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Visible-Light Photocatalytic Ugi/Aza-Wittig Cascade towards 2-Aminomethyl-1,3,4-oxadiazole Derivatives

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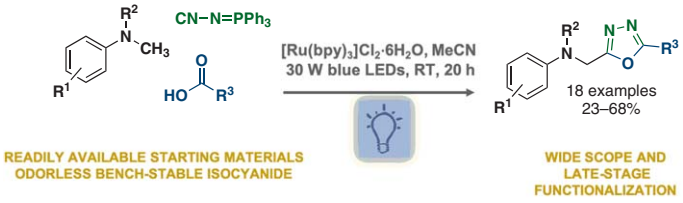
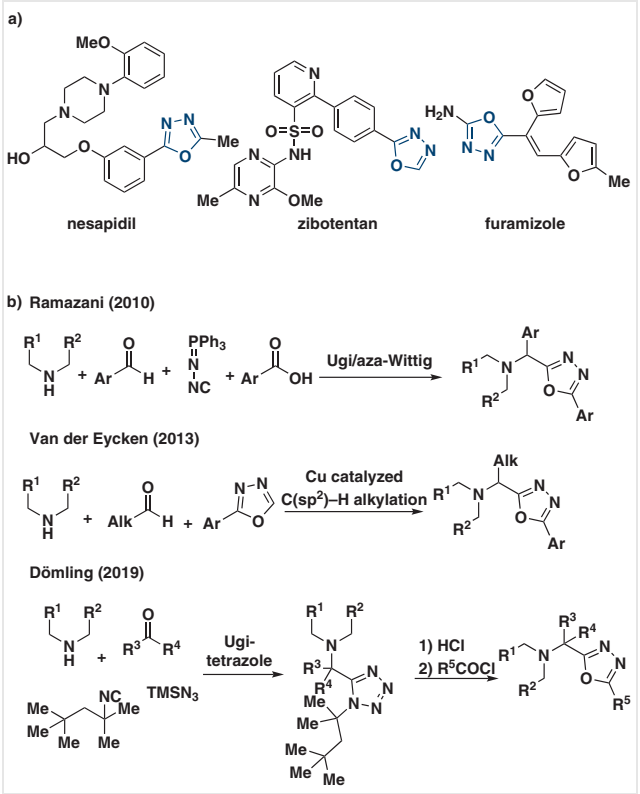


Received: 14.05.2021
Accepted after revision: 02.07.2021
Published online: 02.07.2021
DOI: 10.1055/a-1543-3924; Art ID: ss-2021-z0283-fa

Abstract A new visible-light photocatalytic multicomponent reaction (MCR) involving *N*-alkyl-*N*-methylanilines, *N*-isocyanoiminotriphenylphosphorane, and carboxylic acids leading to 1,3,4-oxadiazole derivatives is reported. The developed mild reaction conditions enable a broad substrate scope and good functional group tolerance, as further highlighted in the late-stage functionalization of amino acids and drugs. Additionally, a two-step one-pot protocol for the synthesis of non-symmetrical diacylhydrazines is also reported.

Key words photoredox catalysis, isocyanide chemistry, Ugi reaction, aza-Wittig reaction, multicomponent reactions, 1,3,4-oxadiazoles

The 1,3,4-oxadiazole core is shared by a wide range of biologically active compounds, such as the antihypertensive nesapidil, the anticancer agent zibotentan, and the antibiotic furamizole (Scheme 1a), thus deserving the status of privileged structure in medicinal chemistry. Accordingly, it can be a key pharmacophoric unit, either contributing to ligand binding or providing appropriate orientation for substituents; it can modulate chemical-physical properties thanks to the ability of increasing water solubility, and, importantly, it can behave as bioisosteric replacement of carbonyl frameworks such as esters, amides, and carbamates.[1–3] To this end, Yudin et al. have shown that the incorporation of a 1,3,4-oxadiazole ring into peptide macrocycles can increase cell membrane penetration compared to amide congeners.[4] As a consequence, a good number of synthetic approaches are nowadays available to get large and diverse libraries of 2,5-disubstituted 1,3,4-oxadiazoles, including one-pot multicomponent reactions (MCRs). The latter, being well-known green chemistry tools, are endowed with a great number of advantages such as saving time, energy, and resources and minimizing waste, thanks to both high atom economy and bond-forming efficiency.[5,6] Representative one-pot multicomponent strategies involve the Ugi-4CR/aza-Wittig sequence reported by Ramazani et al. in 2010[7] and the copper-catalyzed C–H alkylation of preformed 2-substituted 1,3,4-oxadiazoles with both aliphatic amines and aldehydes/ketones described by the Van der Eycken lab in 2013[8] (Scheme 1b).



Scheme 1 (a) Biologically active compounds incorporating the 1,3,4-oxadiazole nucleus and (b) representative multicomponent approaches to 1,3,4-oxadiazoles

More recently, Dömling developed a robust Ugi-tetrazole/Huisgen sequence rapidly enabling structural diversity and gram scalability (Scheme 1b).[9] Nevertheless, the substrate scope of these valuable synthetic methods has been limited to strongly nucleophilic secondary aliphatic amines. To expand the MCR scope to 1,3,4-oxadiazole derivatives incorporating aromatic amines, we reasoned that such a task could be accomplished by harnessing a photoredox, catalytic, in situ oxidation of *N*,*N*-dimethylanilines **1**, followed by a radical/polar crossover interception of the iminium ion with *N*-isocyanoiminotriphenyl phosphorane **2** and a carboxylic acid **3** (Scheme 2).[10]

Biographical Sketches

(from left to right) **Camilla Russo** graduated in 2020 in pharmaceutical chemistry and technology (*summa cum laude*) at the University of Naples Federico II. She is currently attending her first year of the PhD course in pharmaceutical sciences at the same university, under the supervision of Dr. Mariateresa Giustiniano. Her research project focuses on the development of green synthetic methodologies for the synthesis of drug-like bioactive scaffolds, with particular interest in isocyanide chemistry, multicomponent reactions, and photochemical processes.

