.78 (1H, d, 7.1 Hz, H-4), 10.29 (1H, br, N*H*-1), 10.91 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 20.9 (C-24), 21.0 (C-17), 57.4 (C-1), 121.7 (C-4), 122.9 (C-7), 126.9 (C-19, 23), 127.5 (C-12, 16), 127.9 (C-5), 128.4 (C-11), 128.6 (C-20, 22), 129.0 (C-13, 15), 130.5 (C-6), 131.1 (C-18), 132.8 (C-3), 138.8 (C-8), 140.1 (C-21), 142.5 (C-14), 150.2 (C-2), 161.9 (C-9), 165.1 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 108.4 (N-4′), 135.18 (N-2′), 148.47 (N-1′), 227.62 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 2.37 (3H, s, H-24), 2.39 (3H, s, H-17), 4.76 (2H, s, H-1), 7.30 (2H, d, 8.0 Hz, H-20, 22), 7.34 (2H, d, 8.0 Hz, H-13, 15), 7.40−7.50 (1H, m, H-5), 7.60 (1H, t, 8.9 Hz, H-6), 7.61 (1H, d, 7.8 Hz, H-7), 7.84 (2H, d, 8.0 Hz, H-19, 23), 7.89 (2H, d, 8.0 Hz, H-12, 16), 7.92 (1H, d, 7.6 Hz, H-4), 10.78 (1H, br, N*H*-1), 10.91 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 20.9 (C-24), 21.0 (C-17), 53.6 (C-1), 123.4 (C-7), 126.1 (C-4), 127.2 (C-19, 23), 127.6 (C-12, 16), 127.7 (C-5), 128.9 (C-20, 22), 129.0 (C-13, 15), 129.2 (C-3), 129.5 (C-11), 130.9 (C-6), 131.1 (C-18), 140.1 (C-8), 140.8 (C-21), 142.1 (C-14), 160.7 (C-2), 163.3 (C-9), 165.3 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 132.12 (N-2′), 148.06 (N-1′), 230.05 (N-3′). HR-MS (APCI-Orbit trap) m/z calcd for $C_{24}H_{23}N_4O_2$ $[M + H]^+$, 399.1815; found, 399.1823.

4-Methoxy-N-(1-(2-(4-methoxybenzoyl)hydrazono)isoindolin-2-yl)benzamide ***10Cf***. White solid, mp 204−206 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 3.78 (3H, s, H-24), 3.82 (3H, s, H-17), 4.75 (2H, s, H-1), 6.80 (2H, d, 8.4 Hz, H-20, 22), 6.99 (2H, d, 8.4 Hz, H-13, 15), 7.49 (1H, t, 7.3 Hz, H-5), 7.51 (1H, d, 8.1 Hz, H-7), 7.53 (2H, d, 8.8 Hz, H-19, 23), 7.56 (1H, t, 7.9 Hz, H-6), 7.76 (1H, d, 7.6 Hz, H-4), 7.82 (2H, d, 8.8 Hz, H-12, 16), 10.27 (1H, br, N*H*-1), 10.85 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 55.3 (C-24), 55.5 (C-17), 57.4 (C-1), 113.3 (C-20, 22), 113.8 (C-13, 15), 121.7 (C-4), 122.9 (C-7), 123.2 (C-11), 126.0 (C-18), 127.9 (C-5), 128.7 (C-19, 23), 129.5 (C-12, 16), 130.4 (C-6), 132.8 (C-3), 138.8 (C-8), 150.0 (C-2), 161.3 (C-21), 161.4 (C-9), 162.4 (C-14), 164.8 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 103.5 (N-4′), 132.90 (N-2′), 146.3 (N-1′), 226.3 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 3.83 (3H, s, H-24), 3.84 (3H, s, H-17), 4.75 (2H, s, H-1), 7.03 (2H, d, 8.8 Hz, H-20, 22), 7.07 (2H, d, 8.8 Hz, H-13, 15), 7.40−7.50 (1H, m, H-5), 7.57 (1H, t, 6.6 Hz, H-6), 7.58 (1H, d, 8.1 Hz, H-7), 7.92 (1H, d, 8.8 Hz, H-4), 7.92 (2H, d, 8.8 Hz, H-19, 23), 7.97 (2H, d, 8.8 Hz, H-12, 16), 10.71 (1H, br, N*H*-1), 10.85 (1H, br, N*H*-2).^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.7 (C-1), 55.3 (C-24), 55.4 (C-17), 113.7 (C-20, 22), 113.7 (C-13, 15), 123.35 (C-7), 124.4 (C-11), 126.1 (C-4), 126.1 (C-18), 127.7 (C-5), 128.9 (C-19, 23), 129.2 (C-3), 129.5 (C-12, 16), 130.9 (C-6), 140.1 (C-8), 160.7 (C-2), 161.5 (C-21), 162.2 (C-14), 163.0 (C-9), 164.9 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 132.90 (N-2′), 145.05 (N-1′), 229.40 (N-3′). HR-MS (APCI-Orbit trap) m/z calcd for $C_{24}H_{23}N_4O_4$ $[M + H]^+$, 431.1714; found, 431.1722.

