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Accelerating lead optimization of chromone carboxamide scaffold throughout microwave-assisted organic synthesis

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ABSTRACT

Microwave irradiation offers a considerable advantage over conventional synthesis with rate enhancements and cleaner reactions. Accordingly, a new microwave-assisted method for the synthesis of functionalized chromones was developed allowing the obtention of a library of chromone carboxamides. The method has been shown to present several advantages including operational simplicity, good performance, significant reduction in reaction time, less formation of by-products, and easier work-up.

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Microwave chemistry and microwave-assisted organic synthesis (MAOs) are nowadays undeniably effective tools in medicinal chemistry.[1] The availability of safe, single-mode dedicated microwave units has allowed the incorporation of this new technology into accelerating drug-discovery, hit-to-lead, and lead optimization programs. The development of more economical synthetic routes can ameliorate the overall process since drug discovery is a costly exercise with a high attrition rate.[1]

The use of MAOs has been shown to dramatically reduce processing times, increase product yields, and enhance the purity of the product when compared to the conventionally processed experiments.[1] Since there are several manufacturers of professional-grade equipment and a plethora of adapted methods, one can conclude that this interest continues to grow.[2]

Privileged structures, such as benzopyranes are currently described as supportive approaches in drug discovery. In fact, different natural heterocyclic families, such as xanthones and coumarins have been used as scaffolds in medicinal chemistry programs, namely for the search of novel monoamine oxidase inhibitors.[3,4] Chromones (benzopyran-4-one) are a group of similar naturally occurring heterocyclic compounds. They occupy an important place in the realm of natural products and in synthetic organic chemistry due to their particular structural features. Chromone scaffold has been recognized as a pharmacophore of a great number of bioactive molecules. The remarkable biological properties discovered so far have stimulated a continuous search in this field that leads at present to the appearance of some drugs on the market.[5,6] The functionalization of the chromone nucleus originates interesting derivatives, namely those possessing a reactive carbonyl group (aldehyde or carboxylic acid), that are versatile synthons owing to its ability to participate in a wide spectrum of reactions, for instance the reactivity toward nucleophiles.[7,8]

Noteworthy data have been previously acquired to strengthen the interest of chromone carboxamides as potent and selective monoamine oxidase inhibitors (IMAO).[9,10] The reported chromone carboxamide synthesis[9,10] correspond to a one-pot condensation reaction that occurs between the corresponding chromone carboxylic acid and aniline (phenylamine), or its ring-substituted derivatives. The coupling reagent selected for carboxylic acid activation was an organophosphoric compound designated as (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP).[9,10] Although effective this reagent is very expensive and the work-up of the reactions was very tedious and time-consuming.

Keeping in view these observations and in continuation of our project on medium-throughput screenings of diverse chromone carboxamides, toward a number of targets involved in neurodegenerative disorders, a larger number of synthetic analogues are expected to be needed.

In an attempt to accelerate the synthetic process the application of microwave-assisted methods was envisaged. Accordingly, a solid evidence of the benefits of a microwave synthetic approach over the conventional synthetic method (with PyBOP as the coupling agent) has been acquired along this study.

The synthesis of chromone carboxamide (**3**) as a model substrate, using the chromone carboxylic acid (**1**) and aniline (**2**),

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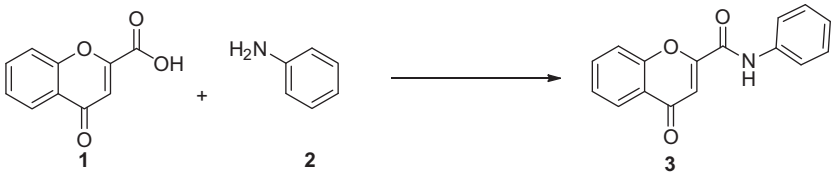
Table 1
Microwave-assisted optimization conditions for the synthesis of chromone carboxamide (**3**)