Rolando Cannalire received his PhD in medicinal chemistry at the University of Perugia in 2016. During his PhD studies, he has been a visiting PhD student at the University of Lisbon and, later, the University of Groningen. In 2016, he held a postdoctoral fellowship from the Italian National Research Council and, from 2017 to mid 2019, he held postdoctoral fellowships at the Department of Pharmaceutical Sciences of the University of Perugia. Since July 2019, he has been appointed Assistant Professor at the Department of Pharmacy of the University of Naples Federico II. His research mainly deals with the design and synthesis of antiviral, antibacterial, and antitumor agents and kinase inhibitors and the development of synthetic methodologies.

Paolo Luciano graduated in Chimica e Tecnologia Farmaceutiche at the Faculty of Pharmacy of the University of Naples Federico II in 2000. He obtained his PhD in Scienza del Farmaco in 2003 with a thesis entitled 'Isolation, chemical and pharmacological characterization of bioactive molecules from Mediterranean Sea tunicates'. In 2009 he was hired as a category C specialist for the needs of the Interdepartmental Instrumental Analysis Service Center (CSIAS) at the Department of Pharmacy of the University of Naples Federico II. Currently he is a level D1 technician-specialist in the Department of Pharmacy of the University of Naples Federico II and manages all the NMR and mass spectrometers of the instrumental analysis laboratory of the Pharmacy Department.

Francesca Brunelli graduated in 2020 in pharmaceutical chemistry and technology (*summa cum laude*) at the University of Piemonte Orientale, Novara, Italy, where she is currently a research fellow. She is working on the discovery of novel isocyanide-mediated multicomponent reactions and the search of novel isocyanides endowed with biological properties.

Gian Cesare Tron is full professor of medicinal chemistry at the Università del Piemonte Orientale. He received his degree in Chimica e Tecnologia Farmaceutiche in 1994 and his PhD in organic chemistry in 2001 from the Università di Torino (Italy) under the supervision of Prof. G. Appendino. He has spent sabbatical leaves in the laboratories of Prof. J. Zhu (Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France), V. Aggarwal (School of Chemistry, Bristol, UK), and V. Fokin (The Scripps Research Institute, La Jolla, USA). His research interests concern the discovery of new multicomponent reactions and their applications in the field of medicinal chemistry.

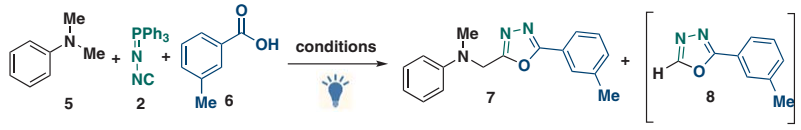
Mariateresa Giustiniano graduated in 2007 in Chimica e Tecnologia Farmaceutiche at the University of Naples Federico II, and in 2010 she obtained her PhD in medicinal chemistry (supervisor: Prof. E. Novellino). She was a visiting student in the laboratories of Prof. G. C. Tron (Università del Piemonte Orientale, Novara) and Prof. J. Zhu (CNRS, Gif-sur-Yvette, Paris). From 2011 to 2016 she held postdoctoral fellowships at the University of Naples Federico II and in 2016 she became assistant professor (RTDB). In 2018 she received National Academic Qualification as an associate professor in medicinal chemistry. Her research interests focus on multicomponent reactions, visible-light photocatalysis, and medicinal chemistry.

The availability of both metal-based and organic photocatalysts (PCs), able to promote either oxidation or reduction of a suitable substrate upon visible-light excitation and via the formation of open-shell intermediates, has been radically transforming the synthetic design of drug-like scaffolds.[11,12] Furthermore, the combination of such light-driven processes with the benefits of MCRs would offer new, efficient, and greener synthetic approaches to new chemical entities (NCEs).[13] In this context, a photoredox catalytic Ugi-like three-component reaction, exploiting the oxidation of *N*,*N*-dimethylanilines, initiated by an iridium-photocatalyst-promoted single-electron transfer (SET), was reported by Rueping et al. in 2013.[14–16] Inspired by this, and with the aim of expanding the substrate scope of the previously reported methodologies leading to 1,3,4-oxadiazoles, we herein describe the development of a one-pot multicomponent reaction via a photoredox catalytic Ugi-like/aza-Wittig domino sequence (Scheme 2).