4-Nitro-N-(1-(2-(4-nitrobenzoyl)hydrazono)isoindolin-2-yl)-benzamide ***10Cg***. Yellow solid, mp 213−215 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.80 (2H, s, H-1), 7.53 (1H, t, 7.4 Hz, H-5), 7.56 (1H, d, 7.9 Hz, H-7), 7.61 (1H, t, 7.9 Hz, H-6), 7.79 (2H, d, 8.8 Hz, H-18, 22), 7.81 (1H, d, 7.5 Hz, H-4), 7.93 (2H, d, 8.7 Hz, H-12, 16), 8.09 (2H, d, 9.2 Hz, H-19, 21), 8.17 (2H, d, 8.4 Hz, H-13, 15), 10.74 (1H, br, N*H*-1), 11.21 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.3 (C-1), 122.1 (C-4), 123.0 (C-7), 123.1 (C-19, 21), 123.4 (C-13, 15), 128.1 (C-5), 128.4 (C-18, 22), 128.9 (C-12, 16), 130.9 (C-6), 132.6 (C-3), 136.8 (C-11), 138.8 (C-8), 139.4 (C-17), 148.5 (C-20), 149.4 (C-14), 153.2 (C-2), 160.4 (C-9), 163.2 (C-10). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.83 (2H, s, H-1), 7.40−7.50 (1H, m, H-5), 7.62 (1H, t, 8.1 Hz, H-6), 7.63 (1H, d, 8.3 Hz, H-7), 7.96 (1H, d, 10.8 Hz, H-4), 8.18 (2H, d, 8.0 Hz, H-18, 22), 8.21 (2H, d, 8.8 Hz, H-12, 16), 8.34 (2H, d, 9.6 Hz, H-19, 21), 8.40 (2H, d, 8.8 Hz, H-13, 15), 11.29 (1H, br, N*H*-1), 11.44 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.7 (C-1), 123.5 (C-7), 123.6 (C-19, 21), 123.8 (C-13, 15), 126.1 (C-4), 127.9 (C-5), 128.7 (C-18, 22), 129.1 (C-12, 16), 131.3 (C-6), 139.5 (C-17), 140.2 (C-8), 148.9 (C-20), 149.5 (C-14), 160.6 (C-2), 161.6 (C-9), 164.0 (C-10). HR-MS (APCI-Orbit trap) m/z calcd for $C_{22}H_{17}N_6O_6$ $[M + H]^+$, 461.1204; found, 461.1210.

