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PAPER

Synthesis of pyrrole and indole quinoxalinone and oxazinone derivatives by intramolecular copper-catalyzed reactions†

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Intramolecular *N*-arylation of pyrrole and indole carboxamides and carboxylates linked with a pendant haloarene by Cu-catalyzed reactions to synthesize pyrrole and indole quinoxalinone and oxazinone derivatives is reported. The ring closure reactions were carried out by conventional heating and MW irradiation. The use of conventional heating affords moderate to good yields of the quinoxalinone and oxazinone derivatives (34–72%), while by using MW heating the best results are obtained (41–99%).

Introduction

The century-old Cu-mediated arylation of amines, the classical Ullmann reaction, has been known as a powerful reaction for C–N bond formation,[1] although the scope of this reaction was limited by the use of a stoichiometric amount of Cu and harsh reaction conditions. However, in the past few years this reaction has been considerably revitalized by the introduction of Cu-catalyzed Ullmann-type reactions and by the development of new procedures.[2] The renewed interest in Ullmann-type reactions was principally developed due to the discovery of versatile and efficient Cu salts with several ligand systems that allowed the use of catalytic amounts of the metal under mild conditions.[3] Cu-catalyzed reactions have been the preferred method for the *N*-arylation of pyrroles, indoles, pyrazoles, indazoles, imidazoles, and triazoles.[3a,4] In addition to intermolecular *N*-arylation, Cu-catalysis has been further extended for the synthesis of nitrogen heterocycles involving intramolecular *N*-arylation.[5]

Nitrogen-containing heterocycles constitute the main structure within a large number of natural products, pharmacologically active compounds and organic materials.[6] Particularly, quinoxaline derivatives have received much attention in recent years owing to their well-known biological properties and pharmaceutical applications. The quinoxalinone moiety is frequently found in compounds displaying a variety of medicinal properties, such as anticancer, anxiolytic, antimicrobial, analgesic and antiallergic activity.[7] Many of these biologically active quinoxalinone compounds have been tested in clinical trials.[8]

Quinoxalinones have been also used as building blocks to obtain indolo and pyrrolo[1,2-*a*]quinoxalines with oral antiallergic activity,[9] HIV-1 reverse transcriptase inhibitory activity[10] and antimalarial activity.[11] Oxazinones also constitute an important class of heterocycles, which has attracted much synthetic interest due to its wide range of biological activities.[12] Many benzoxazinones exhibit diverse pharmacological properties, such as antitumor,[13] antiviral,[14] antithrombotic,[15] antiinflammatory[16] antidiabetic and hypolipidaemic[17] effects. Additional, they have been reported as inhibitors of human leukocyte elastase[18] and serotonin reuptake.[19]

However, despite the growing, general, and widespread interest of medicinal chemistry in these structures, there are relatively few synthetic routes leading to quinoxalinones.[7] Particularly, the construction of pyrrolo[1,2-*a*]quinoxalines was commonly established from 2-nitroanilines and proceeds in three steps including the cyclization with triphosgene.[11,20] These approaches suffer from a limited number of suitable substrates and inconvenient processes. Recently, the Pd-catalyzed intramolecular C–N bond formation strategy from 2-haloanilines and pyrrole-2-carboxylic acids was described.[21] However, the preliminary methylation of the commercially available 2-haloanilines limits the scope of this method. Thus, there is a special need for developing a new methodology that would allow access to this type of quinoxaline derivative.

Ma and Yuan[22] have synthesized a family of pyrrolo[1,2-*a*]quinoxalines, by means of CuI/L-proline system starting from 2-halotrifluoroacetanilides with pyrrole-2-carboxylate esters. The same procedure has been used to provide tetracyclic products from indole-2-carboxylate esters. In similar approaches, aza-fused polycyclic quinolines[23] and pyrrolo[1,2-*a*]quinoxaline[24] were obtained by Cu-catalyzed cascade reactions. Additionally, pyrazolo[1,5-*a*]benzimidazoles were achieved by intramolecular Cu-catalyzed reaction.[25] In this case, when different Pd/ligand systems were used to afford the C–N bond, only low yields were obtained. Therefore, Cu-catalyzed reactions appear to be an efficient strategy to carry out intramolecular arylation of heterocycles.

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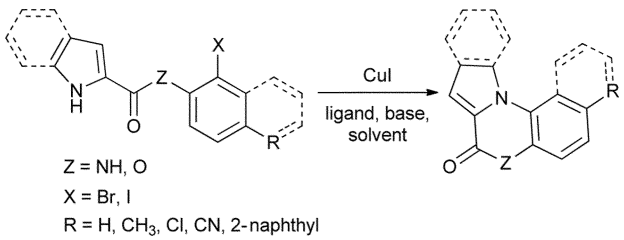
† Electronic supplementary information (ESI) available: Supplementary data associated with experimental details, spectroscopic data for all compounds and ^{1}H NMR and ^{13}C NMR spectra, as well as COSY ^{1}H–^{1}H and HSQC ^{1}H–^{13}C NMR experiments for products **3a–f** and **5a–d**. See DOI: 10.1039/c1ob05269a

In general, these catalyzed reactions require long reaction times. Direct and rapid heating by microwave (MW) irradiation in many cases enables reactions to be carried out in a fraction of the time generally required using conventional heating.[26] MW irradiation has been used in several Cu-catalyzed reactions and excellent yields have been obtained in short times.[27]

Herein, we report a practical and efficient route to pyrrole and indole quinoxalinone and oxazinone derivatives from pyrrole and indole carboxamides and carboxylates *via* Cu-catalyzed intramolecular arylation of the NH group in the heterocyclic moiety (Scheme 1). We also compare the use of the conventional heating *vs.* MW irradiation in these reactions.