Scheme 2 One-pot multicomponent photocatalyzed Ugi-like/aza-Wittig domino sequence described here

To verify the feasibility of such a photocatalytic multicomponent approach, we reacted *N*,*N*-dimethylaniline (**5**), *N*-isocyanoiminotriphenyl phosphorane (**2**), and *m*-toluic acid (**6**), as model substrates, in the presence of $[Ir(ppy)_2bpy]PF_6$ as the photocatalyst, in MeCN as the solvent, under irradiation with 30 W blue LEDs at room temperature (Table 1, entry 1). After 20 hours, the desired product **7** was recovered in a modest 25% yield, probably owing to unproductive degradation pathways of isocyanide **2**. Increasing the isocyanide amount to 2 equiv led to an improved 32% yield (entry 2). While the addition of 3 Å molecular sieves provided some beneficial effect (entry 3), a more concentrated solution of the starting materials (1.0 M rather than 0.1 M) led to a decreased 23% yield (entry 4). A screening of different metal-based and organic photocatalysts, such as *fac*-$Ir(ppy)_3$ and eosin Y, led to detrimental outcomes, even when the number of equivalents of isocyanide **2** and carboxylic acid **6** were increased. In the course of this reaction conditions' survey, we noticed that the product yield was decreased by the formation of a two-component monosubstituted 1,3,4-oxadiazole **8** via the aza-Wittig background reaction[17] between isocyanide **2** and *m*-toluic acid (**6**) (Table 1), probably due to a slow oxidation of *N*,*N*-dimethylamine (**5**) to iminium ion. This observation prompted us to opting for a stronger oxidizing PC compared with iridium complexes, such as $Ru(bpy)_3(PF_6)_2$ (E (Ru^{II*}/Ru^{I}

Table 1 Optimization of Reaction Conditions[a]



Entry	**5** (equiv)	**2** (equiv)	PC (mol%)	Yield (%)
1	2	1	$[Ir(ppy)_2bpy]PF_6$ (1)	25[b]
2	1	2	$[Ir(ppy)_2bpy]PF_6$ (1)	32[b]
3[c]	1	2	$[Ir(ppy)_2bpy]PF_6$ (1)	36[b]
4[c,d]	1	2	$[Ir(ppy)_2bpy]PF_6$ (1)	23[e]
5[c]	1	2	*fac*-$Ir(ppy)_3$ (1)	27[e]
6[c]	1	2	Eosin Y (1)	18[e]
7[c]	1	2.5	Eosin Y (1)	12[e]
8[c]	1	2	Eosin Y (5)	6[b]
9[c]	1	2	$Ru(bpy)_3(PF_6)_2$ (2)	50[b]
10[c]	1	2	$Ru(bpy)_3(PF_6)_2$ (1)	57[b]
11[c]	2	2	$Ru(bpy)_3(PF_6)_2$ (2)	53[b]
12[c]	2	2	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ (2)	67[b]

[a] Reaction conditions: **5**, **2**, **6**, PC, MeCN (0.1 M), 30 W blue LED irradiation, RT, 20 h.
[b] Isolated yield.
[c] Molecular sieves (3 Å) added.
[d] Reaction performed in MeCN (1.0 M).
[e] NMR yield.

= + 0.77 V vs SCE), E (Ir^{III*}/Ir^{II} = + 0.68 V vs SCE) for $[Ir(ppy)_2bpy]PF_6$, and E (Ir^{III*}/Ir^{II} = + 0.31 V vs SCE) for *fac*-$Ir(ppy)_3$, respectively.[18]

Accordingly, when the reaction was performed in the presence of $Ru(bpy)_3(PF_6)_2$, the yield increased to 50% (Table 1, entry 9). Longer reaction time (48 h, entry 10) and *N*,*N*-dimethylaniline equivalents doubling (entry 11) only led to a slight increase in the yield, while the use of $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ provided an optimum 67% yield (entry 12).

By applying the optimized reaction conditions, the substrate scope was investigated by varying both the carboxylic acid and the amine components (Figure 1). The robustness of the synthetic protocol was shown with both aromatic (**9**–**15**) and heteroaromatic carboxylic acids (**16**,**17**), as well as aliphatic ones, as for the functionalization of Cbz-protected phenylalanine (**18**). Tolerated functional groups included methyl, even in the *ortho* position (**9**), halogens such as fluorine (**11**), ethers (**12**), cyano (**14**), nitro (**15**), and carbamate (**18**). Similarly, the scope of the aniline proved that the substitution pattern (*m*- or *p*-methyl, **19** and **20**, respectively) did not affect the reaction efficiency. However, while electron-rich *N*,*N*-dimethylanilines were shown to be suitable starting materials (**21**), the presence of an electron-withdrawing atom, such as chlorine, led to a modest 26% yield (**22**). Interestingly, regioselectivity for CH_3 oxidation was observed when *N*-ethyl-*N*-methylaniline was used as the starting amine component (**23**). To further explore the potential of the mild developed conditions, late-stage functionalization[19] of complex molecular scaffolds such as indomethacin and gemfibrozil afforded derivatives **24** and **25** in 31 and 58% yield, respectively (Figure 1).

To expand the synthetic potential of this transformation, a tandem two-step one-pot conversion of *N*,*N*-dimethylaniline (**5**), *N*-isocyanoiminotriphenylphosphorane (**2**), and *m*-toluic acid (**6**) to non-symmetrical diacylhydrazine