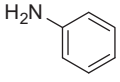
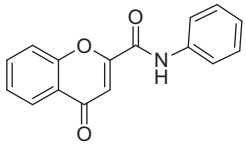
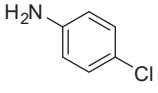
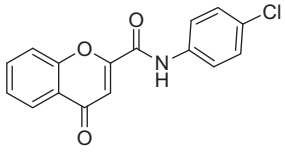
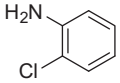
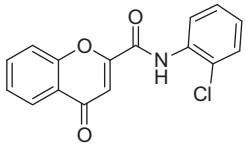
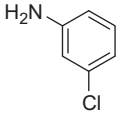
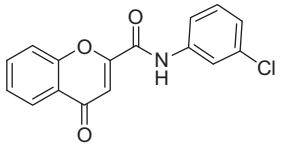


1 + **2** → **3**

Entry	Solvent	T (°C)	Coupling agent (mmol)	**2** (mmol)	Time[a] (min)	Yield (%)
1	DMF	160	PCl_3 (1)	1	5	55
2	DMF	160	PBr_3O (1)	1	5	[b]
3	DMF	160	PCl_3O (1)	1	5	82
4	Xylene	160	PCl_3O (1)	1	5	—
5	Dioxan	160	PCl_3O (1)	1	5	22
6	DMF	100	PCl_3O (1)	1	5	47
7	DMF	200	PCl_3O (1)	1	5	40
8	DMF	160	PCl_3O (1)	1	2	41
9	DMF	160	PCl_3O (1)	1	10	78
10	DMF	160	PCl_3O (1)	4	5	81
11	DMF	160	PCl_3O (0.4)	1	5	35
12	DMF	160	PCl_3O (1.5)	1	5	61

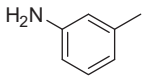
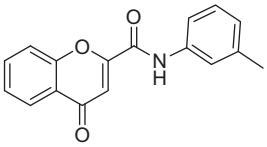
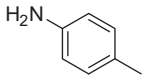
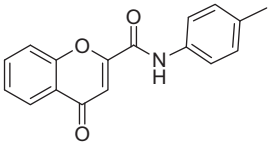
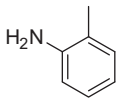
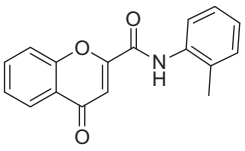
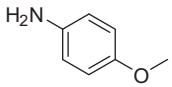
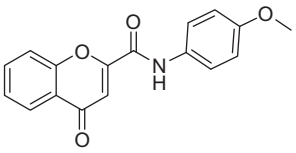
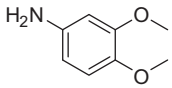
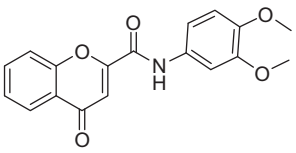
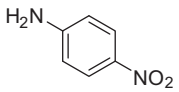
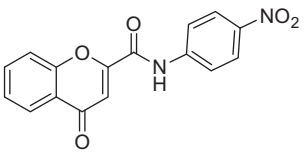
— No reaction.
[a] Irradiation time.
[b] Complex mixture.

Table 2
Data from the comparative study between conventional versus microwave method

Entry	Compound	Aniline Derivative	Chromone carboxamide	Yield (%)	
				PyBop	MW
1	**3**			81	82
2	**4**			50	59
3	**5**			23	76
4	**6**			23	78

(*continued on next page*)

Table 2 (*continued*)

Entry	Compound	Aniline Derivative	Chromone carboxamide	Yield (%)	
				PyBop	MW
5	**7**			38	65
6	**8**			56	65
7	**9**			72	65
8	**10**			85	67
9	**11**			45	71
10	**12**			—	18

—, No reaction.

was initially chosen for the optimization of the microwave reaction conditions (see method A[11]). The simple structure of the compound as well as the synthetic data obtained so far, with other coupling agents such as $SOCl_2$, BOP, EDC, was vital to this decision. Accordingly, different experimental conditions were explored to attain optimization: type of phosphorus coupling agent, solvent, stoichiometry, time, and temperature (Table 1).[12]

Concerning the phosphorus coupling agents used in the experiments, one can say that the best results were obtained with PCl_3O (Table 1, entry 3). The results with PCl_3 (Table 1, entry 1) can be classified as the modest and the worst reagent was PBr_3O (Table 1, entry 2) which gave a complex mixture of by-products. The reaction was also performed in three solvents with different polarity index. The change of DMF by dioxane (Table 1, entry 3 vs 5) or xylene (Table 1, entry 4) revealed to be unproductive. In fact, with dioxane (Table 1, entry 5) only a yield of 22% was obtained, mainly due to the solubility problems with the starting chromone, and with xylene no reaction was observed. As to the influence of temperature, it was concluded that a decrease to 100 °C (Table 1, entry 6) or an increase to 200 °C (Table 1, entry 7) originates lower yields.