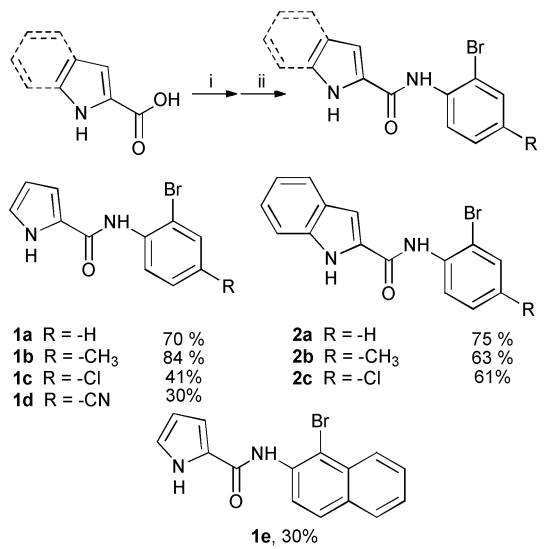


Scheme 1 Cu-catalyzed intramolecular *N*-arylation.

Results and discussion

Synthesis of pyrrole and indole carboxamides and ester derivatives 1a–g and 2a–d

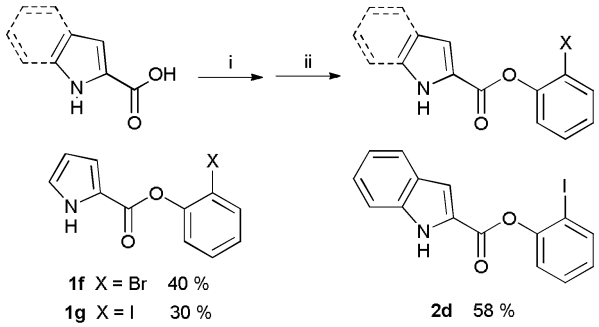
The pyrrole and indole carboxamides **1a–e** and **2a–c** required to carry out the cyclizations were obtained by the reaction of commercially available 2-carboxylic acid of pyrrole and indole with an excess of oxalyl chloride to form the acid chloride derivatives. Without isolation, the acid chloride reacts with 2-haloanilines to give the corresponding amides in moderate to good isolated yields (Scheme 2). We were unable to achieve the pyrrole carboxamide substituted with a NO_2 group.



Reagents and conditions: (i) oxalyl chloride, 50 °C, under N_2 atmosphere, (ii) 2-haloaniline, r. t.

Scheme 2 Synthesis of pyrrole and indole carboxamides.

The pyrrole and indole ester derivatives **1f–g** and **2d** were synthesized by formation of the 1,1′-carbonyldiimidazole (CDI) intermediates followed by reaction with 2-halophenol (Scheme 3).



Reagents and conditions: (i) CDI, (ii) 2-halophenol

Scheme 3 Synthesis of pyrrole and indole ester derivatives.

Cu-catalyzed intramolecular *N*-arylation. Optimization of reaction conditions

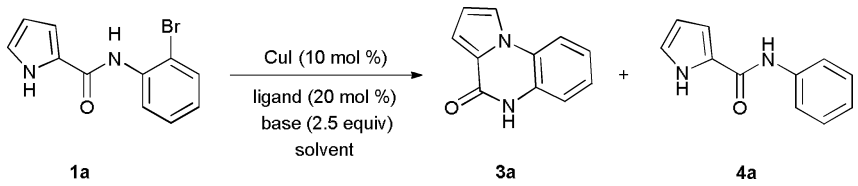
The Cu-catalyzed intramolecular reaction of the *N*-(2-bromophenyl)-1*H*-pyrrole-2-carboxamide (**1a**) was investigated as a model reaction under different reaction conditions, the results of which are shown in Table 1. For this reaction, time, temperature and solvents (entries 1–3, Table 1) as well as bases (entries 4–6, Table 1) and ligands (entries 7–9, Table 1) were evaluated.

The best yield of **3a** was obtained when the reaction was carried out with 10 mol% of CuI in the presence of 20 mol% of L-proline and 2.5 equiv of NaH in dioxane at 110 °C for one hour (entry 3, Table 1). Similar results were found when the reaction was carried out under the same conditions in DMF at reflux (entry 2, Table 1). Screening of different bases established that the strongest base NaH was clearly superior to weaker bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 (entries 4–6, Table 1). Among the different bidentate ligands evaluated for the cyclization (entries 8 and 9, Table 1), L-proline led to the highest yield of **3a**. The effect of varying ligand loading on cyclization was found to be relatively negligible (entry 7, Table 1). Moreover, when the reaction was performed without ligand, 64% of **3a** was obtained (entry 10, Table 1). This behaviour can be explained on the basis of the *ortho*-substituent effect previously described.[28] In some cases, substrate **1a** was recovered (entries 1, 6, 7, 9 and 10, Table 1) and debrominated product **4a** was observed (entries 1–5, Table 1). Control experiments showed that in the reaction carried out in the absence of catalyst; only 48% of **1a** was recovered, while no product was detected.

We then evaluated the intramolecular *N*-arylation reaction of pyrrole carboxamide **1a** by using MW irradiation. Since similar results were obtained with dioxane and DMF as solvent in the cyclization reaction, we decided to use DMF, due to the solvent being more sensitive to MW irradiation.[29] We started with the optimized reaction conditions in DMF (entry 2, Table 1) and explored different methods and systems for MW irradiation, such as dynamic heating at fixed temperature in an open vessel or fixed power in a sealed pressurized system. The results are summarized in the Table 2.