N-(1-(2-Benzoyl)hydrazono)isoindolin-2-yl)benzamide ***10Ch***. White solid, mp 221−224 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.78 (2H, s, H-1), 7.25 (2H, t, 7.2 Hz, H-19, 21), 7.44 (2H, t, 7.6 Hz, H-13, 15), 7.45 (1H, t, 7.5 Hz, H-20), 7.53 (1H, d, 7.9 Hz, H-7), 7.53 (1H, t, 7.4 Hz, H-5), 7.54 (2H, d, 7.5 Hz, H-18, 22), 7.59 (1H, t, 8.1 Hz, H-14), 7.59 (1H, t, 7.4 Hz, H-6), 7.78 (1H, d, 7.2 Hz, H-4), 7.82 (2H, d, 7.6 Hz, H-12, 16), 10.38 (1H, br, N*H*-1), 10.97 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.3 (C-1), 121.8 (C-4), 122.9 (C-7), 126.9 (C-18, 22), 127.5 (C-12, 16), 127.9 (C-5), 127.9 (C-19, 21), 128.4 (C-13, 15), 130.5 (C-6), 130.8 (C-20), 131.1 (C-11), 132.3 (C-14), 132.8 (C-3), 133.9 (C-17), 138.8 (C-8), 150.7 (C-2), 161.9 (C-9), 165.1 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 108.6 (N-4′), 134.5 (N-2′), 149.0 (N-1′), 226.7 (N-3′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.80 (2H, s, H-1), 7.40−7.50 (1H, m, H-5), 7.52 (2H, t, 7.1 Hz, H-19, 21), 7.56 (2H, t, 7.6 Hz, H-13, 15), 7.56 (1H, t, 7.2 Hz, H-6), 7.60 (1H, d, 8.6 Hz, H-7), 7.61 (1H, t, 9.1 Hz, H-20), 7.64 (1H, t, 7.1 Hz, H-14), 7.95 (2H, d, 7.3 Hz, H-18, 22), 7.96 (1H, d, 8.3 Hz, H-4), 8.00 (2H, d, 7.6 Hz, H-12, 16), 10.89 (1H, br, N*H*-1), 11.04 (1H, br, N*H*-2).^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.6 (C-1), 123.4 (C-7), 126.1 (C-4), 127.1 (C-18, 22), 127.6 (C-12, 16), 127.7 (C-5), 128.4 (C-19, 21), 128.5 (C-13, 15), 129.1 (C-3), 130.9 (C-6), 130.9 (C-20), 132.0 (C-14), 132.2 (C-11), 133.9 (C-17), 140.1 (C-8), 160.6 (C-2), 163.3 (C-9), 165.4 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 102.60 (N-4′), 132.99 (N-2′), 148.82 (N-1′), 229.90 (N-3′) HRMS (APCI-Orbit trap) m/z calcd for $C_{22}H_{19}N_4O_2$ $[M + H]^+$, 371.1503; found, 371.1508.

4-Pyridyl-N-(1-(2-(3,4,5-trimethoxybenzoyl)hydrazono)-isoindolin-2-yl)benzamide ***10 Ci***. White solid, mp 291−293 °C. Major isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.79 (2H, s, H-1), 7.50 (2H, d, 6 Hz, H-17, 20), 7.55 (1H, t, 7.6 Hz, H-5), 7.57 (1H, d, 8.2 Hz, H-7), 7.63 (1H, t, 7.8 Hz, H-6), 7.63 (2H, d, 5.2 Hz, H-12, 15), 7.81 (1H, d, 7.6 Hz, H-4), 8.52 (2H, d, 5.6 Hz, H-18, 19), 8.61 (2H, d, 5.6 Hz, H-13, 14), 10.72 (1H, br, N*H*-1), 11.21 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 57.3 (C-1), 120.9 (C-17, 20), 121.1 (C-12, 15), 122.1 (C-4), 123.0 (C-7), 128.1 (C-5), 130.9 (C-6), 132.5 (C-3), 138.3 (C-11), 138.7 (C-8), 140.7 (C-16), 149.7 (C-18, 19), 150.2 (C-13, 14), 153.3 (C-2), 160.0 (C-9), 163.3 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 111.3 (N-4′), 136.9 (N-2′), 150.1 (N-1′), 223.7 (N-3′), 321.6 (N-6′), 325.5 (N-5′). Minor isomer: ^{1}H NMR (400.1 MHz, DMSO-d_6), δ (ppm): 4.82 (2H, s, H-1), 7.40−7.50 (1H, m, H-5), 7.64 (1H, d, 7.6 Hz, H-7), 7.64 (1H, t, 7.6 Hz, H-6), 7.86 (2H, d, 6.0 Hz, H-17, 20), 7.89 (2H, d, 6.0 Hz, H-12, 15), 7.95 (1H, d, 7.6 Hz, H-4), 8.76 (2H, d, 5.6 Hz, H-18, 19), 8.82 (2H, d, 5.6 Hz, H-13, 14), 11.25 (1H, br, N*H*-1), 11.42 (1H, br, N*H*-2). ^{13}C NMR (100.6 MHz, DMSO-d_6), δ (ppm): 53.6 (C-1), 121.2 (C-17, 20), 121.3 (C-12, 15), 123.5 (C-7), 126.1 (C-4), 127.9 (C-5), 128.6 (C-3), 131.3 (C-6), 139.1 (C-11), 140.1 (C-8), 140.7 (C-16), 150.3 (C-18, 19), 150.5 (C-13, 14), 160.6 (C-2), 161.6 (C-9), 164.0 (C-10). ^{15}N NMR (40.6 MHz, DMSO-d_6), δ (ppm): 150.9 (N-1′), 228.5 (N-3′), 322.8 (N-6′), 325.4 (N-5′). HR-MS (APCI-Orbit trap) m/z calcd for $C_{20}H_{17}N_6O_2$ $[M + H]^+$, 373.1408; found, 373.1414.