The microwave-assisted reaction was also optimized in relation to the time of irradiation and stoichiometry: (a) it was observed that a decrease on the irradiation time to 2 min or an increase to 10 min produced a yield reduction (Table 1, entries 9 vs 10); (b) the increase of the phenylamine equivalents had no influence on the reaction whereas the variations on the PCl_3O quantity resulted in a yield decrease (Table 1, entry 11 vs 12).

After optimization of the experimental variables the versatility of the microwave-assisted amidation reaction was tested using different phenylamines as the starting material, (with diverse aromatic substitution patterns) reflecting different effects in the amine nucleophilicity (method A[11]). The results of the reaction (yield corresponding to the pure chromone product) were compared with the conventional synthetic method using PyBOP as the coupling agent (method B[11]). The results obtained with method B were remarkably inferior, except in the case of compounds **9** and **10** (Table 2, entries 7 and 8). No difference between the methods was observed with compound **3** (Table 2, entry 1).

The introduction of substituents in the exocyclic aromatic ring of the chromone carboxamide scaffold was recognized to be a disadvantage for the reaction (Table 2, entry 1), in terms of yield performance, either with anilines possessing electron withdrawing (Table 2, entries 2–4 and 10) or donating substituents (Table 2, entries 5–9). The position of the substituent in the aromatic ring (*ortho*, *meta* or *para)*, had no significant influence on the yield both for a weak electron releasing group (Table 2, entries 5–7,) or for a weak electron withdrawing group (Table 2, entries 2–4). The increase of the number of electron donating substituents did not generate a significant effect on the yield (Table 2, entries 9).

Moreover with the microwave-assisted method, even considering the low yield of the reaction, amide **12** (Table 2, entry 10) was obtained. The procedure was not successful with method B (with PyBOP) due to the presence of a strong electron withdrawing group ($-NO_2$) in the phenylamine. In fact, the coupling between such weakly nucleophilic amines was not trifling with standard coupling reagents.[13]

In conclusion, a convenient procedure for preparing functionalized chromones was developed. Microwave heating enables the formation of aromatic amides from chromone-2-carboxylic acid with very acceptable results. The method is environmentally friendly and allows the formation of the amide bond with a low-price reagent. In addition, the microwave process, when compared with the conventional one has several advantages: reduction of the reaction time, less formation of by-products, and easier work-up. Further, the method does not require dry solvents and/or inert atmosphere and is applicable to scale-up the production.

The very first encouraging result will be the starting point of the development of an automated process suitable for the synthesis of a larger library of new functionalized chromones that can be used in the discovery of new monoamino oxidase inhibitors.

Acknowledgments

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11. General methods used for the synthesis of chromone carboxamides:
    METHOD A–To a solution of chromone-2-carboxylic acid (**1**, 1 mmol) in DMF (1.5 mL), PCl_3O (1 mmol), was added. The mixture was stirred at room temperature for 30 min, with the formation of the corresponding acyl chloride. Then the appropriate aniline was added. The system was heated 160 °C for 5 min in a microwave apparatus. After, the mixture was poured into a beaker and water was added. The formed solid was filtered and purified by recrystallization.
    Microwave-assisted synthesis was performed in a Biotage® Initiator Microwave Synthesizer.
    METHOD B–To a solution of chromone-2-carboxylic (**1**, 1 mmol) in DMF (2.3 mL), DIPEA was added (1 mmol). After cooling the solution in an ice-water bath PyBOP (1 mmol), previously dissolved in 1.5 mL of CH_2Cl_2, and the amine (1 mmol) were added. The mixture was stirred in ice for 30 min and then, at room temperature for 4 h. CH_2Cl_2 was removed under reduced pressure and the solution was diluted with water (10 mL). After extraction with ethyl acetate the combined organic phases were washed successively with HCl (0.5%), $NaHCO_3$ 1 M and water and dried over anhydrous sodium sulfate. After filtration and solvent evaporation the residue was purified by column chromatography followed by recrystallization.
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