It is remarkable that for all reactions under MW irradiation the debrominated product **4a** was not observed. When the open

Table 1 Optimization of reaction conditions for the Cu-catalyzed synthesis of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (**3a**)[a]



1a **3a** **4a**

Entry	Ligand	Base	Solvent/Temperature	Yield **3a**[b]	Yield **4a**[b]	Conversion
1[c]	L-proline	NaH	DMF/90 °C	30%	20%	50%
2	L-proline	NaH	DMF/reflux	66%	20%	100%
3	L-proline	NaH	dioxane/110 °C	73%	18%	100%
4	L-proline	K_2CO_3	DMF/reflux	62%	9%	100%
5	L-proline	K_3PO_4	DMF/reflux	50%	10%	100%
6	L-proline	Cs_2CO_3	DMF/reflux	20%	—	53%
7[d]	L-proline	NaH	DMF/reflux	68%	—	69%
8	DMEDA[e]	NaH	DMF/reflux	68%	—	100%
9	1,10-phen[f]	NaH	DMF/reflux	36%	—	45%
10	—	NaH	DMF/reflux	64%	—	83%
11[g]	—	NaH	DMF/reflux	—	—	52%

[a] The reactions were performed using 0.25 mmol of substrate, 10 mol% of CuI, 20 mol% of ligand and 0.62 mmol of base in 2.5 mL of anhydrous DMF or dioxane under N_2 atmosphere for 1 h. [b] Yields were determined by GC (internal standard method). [c] 24 h. [d] 10 mol% of L-proline. [e] *N*,*N*-dimethylethylenediamine. [f] 1,10-phenanthroline. [g] Without CuI.

Table 2 Different reaction conditions for the Cu-catalyzed synthesis of **3a** from **1a** under MW irradiation

Entry	MW conditions	System	Yield **3a**[a]	Conversion
1	Dynamic method: 2 min 130 °C–3 min 140 °C	Open-vessel	33%	66%
2	Dynamic method: 3 min 140 °C–7 min 150 °C	Open-vessel	57%	60%
3	Dynamic method; 2 min 140 °C–3 min 150 °C	Sealed-vessel	82%	88%
4	Dynamic method; 12 min 150 °C	Sealed-vessel	64%	86%
5	Fixed Power 50 w; 10 min 140–160 °C	Sealed-vessel	82%	100%
6	Fixed Power 50 w; 5 min 140–160 °C	Sealed-vessel	99%	100%

[a] Yields were determined by GC (internal standard method).

vessel system was used, substrate **1a** was recovered in high amount (entries 1 and 2, Table 2). As expected, MAOS in sealed-vessel techniques provided more satisfactory results. The best system for the cyclization reaction was that using a sealed-vessel in a pressurized system and when a fixed power of 50 watts was applied, reducing the reaction times (entry 6, Table 2).

Synthesis of pyrrole and indole quinoxalinone and oxazinone derivatives

Once the reaction conditions with pyrrole carboxamide **1a** had been thoroughly optimized, we examined the scope and generality of the method by exploring the effects of aryl substituents in pyrrole and indole carboxamides **1b–e** and **2a–c** on the intramolecular cyclization to obtain quinoxalines. In addition, we evaluated the possibility of extending the methodology to achieve oxazinone derivatives by employing pyrrole and indole esters **1f–g** and **2d**. The results are summarized in the Table 3.

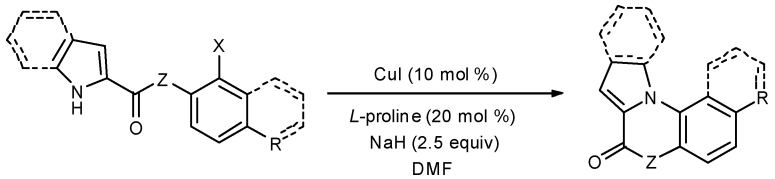
For all substrates, the best results were accomplished when the reaction was carried out under MW irradiation, where higher yields in lower reaction times were achieved. Furthermore, in MW heated reactions only traces of dehalogenated products were observed and the reaction mixtures were cleaner than those when conventional heating was applied.

The presence of substituents such as methyl and chloride groups on the aryl moiety in the *para* position decreased the yields of the ring closed products (entries 2–3, Table 3). Moreover, for chlorine derivative **1c**, a high amount of reduction product was observed (entry 3, Table 3). With the pyrrole carboxamide **1d** a complex mixture of products and hydrolyzed substrate was achieved under conventional and MW heating. Using K_2CO_3 as base and only under MW irradiation the product **3d** was obtained in 32% yield (entry 4, Table 3). Our general reaction conditions were effective to acquire benzo[*h*]pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **3e** (entry 5, Table 3).

To further develop the described methodology, we carried out the intramolecular *N*-arylation with esters. The ester **1f** did not provide any cyclization product under the optimized conditions, and only 2-bromophenol was found as product (entry 6, Table 3). No improvement was found by using a weaker base such as K_2CO_3 under conventional heating or MW irradiation, and only **1f** was recovered (entry 7, Table 3). When the halogen of the pyrrolo ester was iodide, 41% of product **3f** was achieved under MW irradiation (entry 8, Table 3). However, the reaction was successfully carried with **1g** when K_2CO_3 was used as base. The yields of **3f** were increased by both conventional heating (72%, entry 9, Table 3) and MW irradiation (92%, entry 9, Table 3).

The amide derivatives from indole required longer reaction times under conventional heating. For instance, substrate **2a** did

Table 3 Synthesis of benzo-quinoxaline and oxazinone derivatives from pyrrole and indole systems[a]