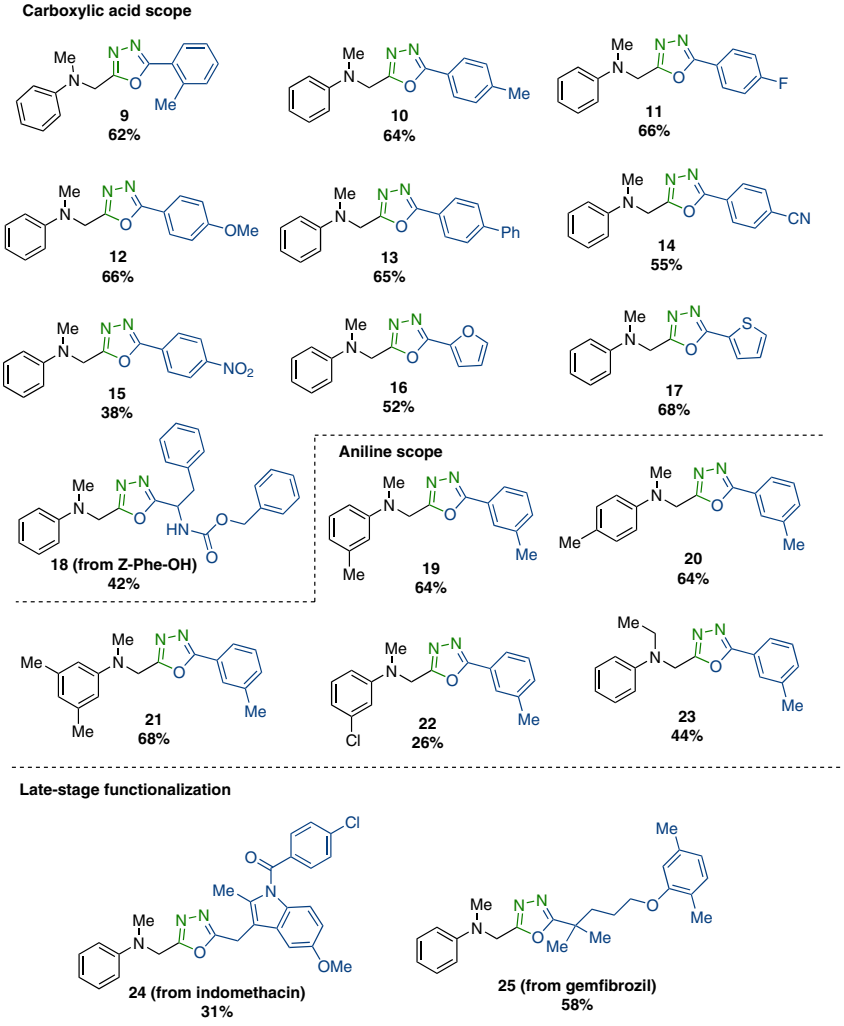


Figure 1 Reaction scope (standard reaction conditions as in Table 1, entry 12)

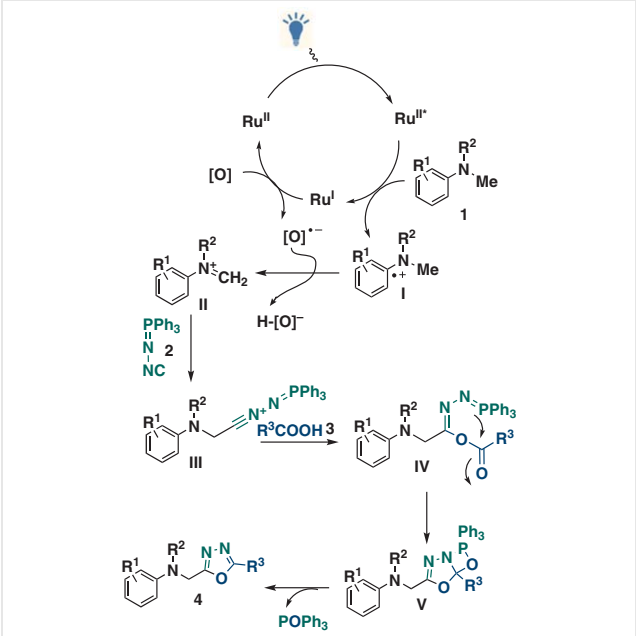
Scheme 3 Tandem two-step one-pot synthesis of non-symmetrical diacylhydrazine derivative **26**

26 was attempted (Scheme 3). To achieve this, the 1,3,4-oxadiazole derivative **7** was formed according to the standard reaction conditions (Table 1, entry 12); subsequent in situ addition of 6 N HCl (final concentration 1:1 *v*/*v* with respect to the standard reaction solvent), at room temperature, led, after 20 hours, to the hydrolysis of the heterocyclic core, thus providing facile and expeditious access to pharmaceutically relevant scaffold **26** (Scheme 3). [20–22] It is worth noting that a representative synthesis of scaffolds similar to **26** has been reported in three steps with overall yields of ca. 29%.[23]

A working hypothesis for the reaction mechanism relies on a reductive quenching cycle (Scheme 4). Under visible-light irradiation, the photocatalyst $[Ru(bpy)_3]Cl_2{\cdot}6H_2O$ undergoes a metal-to-ligand charge transfer (MLCT), populating the excited state Ru^{II*} (E (Ru^{II*}/Ru^{I} = + 0.77 V vs SCE)),[15] which is quenched by *N*,*N*-dimethylaniline (**1**) (E (**1**/$\mathbf{I}^{\bullet+}$ = +0.74 V vs SCE))[24], affording Ru^{I} and the corresponding radical cation $\mathbf{I}^{\bullet+}$. Regeneration of the catalyst in the presence of oxygen as the oxidant provides a superoxide radical anion, which triggers the formation of the iminium ion **II** upon hydrogen atom abstraction from $\mathbf{I}^{\bullet+}$, thus leading to a radical/polar crossover. Hence, the iminium ion undergoes nucleophilic attack by *N*-isocyanoiminotriphenylphosphorane (**2**), to generate the nitrilium ion **III**, followed by addition of the carboxylate to give the α-adduct **IV**. The latter eventually provides the desired 1,3,4-oxadiazole **4** after a domino intramolecular aza-Wittig reaction, with loss of triphenylphosphine oxide ($POPh_3$).