General Experimental Procedure for the Synthesis of Bis-1,3,4-oxadiazoles 5. An oven-dried flask was charged with **10** (0.50 mmol) and PIFA (3 equiv, 1.5 mmol, 0.64 g) and filled with argon. Dry dichloromehane (10 mL) was added through the septum, and the mixture was stirred overnight at room temperature. The solvent was removed *in vacuo*, and the residue was treated with ethyl acetate (30 mL) and neutralized with a solution of 5% sodium bicarbonate (3 × 20 mL). The organic layers were then washed with water and brine and dried over anhydrous magnesium sulfate, and the solvent was removed

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in vacuo. The residue was chromatographed using as eluent various mixtures of solvents to afford the pure product.

1,2-Bis[5-(3′,4′,5′-trimetoxiphenyl)-1,3,4-oxadiazol-2-yl]benzene ***5a***. White solid, mp 212−213 °C, overall isolated yield 117 mg (43%), R_f = 0.45 (silica gel, EtOAc/DCM = 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm): 3.84 (12H, s, OCH_3), 3.87 (s, 6H, OCH_3), 7.11 (s, 4H, H-7), 7.76−7.80 (2H, m, H-3), 8.15−8.20 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 56.2 (CH3-8), 61.0 (CH3-9), 104.0 (C-7), 118.2 (C-6), 123.4 (C-1), 130.8 (C-2), 131.9 (C-3), 141.3 (C-9), 153.6 (C-8), 163.3 (C-4), 165.2 (C-5). MS (ES^+): *m/z*, 547.2 $[M + H]^+$; 569.2 $[M + Na]^+$; 813.4 $[3M + H + Na]^{2+}$; 839.4 $[3M + H + K]^{2+}$. HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{28}H_{27}N_4O_8$ $[M + H]^+$, 547.1823; found, 547.1829.

1,2-Bis[5-(4′-bromophenyl)-1,3,4-oxadiazol-2-yl]benzene ***5b***. White solid, mp 249−250 °C, overall isolated yield 102 mg (39%), R_f = 0.46 (silica gel, EtOAc/petroleum ether = 1:3). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.57 (4H, d, 8.8 Hz, H-8), 7.75−7.79 (2H, m, H-3), 7.80 (4H, d, 8.8 Hz, H-7), 8.11−8.15 (2H, m, H-2).^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 122.3 (C-6), 123.4 (C-1), 126.8 (C-9), 128.2 (C-7), 130.8 (C-2), 131.9 (C-3), 132.5 (C-8), 163.4 (C-4), 164.5 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{22}H_{13}Br_2N_4O_2$ $[M + H]^+$, 524.9379; found, 524.9385.

1,2-Bis[5-(4′-clorophenyl)-1,3,4-oxadiazol-2-yl]benzene ***5c***. White solid, mp 212−214 °C, overall isolated yield 102 mg (47%), R_f = 0.75 (silica gel, EtOAc/DCM = 1:2). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.41 (4H, d, 8.8 Hz, H-8), 7.77−7.79 (2H, m, H-3), 7.87 (4H, d, 8.4 Hz, H-7), 8.12−8.15 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 121.8 (C-6), 123.4 (C-1), 128.1 (C-7), 129.5 (C-8), 130.8 (C-2), 131.9 (C-3), 138.4 (C-9), 163.4 (C-5), 164.4 (C-4). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{22}H_{13}Cl_2N_4O_2$ $[M + H]^+$, 435.0410; found, 435.0421.

1,2-Bis[5-(3′-clorophenyl)-1,3,4-oxadiazol-2-yl]benzene ***5d***. White solid, mp 133−136 °C, overall isolated yield 80 mg (37%), R_f = 0.41 (silica gel, EtOAc/petroleum ether = 0.5:1). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.37 (2H, t, 8.0 Hz, H-10), 7.47 (2H, d, 8.4 Hz, H-9), 7.77−7.81 (2H, m, H-3), 7.85 (2H, d, 7.6 Hz, H-11), 7.93 (2H, s, H-7), 8.13−8.16 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 123.4 (C-1), 124.9 (C-6 and C-11), 126.9 (C-7), 130.5 (C-10), 130.8 (C-2), 132.0 (C-3 and C-9), 135.3 (C-8), 163.5 (C-4), 164.1 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{22}H_{13}Cl_2N_4O_2$ $[M + H]^+$, 435.0410; found, 435.0421.