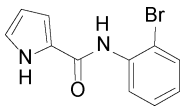
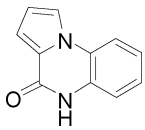
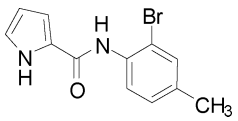
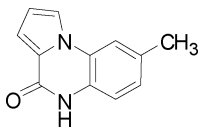
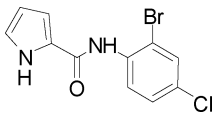
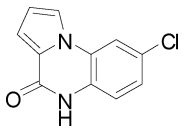
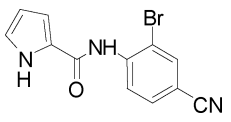
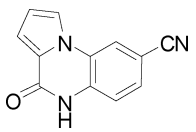
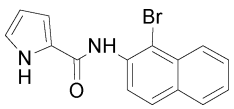
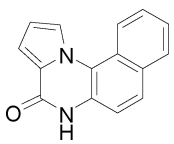
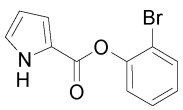
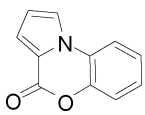
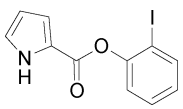
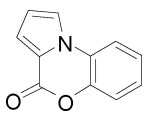
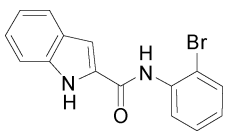
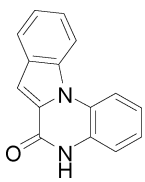
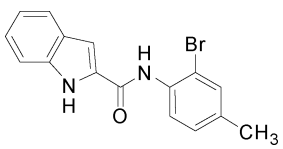
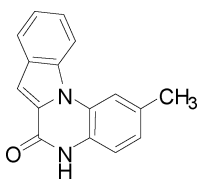
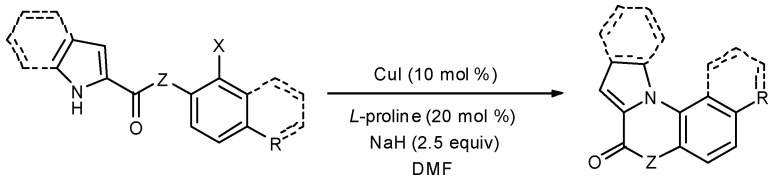
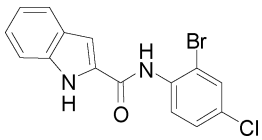
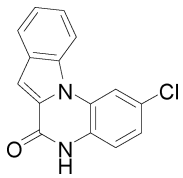
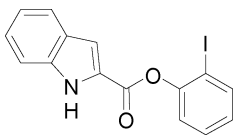
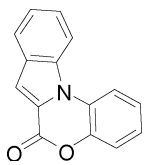
Entry	Substrate	Product	Conventional heating[a,b] Time (min)	Conventional heating[a,b] Yield (%)[d]	MW heating[a,c] Time (min)	MW heating[a,c] Yield (%)[d]
1	**1a** 	**3a** 	60	66	5	99 (91)
2	**1b** 	**3b** 	60	40	5	58 (48)
3	**1c** 	**3c** 	120	34	25	44 (40)
4[e]	**1d** 	**3d** 	60	—[f]	5	32 (19)
5	**1e** 	**3e** 	60	40	5	61 (54)
6	**1f** 	**3f** 	60	—[g]	5	—[g]
7[e]			60	—[h]	5	—[h]
8	**1g** 	**3f** 	60	—[i]	5	41
9[e]			60	72	5	92 (81)
10	**2a** 	**5a** 	60	56[j]	5	87 (80)
11			120	67		
12	**2b** 	**5b** 	120	60	5	73 (65)

Table 3 *(Contd.)*



Entry	Substrate	Product	Conventional heating[a,b]		MW heating[a,c]	
			Time (min)	Yield (%)[d]	Time (min)	Yield (%)[d]
13	**2c** 	**5c** 	120	58	5	77 (68)
14	**2d** 	**5d** 	120	—	5	41 (32)

[a] The reactions were performed using 0.25 mmol of substrate, 10 mol% of CuI, 20 mol% L-proline and 0.62 mmol of NaH (2.5 equiv) in 2.5 mL of anhydrous DMF under N_2 atmosphere. [b] Conventional heating, 140 °C. [c] MW irradiation, sealed-vessel at fixed power (50 watts), 140–160 °C. [d] Yields were determined by GC (internal standard method). Isolated yields in brackets. [e] K_2CO_3 was used as base. [f] Complex mixture of products and hydrolyzed substrate was observed. [g] 2-Bromophenol as hydrolyzed substrate was observed. [h] Substrate without reaction was recovered. [i] 2-Iodophenol as hydrolyzed substrate was observed. [j] 26% of substrate was recovered.

not react completely after 1 h (entry 10, Table 3), and 2 h were needed to complete the reaction (entry 11, Table 3). Therefore, this reaction time was used for all indole derivatives. Excellent yields of indolo quinoxalinone **5a** were observed with MW irradiation (entry 10, Table 3). The intramolecular *N*-arylation of substituted indole derivatives gave very good yields of the corresponding quinoxalinones when MW irradiation was applied (entries 12 and 13). However, in the same reaction conditions the indolo ester **2d** afforded product **5d** in moderate yield (entry 14, Table 3).

Conclusions

We have developed a practical and efficient synthetic approach to obtain new quinoxalinones and oxazinones derived from pyrrole and indole by intramolecular Cu-catalyzed Ullmann-type reactions. We also established that MW-assisted organic synthesis is a useful tool to carry out these reactions, rapidly and in high yields.

In addition, the interest in this simple methodology is further enhanced by the potential usefulness of pyrrole and indole quinoxalinones and oxazinone derivatives as building blocks to achieve compounds with biological applications.

Experimental section

General

1*H*-pyrrole-2-carboxylic acid, 1*H*-indole-2-carboxylic acid, oxalyl chloride, 2-bromoaniline, 2-bromophenol, 2-iodophenol, 1,1′-carbonyldiimidazole, 2-bromo-4-methylaniline, sodium hydride, potassium carbonate, potassium phosphate, caesium carbonate, L-proline, 1,10-phenanthroline, *N*,*N*-dimethylethylendiamine and CuI were commercially available and used as received from the supplier. 2-Bromo-4-chloroaniline 4-amino-3-bromobenzonitrile, 2-bromo-4-nitroaniline and 1-bromo-2-naphthylamine were obtained by reported methods.[30] THF and DMF were dried and store under nitrogen, over molecular sieves (4 Å). The purification of compounds was carried out by chromatography column on silica gel or by radial thin layer chromatography. In all purifications analytical grade solvents were distilled before used.