In conclusion, a novel visible-light photocatalytic multicomponent reaction leading to 2-aminomethyl-1,3,4-oxadiazole derivatives was developed. The transformation relies on the photocatalytic oxidation of *N*,*N*-dimethylanilines to the corresponding iminium ions, promoted by a ruthenium photocatalyst and enabling a radical/polar crossover towards an Ugi-like/aza-Wittig sequence. A wide range of carboxylic acids and amine components provided evidence for a good substrate scope, and the functional group tolerance was further highlighted in the late-stage functionalization of amino acids and drugs. Interestingly, during the reaction, three new bonds (one C–C, one C–O, and one C–N) were formed in one pot, with a formal loss of only one equivalent of hydrogen and one of $POPh_3$, i.e. with high atom economy. In addition, we also showed how the reported procedure could lead to pharmaceutically relevant non-symmetrical diacylhydrazines via a tandem two-step one-pot synthesis, involving the photocatalytic MCR followed by acid hydrolysis of the 1,3,4-oxadiazole derivatives. To our knowledge, the latter stands for the first photocatalytic multicomponent process leading to such valuable scaffolds. Undoubtedly, this newly developed synthetic methodology demonstrated how the merging of photoredox catalysis and multicomponent reactions could further expand the chemical space accessible via efficient and sustainable approaches.[25]

Commercially available reagents and solvents were used without further purification. When necessary, the reactions were performed in oven-dried glassware under a positive pressure of anhydrous nitrogen. Photochemical reactions were carried out using a PhotoRedOx Box (EvoluChem™) with a 30 W blue LED (EvoluChem™, model: HCK1012-01-008, wavelength 450 nm, LED: CREE XPE. A holder suitable for 4 mL scintillation vials (45 × 14.7 mm) has been fitted with the Schlenk flask: this allows a fixed sample placement distance from the light source). All NMR spectra were obtained on a Bruker Avance NEO 400 MHz instrument. Experiments for structure elucidation



Scheme 4 Mechanistic hypothesis

were performed in $CDCl_3$ at 25 °C with a RT-DR-BF/1H-5 mm-OZ SmartProbe. ESI-HRMS spectra were performed on a Thermo LTQ Orbitrap XL mass spectrometer. The spectra were recorded by infusion into the ESI source using MeOH as the solvent. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak. Homonuclear ^1H correlations were determined by COSY experiments; one-bond heteronuclear ^1H–^{13}C correlations by the HSQC experiment; and two- and three-bond ^1H–^{13}C correlations by gradient-HMBC experiments optimized for a $^{2,3}J$ value of 8 Hz. Column chromatography was performed on silica gel (70–230 mesh ASTM) using the reported eluents. TLC was carried out on 5 × 20 cm plates with a layer thickness of 0.25 mm (Silica gel 60 F254) to monitor the reaction by using UV and/or $KMnO_4$ as the revelation methods.

N-Methyl-*N*-[(1,3,4-oxadiazol-2-yl)methyl]anilines 7, 9–25; General Procedure

To a 4 mL colorless glass vial equipped with a magnetic stir bar were added the carboxylic acid (0.08 mmol, 1 equiv), (*N*-isocyanoimino)triphenylphosphorane (0.16 mmol, 2 equiv), the aniline derivative (0.16 mmol, 2 equiv), and $[Ru(bpy)_3]Cl_2·6H_2O$ (0.0016 mmol, 2 mol%). Then 800 µL of anhydrous MeCN (0.1 M) was added to the reaction vial via a syringe and 3 Å activated molecular sieves (80 mg) were added to the resulting mixture, which was stirred as an open flask in a PhotoRedOx Box, under 30 W blue LED irradiation, at room temperature for 20 h. After completion of the reaction, as monitored by TLC (CH_2Cl_2/EtOAc 9:1), the solvent was removed under vacuum and the crude was purified as specified for each compound.

N-Methyl-*N*-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (7)

The crude material was purified by column chromatography (hexane/EtOAc 97:3).

Yield: 14.9 mg (67%); yellow amorphous solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1). For 1D- and 2D-NMR data see Supporting Information.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O^+$: 280.1444; found: 280.1446.

N-Methyl-*N*-{[5-(*o*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (9)

The crude material was purified by column chromatography (hexane/EtOAc 96:4).

Yield: 13.9 mg (62%); off-white amorphous solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1).

^1H NMR (700 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 7.8 Hz, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.26–7.20 (m, 4 H), 6.87 (d, *J* = 8.4 Hz, 2 H), 6.76 (t, *J* = 7.3 Hz, 1 H), 4.74 (s, 2 H), 3.09 (s, 3 H), 2.55 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 165.5, 163.4, 148.4, 138.4, 131.7, 131.3, 129.3, 129.0, 126.1, 122.8, 118.3, 113.3, 47.6, 39.0, 22.0.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O^+$: 280.1444; found: 280.1444.

N-Methyl-*N*-{[5-(*p*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (10)

The crude material was purified by column chromatography (hexane/EtOAc 96:4).

Yield: 14.4 mg (64%); off-white amorphous solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1).

^1H NMR (700 MHz, $CDCl_3$): δ = 7.81–7.77 (m, 2 H), 7.22–7.17 (m, 4 H), 6.86–6.82 (m, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 4.68 (s, 2 H), 3.06 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 165.4, 163.6, 148.5, 142.3, 129.7, 129.3, 126.9, 121.0, 118.3, 113.3, 47.7, 39.0, 21.6.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O^+$: 280.1444; found: 280.1445.