1,2-Bis[5-(4′-methylphenyl)-1,3,4-oxadiazol-2-yl]benzene ***5e***. White solid, mp 175−176 °C, overall isolated yield 82 mg (42%), R_f = 0.57 (silica gel, EtOAc/DCM = 0.5:1). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 2.37 (6H, s, CH_3), 7.19 (4H, d, 8.0 Hz, H-8), 7.73−7.76 (2H, m, H-3), 7.80 (4H, d, 8.0 Hz, H-7), 8.12−8.15 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 21.6 (CH_3), 120.6 (C-6), 123.6 (C-1), 126.8 (C-7), 129.7 (C-8), 130.8 (C-2), 131.7 (C-3), 142.4 (C-9), 163.1 (C-4), 165.4 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{24}H_{19}N_4O_2$ $[M + H]^+$, 395.1503; found, 395.1514.

1,2-Bis[5-(4-metoxiphenyl)-1,3,4-oxadiazol-2-yl]benzene ***5f***. White solid, mp 165−166 °C, overall isolated yield 92 mg (43%), R_f = 0.44 (silica gel, EtOAc/DCM = 1:4). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 3.83 (6H, s, CH_3), 6.88 (4H, d, 8.8 Hz, H-8), 7.73−7.75 (2H, m, H-3), 7.84 (4H, d, 8.8 Hz, H-7), 8.13−8.15 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 55.4 (CH_3), 114.5 (C-8), 115.9 (C-6), 123.6 (C-1), 128.7 (C-7), 130.8 (C-2), 131.7 (C-3), 162.4 (C-9), 162.9 (C-4), 165.2 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{24}H_{19}N_4O_4$ $[M + H]^+$, 427.1401; found, 427.1404.

1,2-Bis[5-(4′-nitrophenyl)-1,3,4-oxadiazol-2-yl]benzene ***5g***. White solid, mp 246−248 °C, overall isolated yield 73 mg (32%), R_f = 0.26 (silica gel, EtOAc/DCM = 1:2). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.83−7.85 (2H, m, H-3), 8.14−8.16 (2H, m, H-2), 8.20 (4H, d, 9.2 Hz, H-7), 8.34 (4H, d, 8.8 Hz, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 123.3 (C-1), 124.5 (C-8), 127.9 (C-7), 128.9 (C-6), 130.9 (C-2), 132.4 (C-3), 149.8 (C-9), 163.5 (C-5), 163.5 (C-4). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{22}H_{13}N_6O_6$ $[M + H]^+$, 457.0891; found, 457.0901.

1,2-Bis[5-phenyl-1,3,4-oxadiazol-2-yl]benzene ***5h***. White solid, mp 124−126 °C, overall isolated yield 84 mg (46%), R_f = 0.52 (silica gel, EtOAc/petroleum ether = 1:1). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.39 (4H, t, 7.2 Hz, H-8), 7.47 (2H, t, 7.2 Hz, H-9), 7.75−7.79 (2H, m, H-3), 7.92 (4H, d, 6.8 Hz, H-7), 8.14−8.18 (2H, m, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 123.4 (C-1), 123.6 (C-6), 126.9 (C-7), 129.1 (C-8), 130.8 (C-2), 131.8 (C-9), 131.9 (C-3), 163.3 (C-4), 165.3 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{22}H_{15}N_4O_2$ $[M + H]^+$, 367.1190; found, 367.1195.

1,2-Bis[5-(4-piridyl)-1,3,4-oxadiazol-2-yl]benzene ***5i***. White solid, mp 210−212 °C, overall isolated yield 66 mg (36%), R_f = 0.50 (alox, EtOAc/DCM = 3:1). ^{1}H NMR (400.1 MHz, $CDCl_3$), δ (ppm): 7.83 (4H, d, 6.0 Hz, H-7), 7.82−7.84 (2H, m, H-3), 8.14−8.16 (2H, m, H-2), 8.77 (4H, d, 5.6 Hz, H-8). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ (ppm): 120.2 (C-7), 123.3 (C-1), 130.5 (C-6), 130.9 (C-2), 132.3 (C-3), 151.0 (C-8), 163.4 (C-4), 163.9 (C-5). HR-MS (APCI-Orbit trap) *m/z* calcd for $C_{20}H_{13}N_6O_2$ $[M + H]^+$, 369.1100; found, 369.1095.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details about synthesis, X-ray diffraction, NMR and HR-MS spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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