^{1}H NMR (400.16 MHz) and ^{13}C NMR (100.62 MHz) were conducted on a High Resolution Spectrometer Bruker Advance 400 in Cl_3CD or DMSO-*d6* as a solvent otherwise indicated, and referenced with residual solvent signal. Gas Chromatographic (GC) analyses were performed on an instrument with a flame ionization detector equipped with a VF-5ms column (30 m × 0.25 mm × 0.25 μm). Gas Chromatographic-Mass Spectrometer analyses were carried out on a GC-MS QP 5050 equipped with a quadrupole detector and a VF-5ms column (30 m × 0.25 mm × 0.25 μm). High Resolution Mass Spectra were performed in a MS/MS instrument on pure products. These data were obtained by ESI or APPI mode ionization and TOF detection. Melting points were performed with an electrical instrument and are uncorrected. MW-induced reactions were performed in a CEM Focused Microwave™ Synthesis System, Model Discover single mode instrument equipped with non-contact infrared sensor to measure the temperature, direct pressure control system by measurement of pressure of the reaction vessel contents and

cooling system by compressed air. Quantification by GC was performed by the Internal Standard Method.

Procedure for the preparation of *N*-(2-bromophenyl)-1*H*-pyrrole-2-carboxamide (1a)

1-*H*-Pyrrole-2-carboxylic acid (2.00 mmol, 222 mg) was heated at 50 °C under nitrogen in oxalyl chloride (1 mL) for 1 h. The oxalyl chloride was then evaporated, and the resulting solid was dissolved in anhydrous dichloromethane (3 mL). The reaction was cooled in an ice bath and 2-bromoaniline (5.0 mmol, 860 mg) was added. After addition, the mixture was warmed to r.t. and stirred overnight. Water (100 mL) was then added and the reaction mixture was extracted with dichloromethane (3 × 30 ml). The organic layer was dried with sodium sulphate, filtered and concentrated under vacuum. The pure product was obtained by chromatography (silica gel, petroleum ether/dichloromethane). The product was isolated as a white solid, mp: 172–174 °C (lit:[31] 174–177 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (m, 1H), 6.80 (m, 1H), 7.00 (m, 2H), 7.34 (m, 1H), 7.56 (dd, 1H, J = 8.0 Hz, 1.5 Hz), 8.24 (bs, 1H), 8.48 (dd, 1H, J = 8.3 Hz, 1.5 Hz), 10.18 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.2, 110.3, 113.4, 121.4, 123.2, 124.8, 125.8, 128.5, 132.3, 135.8, 159.0. GC-MS (*m*/*z*): 265 (13), 264 (M+, 11), 263 (21), 261 (21), 91 (100), 65 (13). The spectroscopic data agree with those of the literature.[31]

N-(2-Bromo-4-methylphenyl)-1*H*-pyrrole-2-carboxamide (1b)

This compound was obtained following the procedure used for **1a**. The product was isolated as a white solid, mp: 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.32 (s, 3H), 6.31 (m, 1H), 6.78 (m, 1H), 7.01 (m, 1H), 7.15 (dd, 1H, J = 8.5 Hz, 1.0 Hz), 7.40 (d, 1H, J = 1.1 Hz), 8.12 (bs, 1H), 8.30 (d, 1H, J = 8.3 Hz), 9.69 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.5, 109.9, 110.3, 113.2, 121.3, 122.7, 126.0, 129.1, 132.5, 133.2, 134.0, 158.8. GC-MS (*m*/*z*): 280 (16), 279 (8), 278 (M+, 18), 199 (52), 198 (10), 78 (20). HRMS (ESI) calcd. for $C_{12}H_{12}BrN_2O$ [M+ H^+] 279.0128, found 279.0129.

N-(2-Bromo-4-chlorophenyl)-1*H*-pyrrole-2-carboxamide (1c)

This compound was obtained following the procedure applied for **1a**. The product was isolated as a white solid, mp: 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.33 (m, 1H), 6.79 (m, 1H), 7.32 (dd, 1H, J = 8.9 Hz, 2.5 Hz), 7.57 (d, 1H, J = 2.5 Hz), 8.14 (bs, 1H), 8.43 (d, 1H, J = 8.9 Hz), 9.46 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.2, 110.6, 113.3, 121.9, 123.0, 125.7, 128.6, 129.0, 131.7, 134.6, 158.6. GC-MS (*m*/*z*): 300 (7), 299 (M+, 2), 298 (10), 219 (23), 209 (11), 207 (59), 205 (46), 94 (100), 66 (49), 63 (11). HRMS (APPI) [M+ H^+] calcd. for $C_{11}H_8BrClN_2O$ 300.9560, found 300.9585.

N-(2-Bromo-4-cyanophenyl)-1*H*-pyrrole-2-carboxamide (1d)

This compound was obtained following the procedure applied for **1a**. The product was isolated as a white, mp: 214.6–215.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (m, 1H), 6.84 (m, 1H), 7.07 (m, 1H), 7.63 (dd, 1H, J = 8.6 Hz, 1.9 Hz), 7.86 (d, 1H, J = 1.9 Hz), 8.38 (bs, 1H), 8.68 (d, 1H, J = 8.6 Hz), 9.40 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.9, 111.0, 111.6, 117.5, 119.7, 120.5, 123.8, 129.1, 132.6, 135.7, 140.1, 158.6. GC-MS (*m*/*z*): 291 (6), 289 (5), 210 (15), 94 (100), 66 (26). HRMS (ESI) [M+ H^+] calcd. for $C_{12}H_8BrN_3O$ 289.9924, found 289.9931.