N-{[5-(4-Fluorophenyl)-1,3,4-oxadiazol-2-yl]methyl}-*N*-methylaniline (11)

The crude material was purified by flash column chromatography (hexane/EtOAc 97:3).

Yield: 15.0 mg (66%); colorless sticky solid; R_f = 0.5 (TLC: CH_2Cl_2/EtOAc 9:1).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.98–7.91 (m, 2 H), 7.27–7.22 (m, 2 H), 7.16–7.09 (m, 2 H), 6.87 (d, *J* = 8.1 Hz, 2 H), 6.78 (t, *J* = 7.3 Hz, 1 H), 4.72 (s, 2 H), 3.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (d, *J* = 220 Hz, CF *ArF*), 164.4, 163.6, 148.5, 129.4, 129.2 (d, *J* = 10.0 Hz, 2 x CH *ArF*), 120.0 (d, *J* = 3.0 Hz, C *ArF*), 118.4, 116.4 (d, *J* = 20.0 Hz, 2 x CH *ArF*), 113.3, 47.7, 39.0

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}FN_3O^+$: 284.1194; found: 284.1194.

N-{[5-(4-Methoxyphenyl)-1,3,4-oxadiazol-2-yl]methyl}-*N*-methylaniline (12)

The crude material was purified by flash column chromatography (hexane/EtOAc 9:1).

Yield: 15.6 mg (66%); pale-yellow amorphous solid; R_f = 0.4 (TLC: CH_2Cl_2/EtOAc 9:1).

^1H NMR (700 MHz, $CDCl_3$): δ = 7.93–7-88 (m, 2 H), 7.30–7-25 (m, 2 H), 7.00–6.95 (m, 2 H), 6.93–6.88 (m, 2 H), 6.81 (t, *J* = 7.3 Hz, 1 H), 4.74 (s, 2 H), 3.86 (s, 3 H), 3.13 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 165.2, 163.4, 162.4, 148.5, 129.3, 128.7, 118.2, 116.2, 114.4, 113.3, 55.5, 47.7, 38.9.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}N_3O_2^+$: 296.1394; found: 296.1391.

N-{[5-(1,1′-Biphenyl-4-yl)-1,3,4-oxadiazol-2-yl]methyl}-*N*-methylaniline (13)

The crude material was purified by flash column chromatography (hexane/EtOAc 95:5).

Yield: 17.9 mg (65%); off-white solid; R_f = 0.6 (TLC: CH_2Cl_2/EtOAc 9:1).

^1H NMR (700 MHz, $CDCl_3$): δ = 8.10–8.00 (m, 2 H), 7.73–7.68 (m, 2 H), 7.65–7.60 (m,, 2 H), 7.50–7.45 (m, 2 H), 7.41 (d, J = 7.4 Hz, 1 H), 7.32–7.28 (m, 2 H), 6.97–6.92 (m, 2 H), 6.83 (t, J = 7.3 Hz, 1 H), 4.79 (s, 2 H), 3.16 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 163.9, 148.5, 144.6, 139.8, 122.4, 129.0, 128.2, 127.7, 127.4, 127.2, 122.5, 118.4, 113.4, 47.8, 39.0

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}N_3O^+$: 342.1601; found: 342.1600.

4-(5-{[Methyl(phenyl)amino]methyl}-1,3,4-oxadiazol-2-yl)benzonitrile (14)

The crude material was purified by flash column chromatography (hexane/EtOAc 93:7).

Yield: 12.8 mg (55%); colorless sticky solid; R_f = 0.6 (TLC CH_2Cl_2/EtOAc 9:1).

^1H NMR (700 MHz, $CDCl_3$): δ = 8.10–8.00 (m, 2 H), 7.76–7.71 (m, 2 H), 7.25–7.20 (m, 2 H), 6.89–6.83 (m, 2 H), 6.78 (t, *J* = 7.3 Hz, 1 H), 4.75 (s, 2 H), 3.10 (s, 3 H).

^{13}C NMR (176 MHz, $CDCl_3$): δ = 164.8, 163.7, 148.3, 132.8, 129.4, 127.6, 127.4, 118.6, 117.8, 115.3, 113.3, 47.8, 39.1.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{15}N_4O^+$: 291.1240; found: 291.1240.

_N_-Methyl-_N_-{[5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (15)

The crude material was purified by flash column chromatography (hexane/EtOAc 9:1).

Yield: 9.5 mg (38%); yellow amorphous solid; R_f = 0.5 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33–8.28 (m, 2 H), 8.15–8.10 (m, 2 H), 7.25–7.20 (m, 2 H), 6.88–6.83 (m, 2 H), 6.79 (t, *J* = 7.3 Hz, 1 H), 4.76 (s, 2 H), 3.10 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.03 163.5, 149.6, 148.3, 129.4, 129.2, 127.9, 124.4, 118.6, 113.4, 47.8, 39.1

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}N_4O_3^+$: 311.1139; found: 311.1134.

_N_-{[5-(2-Furyl)-1,3,4-oxadiazol-2-yl]methyl}-_N_-methylaniline (16)

The crude material was purified by flash column chromatography (hexane/EtOAc 95:5).

Yield: 10.6 mg (52%); brownish amorphous solid; R_f = 0.5 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.60 (d, *J* = 1.2 Hz, 1 H), 7.29–7.23 (m, 2 H), 7.10 (d, *J* = 3.5 Hz, 1 H), 6.90–6.85 (m, 2 H), 6.80 (t, *J* = 7.3 Hz, 1 H), 6.56 (dd, *J* = 3.5, 1.8 Hz, 1 H), 4.74 (s, 2 H), 3.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 158.1, 148.4, 145.7, 139.3, 129.3, 118.4, 114.2, 113.3, 112.1, 47.6, 39.0.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3O_2^+$: 256.1081; found: 256.1079.