N-(1-Bromonaphthalen-2-yl)-1*H*-pyrrole-2-carboxamide (1e)

This compound was obtained following procedure for **1a**. The product was isolated as white solid, mp: 258–260 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.36 (m, 1H), 6.89 (m, 1H), 7.05 (m, 1H), 7.46 (m, 1H), 7.59 (m, 1H), 7.83 (t, 2H, J = 8.9 Hz), 8.18 (d, 1H, J = 8.5), 8.50 (bs, 1H), 8.62 (d, 1H, J = 8.9 Hz), 9.49 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.3, 110.6, 111.3, 120.5, 122.9, 125.4, 126.0, 126.5, 127.8, 128.2, 128.4, 131.4, 132.1, 134,4, 158.9. GC-MS (*m*/*z*): 316 (13), 314 (M+,13), 296 (20), 295 (13), 285 (20), 284 (10), 268 (13), 257 (11), 247 (10), 236 (27), 235 (98), 234 (11), 226 (12), 224 (31), 223 (100), 222 (20), 221 (88), 207 (53), 170 (10), 166 (18), 163 (12), 162 (17), 160 (11), 151 (11), 144 (15), 142 (12), 141 (31), 140 (29), 126 (20), 119 (20), 118 (15), 114 (22), 113 (19), 105 (20), 101 (15), 95 (29), 94 (36), 69 (11), 66 (43). HRMS (ESI) [M+ Na^+] calcd. for $C_{15}H_{11}BrN_2O$ 336.9947, found 336.9971.

N-(2-Bromophenyl)-1*H*-indole-2-carboxamide (2a)

This compound was obtained following the procedure applied for **1a**. The product was isolated as a white solid, mp: 216–218 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (td, 1H, J = 7.6 Hz, 1.5 Hz), 7.09 (d, 1H, J = 1.7 Hz), 7.18 (m, 1H), 7.36 (m, 2H), 7.48 (dd, 1H, J = 8.4 Hz, 0.7 Hz), 7.60 (dd, 1H, J = 8.1 Hz, 1.4 Hz), 7.72 (d, 1H, J = 8.1 Hz), 8.54 (m, 2H), 9.51 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 103.2, 112.1, 113.5, 121.1, 121.6, 122.3, 125.2, 125.3, 127.6, 128.6, 130.5, 132.4, 135.5, 136.8, 159.4. GC-MS (*m*/*z*): 316 (16), 314 (M+, 14), 236 (16), 235 (90), 145 (12), 144 (100), 143 (29), 118 (23), 116 (23), 89 (60). HRMS (ESI) [M+ H^+] calcd. for $C_{15}H_{11}BrN_2O$ 315.0128, found 315.0137.

N-(2-Bromo-4-methylphenyl)-1*H*-indole-2-carboxamide (2b)

This compound was obtained following the procedure used for **1a**. The product was isolated as a white solid, mp: 259–260 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H), 7.08 (m, 1H), 7.19 (m, 2H), 7.33 (m, 1H), 7.43 (d, 1H, J = 1.3 Hz), 7.47 (dd, 1H, J = 8.3 Hz, 0.8 Hz), 7.72 (dd, 1H, J = 8.0 Hz, 0.7 Hz), 8.38 (d, 1H, J = 8.3 Hz), 8.43 (bs, 1H), 9.42 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.6, 103.0, 112.0, 113.4, 121.0, 121.4, 122.2, 125.1, 127.7, 129.2, 130.6, 132.6, 132.9, 135.4, 136.7, 159.3. GC-MS (*m*/*z*): 330 (18), 328 (M+, 13), 250 (28), 249 (100), 187 (29), 185 (25), 144 (83), 143 (20), 124 (13), 116 (34), 115 (13), 106 (14), 89 (79), 77 (16), 63 (10). HRMS (ESI) [M+ H^+] calcd. for $C_{16}H_{13}BrN_2O$ 329.0284, found 329.0294.

N-(2-Bromo-4-chlorophenyl)-1*H*-indole-2-carboxamide (2c)

This compound was obtained following the procedure adopted for **1a**. The product was isolated as a white solid, mp: 195–197 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.08 (d, 1H, J = 1.5 Hz), 7.20 (m, 1H), 7.37 (m, 1H), 7.47 (dd, 1H, J = 8.3 Hz, 0.8 Hz), 7.61 (d, 1H, J = 2.3 Hz), 7.72 (dd, 1H, J = 8.0 Hz, 0.8 Hz), 8.44 (bs, 1H), 8.50 (d, 1H, J = 8.9 Hz), 9.20 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.0, 111.3, 111.7, 120.1, 121.1, 122.1, 124.2, 125.2, 125.6, 128.1, 130.8, 137.6, 140.5, 150.8, 158.4. GC-MS (*m*/*z*):353 (3), 350 (M+, 3), 348 (3), 269 (18), 145 (11), 144 (100), 143 (20),

116 (24), 115 (11), 89 (80), 63 (25). HRMS (ESI) [M+ Na^+] calcd. for $C_{15}H_{10}BrClN_2O$ 370.9557, found 370.9576.

Procedure for the preparation of 2-bromophenyl-1*H*-pyrrole-2-carboxylate (1f)

A mixture of 1*H*-pyrrole-2-carboxylic acid (2.00 mmol, 222 mg) and CDI (2.20 mmol, 357 mg) in dry THF, under nitrogen, was heated at reflux for 3 h. Then, the reaction was cooled to r.t. and 2-bromophenol (2.00 mmol, 346 mg) was added and stirred for 24 h. The solvent was evaporated under vacuum. The pure product was obtained by chromatography (silica gel, petroleum/dichloromethane), as transparent oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.33 (m, 1H), 7.03 (m, 1H), 7.11 (m, 1H), 7.23 (dd, 1H, J = 8.1 Hz, 1.69 Hz), 7.33 (m, 1H), 7.60 (dd, 1H, J = 8.1 Hz, 1.54 Hz), 9.23 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.1, 116.5, 117.5, 121.4, 124.0, 124.3, 127.3, 128.5, 133.4, 148.0, 158.3. GC-MS (*m*/*z*): 267 (2), 265 (M+, 2), 94 (100), 66 (21). HRMS (ESI) calcd. for $C_{11}H_8INO_2$ [M+ H+] 265.9816, found 265.9811.