_N_-Methyl-_N_-{[5-(2-thienyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (17)

The crude material was purified by flash column chromatography (hexane/EtOAc 96:4).

Yield: 14.8 mg (68%); off-white amorphous solid; R_f = 0.6 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.64 (dd, *J* = 3.7, 1.1 Hz, 1 H), 7.49 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.25–7.20 (m, 2 H), 7.10 (dd, *J* = 5.0, 3.8 Hz, 1 H), 6.90–6.95 (m, 2 H), 6.78 (t, *J* = 7.3 Hz, 1 H), 4.70 (s, 2 H), 3.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 161.4, 148.5, 130.3, 129.9, 129.3, 128.1, 118.4, 113.4, 47.7, 39.0.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_3OS^+$: 272.0852; found: 272.0851.

Benzyl [1-(5-{[Methyl(phenyl)amino]methyl}-1,3,4-oxadiazol-2-yl)-2-phenylethyl]carbamate (18)

The crude material was purified by preparative TLC (hexane/Et_2O 2:8).

Yield: 14.9 mg (42%); off-white amorphous solid; R_f = 0.4 (TLC CH_2Cl_2/EtOAc 9:1).

1 H NMR (700 MHz, DMSO-d_6) δ = 8.15 (d, *J* = 8.0 Hz, 1 H), 7.35–7.30 (m, 3 H), 7.27–7.21 (m, 2 H), 7.21–7.17 (m, 5 H), 7.15–7.10 (m, 2 H), 6.83–6.78 (m, 2 H), 6.71 (t, *J* = 7.1 Hz, 1 H), 5.05–4.98 (m, 3 H), 4.79 (s, 2 H), 3.18 – 3.11 (m, 1 H), 3.09 (d, *J* = 9.4 Hz, 1 H), 2.98 (s, 3 H).

13C NMR (176 MHz, DMSO-d_6): δ = δ 166.8, 164.6, 156.0, 148.8, 137.2, 137.1, 129.6, 129.4, 128.8, 128.7, 117.8, 113.3, 66.0, 49.2, 46.8, 39.6, 38.0.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{27}N_4O_3^+$: 443.2078; found: 443.2070.

_N_,3-Dimethyl-_N_-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (19)

The crude material was purified by column chromatography (hexane/EtOAc 97:3).

Yield: 15.0 mg (64%); yellow amorphous solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.77 (d, *J* = 7.3 Hz, 1 H), 7.40–7.30 (m, 2 H), 7.17 (dd, *J* = 9.0, 7.5 Hz, 1 H), 6.76 – 6.70 (m, 2 H), 6.64 (d, *J* = 7.4 Hz, 1 H), 4.74 (s, 2 H), 3.12 (s, 3 H), 2.41 (s, 3 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 163.9, 148.6, 139.1, 138.9, 132.6, 129.2, 128.9, 127.5, 124.1, 123.6, 119.3, 114.1, 110.6, 47.8, 39.0, 21.9, 21.3.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O^+$: 294.1601; found: 294.1610.

_N_,4-Dimethyl-_N_-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (20)

The crude material was purified by column chromatography (hexane/EtOAc 97:3).

Yield: 15.0 mg (64%); orange amorphous solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.77 (d, *J* = 7.3 Hz, 1 H), 7.40–7.30 (m, 2 H), 7.12–7.05 (m, 2 H), 6.87–6.82 (m, 2 H), 4.72 (s, 2 H), 3.10 (s, 3 H), 2.40 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 164.0, 146.5, 138.9, 132.6, 129.9, 128.9, 127.8, 127.5, 124.1, 123.6, 113.8, 48.1, 39.2, 21.3, 20.3.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O^+$: 294.1601; found: 294.1597.

_N_,3,5-Trimethyl-_N_-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (21)

The crude material was purified by preparative TLC (CH_2Cl_2/EtOAc 9:1).

Yield: 16.7 mg (68%); off-white amorphous solid; R_f = 0.6 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.78 (d, *J* = 7.4 Hz, 1 H), 7.39–7.30 (m, 2 H), 6.55 (s, 2 H), 6.48 (s, 1 H), 4.73 (s, 2 H), 3.11 (s, 3 H), 2.41 (s, 3 H), 2.29 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 164.0, 148.7, 138.9, 138.89, 132.6, 128.9,127.5, 123.7, 120.4, 111.4, 47.8, 39.0, 21.7, 21.3.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}N_3O^+$: 308.1757; found: 308.1755.

3-Chloro-_N_-methyl-_N_-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}-aniline (22)

The crude material was purified by flash column chromatography (hexane/EtOAc 96:4).

Yield: 6.6 mg (23%); colorless sticky solid; R_f = 0.6 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.77 (d, *J* = 7.3 Hz, 1 H), 7.38–7.32 (m, 2 H), 7.17 (t, *J* = 8.1 Hz, 1 H), 6.87 (t, *J* = 2.2 Hz, 1 H), 6.80.6.75 (m, 2 H), 4.75 (s, 2 H), 3.13 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 163.3, 149.6, 139.0, 135.2, 132.7, 130.3, 129.0, 127.5, 124.1, 123.5, 118.1, 113.2, 111.3, 47.5, 39.0, 21.3.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}ClN_3O^+$: 314.1055; found: 314.1055.