2-Iodophenyl-1*H*-pyrrole-2-carboxylate (1g)

This compound was obtained following the procedure carried out for **1f**. The product was isolated as a yellowish solid, mp: 80–81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (m, 1H), 7.00 (td, 1H, J = 7.6 Hz, 1.4 Hz), 7.08 (m, 1H), 7.21–7.26 (m, 2H), 7.40 (m, 1H), 7.86 (dd, 1H, J = 8.1 Hz, 1.44 Hz), 9.33 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 90.5, 111.1, 117.6, 121.7, 123.3, 124.3, 127.5, 129.4, 139.4, 150.8, 158.3. HRMS (ESI) calcd. for $C_{11}H_8INO_2$ [M+ Na^+] 335.9492, found 335.9488.

2-Iodophenyl-1*H*-indole-2-carboxylate (2d)

This compound was obtained following the procedure used for **1f**. The product was isolated as a white solid, mp: 174–176 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04 (td, 1H, J = 7.6 Hz, 1.5 Hz), 7.20 (m, 1H), 7.30 (dd, 1H, J = 8.2 Hz, 1.3 Hz), 7.36–7.47 (m, 3H), 7.55 (m, 1H), 7.76 (dd., 1H, J = 8.1 Hz, 0.6 Hz), 7.89 (dd, 1H, J = 7.9 Hz, 1.5 Hz), 9.04 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 90.3, 111.1, 112.1, 121.2, 123.0, 123.2, 126.0, 126.2, 127.5, 127.8, 129.5, 137.4, 139.6, 150.8, 159.3. GC-MS (*m*/*z*): 363 (M+, 8), 355 (5), 270 (26), 236 (46), 207 (37), 115 (12), 114 (149, 94 (100), 73 (22), 66 (17). HRMS (ESI) calcd. for $C_{15}H_{11}INO_2$ [M+ H^+] 363.9829, found 363.9819.

General procedure for the preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 3a–e and indolo[1,2-*a*]quinoxalin-6(5*H*)-one 5a–c and oxazinone 3f under conventional heating

A mixture of 10 mol% of CuI (0.025 mmol, 5.0 mg), 20 mol% of L-proline (0.05 mmol, 6 mg), amide or ester derivative (0.25 mmol, 1.0 equiv) and NaH (0.62 mmol, 15 mg, 2.5 equiv) in 2.5 mL of anhydrous DMF and under nitrogen, was heated at 140 °C for 1 h. After that, the reaction was cooled to r.t. and the crude was then filtered through a short column of silica gel and eluted with dichloromethane. DMF was evaporated under vacuum. The pure product was obtained by chromatography (silica gel, petroleum/ethyl ether).

General procedure for the preparation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one 3a–e, indolo[1,2-*a*]quinoxalin-6(5*H*)-one 5a–c and oxazinones 3f and 5d under MW-assisted heating

A tube was charged with 10 mol% of CuI (0.025 mmol, 5.0 mg), 20 mol% of L-proline (0.05 mmol, 6.0 mg), amide or ester derivative (0.25 mmol, 1 equiv) and NaH (0.62 mmol, 15 mg, 2.5 equiv) in 2.5 mL of anhydrous DMF and under nitrogen. Then the tube was sealed with a rubber cap and heated to 140–160 °C for 5 min under MW irradiation (Fixed Power, 50 W) using air cooling. After that, the reaction was cooled to r.t. and the crude was then filtered through a short column of silica gel and eluted with dichloromethane. DMF was evaporated under vacuum. The pure product was obtained by chromatography (silica gel, petroleum/ethyl ether).

N-Phenyl-1*H*-pyrrole-2-carboxamide (4a)

This compound was obtained following the procedure described for **1a**. The product was isolated as a white solid, mp: 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.27 (m, 1H), 6.77 (m, 1H), 6.97 (m, 1H), 7.11 (m, 1H), 7.34 (m, 2H), 7.62 (m, 1H), 7.89 (bs, 1H), 8.02 (bs, 1H), 9.99 8bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 104.2, 109.9, 110.1, 120.1, 122.5, 124.1, 126.1, 129.0, 137.9, 159.3, 162.7. GC-MS (*m*/*z*): 186 M+, 25), 94 (47), 93 (100), 66 (31). HRMS (ESI) calcd. for $C_{11}H_{10}N_2O$ [M+ H^+] 187.0866, found 187.0866.

Pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3a)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 188.5–190.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (m, 1H), 7.05 (m, 1H), 7.10 (m, 1H), 7.32 (m, 2H), 7.54 (m, 1H), 7.66 (m, 1H), 10.51 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.4, 110.8, 113.2, 118.8, 119.8, 123.0, 124.4, 124.6, 141.8, 150.2, 158.2. 185 (13), 184 (M+, 100), 92 (11), 64 (13), 63 (13). The spectroscopic data agree with those of the literature.[22]

8-Methylpyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3b)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 168–170 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.44 (s, 3H), 6.27 (m, 1H), 6.93 (m, 1H), 7.09 (m, 1H), 7.16 (d, 1H, J = 8.1 Hz), 7.49 (s, 1H), 7.53 (d, 1H, J = 8.1 Hz), 12.19 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 21.2, 110.0, 110.4, 112.4, 118.1, 118.9, 123.7, 125.5, 134.2, 139.5, 149.7, 157.2. GC-MS (*m*/*z*): 199 (52), 198 (M+, 100), 78 (20). The spectroscopic data agree with those of the literature.[22]

8-Chloropyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3c)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 220–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.38 (m, 1H), 7.05 (m, 1H), 7.09 (m, 1H), 7.30 (dd, 1H, J = 8.4 Hz, 1.9 Hz), 7.54 (m, 2H), 10.10 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.0, 111.1, 113.6, 119.2, 119.4, 123.3, 125.2, 129.8, 140.6, 150.3, 158.7. GC-MS (*m*/*z*): 220 (29), 219 (14), 218 (M+, 100), 191 (12), 155 (22), 63 (31). The spectroscopic data agree with the literature.[11]

8-Cyanopyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3d)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 250–252 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.34 (m, 1H), 7.08 (m, 1H), 7.21 (m, 1H), 7.80 (m, 2H), 8.23 (bs, 1H), 12.45 (bs, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 105.8, 110.8, 114.6, 114.7, 117.8, 119.0, 119.5, 125.6, 129.3, 146.0, 148.9, 160.4. GC-MS (*m*/*z*): 210 (14), 209 (M+, 100). HRMS (ESI) calcd. for $C_{12}H_7N_3O$ [M–H$^+$] 208,0488, found 208.0505.

Benzo[*h*]pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one (3e)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as white solid, mp: 234–236 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.41 (m, 1H), 7.06 (m, 1H), 7.16 (m, 1H), 7.52 (m, 1H), 7.64 (m, 1H), 7.78 (d, 2H, J = 1.3 Hz), 7.97 (d, 1H, J = 8.3 Hz), 8.27 (d, 1H, J = 8.3 Hz), 9.84 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 110.9, 112.4, 118.0, 120.0, 120.2, 120.3, 122.4, 125.3, 125.4, 126.9, 128.7, 131.4, 138.2, 145.6, 157.5. GC-MS (*m*/*z*): 235 (16), 234 (M+, 100), 117 (11), 114 (43), 113 (21), 88 (14). HRMS (ESI) calcd. for $C_{15}H_{10}N_2O$ [M+ H$^+$] 235.0866, found 235.0885.

4*H*-Benzo[*b*]pyrrolo[1,2-*d*][1,4]oxazin-4-one (3f)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 132–134 °C (lit:[32] 132–133 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.68 (dd, 1H, J = 4.0 Hz, 2.8 Hz), 7.30 (m, 2H), 7.37 (m, 2H), 7.60 (m, 1H), 7.64 (dd, 1H, J = 2.7 Hz, 1.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 114.1, 114.2, 117.5, 117.6, 118.4, 118.5, 122.6, 124.8, 126.4, 143.1, 153.9. GC-MS (*m*/*z*): 186 (11), 185 (M+, 100), 157 (16), 141 (10), 140 (13), 130 (12), 129 (12), 114 (15), 102 (19), 79 (11), 76 (10).

Indolo[1,2-*a*]quinoxalin-6(5*H*)-one (5a)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 245–247 °C (97% of purity by ^{1}H NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (m, 1H), 7.31 (m, 1H), 7.37 (m, 2H), 7.41 (m, 2H), 7.61 (m, 1H), 7.73 (m, 2H), 9.76 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 106.5, 110.6, 111.7, 119.6, 120.9, 122.0, 124.8, 124.9, 124.9, 125.2, 128.1, 137.5, 141.64, 150.6, 157.9. GC-MS (*m*/*z*): 235 (17), 234 (M+, 100), 205 (13), 117 (13). HRMS (ESI) calcd. for $C_{15}H_{10}N_2O$ [M+ H$^+$] 235.0866, found 235.0883.

2-Methylindolo[1,2-*a*]quinoxalin-6(5*H*)-one (5b)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 226–228 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 7.18 (m, 2H), 7.29 (m, 1H), 7.36 (d, 1H, J = 1.1 Hz), 7.40 (m, 2H), 7.59 (d, 1H, J = 8.2 Hz), 7.73 (d, 1H, J = 8.2 Hz), 9.69 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0, 106.2, 110.9, 111.8, 119.1, 121.0, 122.1, 124.9, 125.1, 126.2, 128.3, 135.9, 137.6, 139.6, 151.0, 157.5. GC-MS (*m*/*z*): 249 (25), 248 (M+, 100), 247 (27), 124 (22). The spectroscopic data agree with those of the literature.[22]

2-Chloroindolo[1,2-*a*]quinoxalin-6(5*H*)-one (5c)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 185–186 °C (decompose). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19 (m, 1H), 7.33 (m, 2H), 7.40 (m, 2H), 7.61 (m, 2H), 7.73 (dd, 1H, J = 8.0 Hz, 0.7 Hz), 9.53 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.0, 111.3, 111.7, 120.0, 121.1, 122.1, 124.2, 125.2, 125.6, 128.1, 130.8, 137.6, 140.5, 150.8, 158.4. GC-MS (*m*/*z*): 270 (33), 269 (18), 268 (M+, 100), 205 (15), 134 (15), 115 (12), 89 (11), 63 (21). HRMS (ESI) calcd. for $C_{15}H_9ClN_2O$ [M+ H$^+$] 269.0476, found 269.0451.

4*H*-Benzo[*b*]indolo[1,2-*d*][1,4]oxazin-4-one (5d)

This compound was obtained following the procedure described for the MW-assisted reactions. The product was isolated as a white solid, mp: 204–205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 1H), 7.40 (m, 3H), 7.58 (m, 1H), 7.73 (d, 1H, J = 0.79 Hz), 7.88 (m, 1H), 8.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 111.8, 113.8, 115.2, 118.5, 122.2, 122.9, 123.8, 124.9, 125.1, 125.2, 127.3, 128.8, 134.8, 142.3, 155.3. GC-MS (*m*/*z*): 236 (36), 235 (M+, 100), 191 (18), 190 (31), 178 (22), 164 (15), 152 (26), 117 (10), 90 (12), 89 (48), 76 (19), 75 (15), 74 (12), 63 (14). HRMS (ESI) calcd. for $C_{15}H_9NO_2$ [M+ H$^+$] 236.0706, found 236.0725.

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