N-Ethyl-N-{[5-(*m*-tolyl)-1,3,4-oxadiazol-2-yl]methyl}aniline (23)

The crude material was purified by preparative TLC (CH_2Cl_2/EtOAc 95:5).

Yield: 10.3 mg (44%); orange sticky solid; R_f = 0.7 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (s, 1 H), 7.77 (d, *J* = 7.3 Hz, 1 H), 7.39–7.30 (m, 2 H), 7.28–7.23 (m, 2 H), 6.93–6.88 (m, 2 H), 6.78 (t, *J* = 7.2 Hz, 1 H), 4.73 (s, 2 H), 3.57 (q, *J* = 7.1 Hz, 2 H), 2.41 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 164.3, 147.4, 138.9, 132.6, 129.4, 128.9, 127.4, 124.1, 123.6, 117.8, 113.1, 45.6, 45.3, 21.3, 12.2.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}N_3O^+$: 294.1601; found: 294.1601.

(4-Chlorophenyl){5-methoxy-2-methyl-3-[(5-{[methyl(phenyl)-amino]methyl}-1,3,4-oxadiazol-2-yl)methyl]-1*H*-indol-1-yl}-methanone (24)

The crude material was purified by preparative TLC (CH_2Cl_2/EtOAc 9:1).

Yield: 12.5 mg (31%); yellow oil; R_f = 0.4 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68–7.61 (m, 2 H, Ar-H), 7.50–7.44 (m, 2 H, Ar-H), 7.24–7.17 (m, 2 H, ArH), 6.94 (d, *J* = 2.5 Hz, 1 H, Ar-H-4 indole), 6.84 (d, *J* = 9.0 Hz, 1 H, Ar-H-7 indole), 6.81–6.74 (m, 3 H, Ar-H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1 H, Ar-H-6 indole), 4.61 (s, 2 H, NCH_2), 4.19 (s, 2 H, CH_2), 3.78 (s, 3 H, OCH_3), 3.02 (s, 3 H, NCH_3), 2.37 (d, J = 8.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3, 165.2, 164.4, 156.2, 148.4, 139.5, 136.1, 133.7, 131.2, 130.8, 130.0, 129.3, 129.2, 118.3, 115.0, 113.2, 112.1, 111.8, 100.9, 55.7, 47.6, 38.8, 20.9, 13.2.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{26}ClN_4O_3^+$: 501.1688; found: 501.1690.

N-({5-[5-(2,5-Dimethylphenoxy)-2-methylpentan-2-yl]-1,3,4-oxadiazol-2-yl}methyl)-N-methylaniline (25)

The crude material was purified by preparative TLC (CH_2Cl_2/EtOAc 95:5).

Yield: 18.3 mg (58%); pinkish oil; R_f = 0.6 (TLC: CH_2Cl_2/EtOAc 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20–7.26 (m, 2 H, Ar-H), 7.00 (d, *J* = 7.4 Hz, 1 H, Ar-H), 6.87–6.82 (m, 2 H, Ar-H), 6.79 (t, *J* = 7.3 Hz, 1 H, Ar-H), 6.66 (d, *J* = 7.4 Hz, 1 H, Ar-H), 6.55 (s, 1 H, Ar-H), 4.63 (s, 2 H, NCH_2), 3.79 (t, *J* = 6.1 Hz, 2 H,OCH_2), 3.04 (s, 3 H, NCH_3), 2.31 (s, 3 H. CH_3), 2.16 (s, 3 H, CH_3), 1.85 – 1.78 (m, 2 H, CH_2), 1.63–1.57 (s, 2 H, CH_2), 1.38 (s, 6 H, 2 x CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.8, 164.0, 156.8, 148.6, 136.5, 130.3, 129.2, 123.5, 120.8, 118.4, 113.5, 111.9, 67.4, 47.7, 38.9, 37.9, 35.6, 26.0, 24.8, 21.4, 15.8.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{32}N_3O_2^+$: 394.2489; found: 394.2489.

3-methyl-N′-(*N*-methyl-*N*-phenylglycyl)benzohydrazide (26)

The crude material was purified by preparative TLC (CH_2Cl_2/EtOAc 8:2).

Yield: 5.7 mg (24%); dark yellow sticky solid; R_f = 0.3 (TLC: CH_2Cl_2/EtOAc 8:2).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.29 (s, 1 H, NH), 10.02 (s, 1 H, NH), 7.69 (s, 1 H, Ar-H), 7.67 – 7.62 (m, 1 H, ArH), 7.39–7.33 (m, 2 H, ArH), 7.20–7.15 (m, 2 H, ArH), 6.77–6.70 (m, 2 H, ArH), 6.65 (d, *J* = 7.3 Hz, 1 H, ArH), 4.05 (s, 2 H, NCH_2), 3.02 (s, 3 H, NCH_3), 2.35 (s, 3 H, CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 169.8, 166.0, 149.7, 138.2, 132.9, 132.8, 129.3, 128.8, 128.5, 125.0, 116.8, 112.6, 54.5, 21.4.

HRMS–ESI: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N_3O_2^+$: 298.1550; found: 298.1547.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

Financial support from Università degli Studi di Napoli Federico II and Università del Piemonte Orientale, Novara, Italy is acknowledged. M. G. acknowledges PROGEMA support (ARS01_X00432, PON R&I 2014-2020). R. C. acknowledges support from Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR; Italian Ministry of Education, University and Research), PON R&I 2014-2020-AIM (Attraction and International Mobility), project AIM1873131 - Num. Attività 2 - Linea 2.1.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1543-3924.

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