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FULL PAPER

# New efficient eco-friendly supported catalysts for the synthesis of amides with antioxidant and anti-inflammatory properties

Pierrick Dufrénoy,[a] Rogatien Charlet,[b] Marie Hechelski,[c] Adam Daïch,[d] Christophe Waterlot,[c],[e] Samir Jawhara,[b] and Alina Ghinet[a],[f],*

[a] Dr. Pierrick Dufrénoy
Dr. Alina Ghinet, corresponding author. E-mail: alina.ghinet@yncrea.fr; https://orcid.org/0000-0001-6468-4331
Yncréa Hauts-de-France, Hautes Etudes d'Ingénieur (HEI), UCLille, Health & Environment Department, Team Sustainable Chemistry, Laboratoire de chimie durable et santé, 13 rue de Toul, F-56046 Lille, France.

[b] Rogatien Charlet, PhD Student,
Dr. Samir Jawhara, https://orcid.org/0000-0002-2759-975X
LIRIC, UMR 995, Inserm, Université de Lille, CHU de Lille, Faculté de Médecine, Pôle Recherche, 4ème étage Epicentre Est, Place Verdun, F-59045 Lille Cedex.

[c] Dr. Marie Hechelski
Dr. Christophe Waterlot, https://orcid.org/0000-0002-4695-0082
Yncréa Hauts-de-France, Institut Supérieur d'Agriculture, UCLille, Health & Environment Department, Team Environment, Laboratoire Génie Civil et géoEnvironnement, 48 boulevard Vauban, 59046 Lille Cedex, France.

[d] Prof. Adam Daïch, https://orcid.org/0000-0002-6942-0519
Normandie Univ, UNILEHAVRE, URCOM EA 3221, INC3M CNRS-FR 3038, UFR des Sciences et Techniques, Université Le Havre Normandie, BP: 1123, 25 rue Philipe Lebon, F-76063 Le Havre Cedex, France.

[e] Dr. Christophe Waterlot
Yncréa Hauts-de-France, Institut Supérieur d'Agriculture, UCLille, Equipe Biotechnologie et Gestion des Agents Pathogènes en agriculture, 48 boulevard Vauban, 59046 Lille Cedex, France.

[f] Dr. Alina Ghinet
'Al. I. Cuza' University of Iasi, Faculty of Chemistry, Bd. Carol I, nr. 11, 700506 Iasi, Romania.

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**Abstract:** New environment friendly approach for the synthesis of idrocilamide (**1**), the marketed myorelaxant and anti-inflammatory agent, is reported. The synthetic strategy involves a solvent free aminolysis reaction catalyzed by zinc-containing catalysts ($ZnCl_2$, montmorillonite K10 (MK10) impregnated with $ZnCl_2$ or ecocatalysts). The latter have been prepared from the aerial parts of *Lolium perenne* L. plants grown on contaminated soils from North of France region without and with thermal activation at 120°C and supported on MK10 (Ecocat1 and Ecocat2, respectively). The best aminolysis catalysts in the current study ($ZnCl_2$ and Ecocat2) have been selected for additional aminolyses. Compared to $ZnCl_2$, Ecocat2 had the advantage of being reusable over five tested runs and constituted a sustainable catalyst allowing a green route to idrocilamide. Synthesized derivatives **1**-**4**, **6** and **9** have been first evaluated for their effect on reactive oxygen species (ROS) generation from macrophages and displayed antioxidant properties by preventing ROS production. Next, the analysis of the effect of molecules **1**-**4**, **6** and **9** on macrophage migration between epithelial cells to human opportunistic fungus *Candida albicans* indicated that molecules **2**-**4**, **6** and **9** exert anti-inflammatory properties via reducing macrophage migration while parent idrocilamide (**1**) did not show any significant effect. This work opens the way for the discovery of new analogues of idrocilamide with improved properties.

## Introduction

The modern synthetic methodologies aim to use less toxic reagents and solvents, produce less waste, limit halogenated effluents particularly, proceed under milder conditions of pressure and temperature and render chemical transformations faster than conventional kinetics by using often catalytic conditions. For this purpose, green chemistry emerged in the last decades and encourage to use new eco-friendly conditions in organic syntheses. The construction of conventional functional groups in organic chemistry, such as esters, amides or carboxylic acids, etc… in greener conditions, constitutes a contemporary challenge for increasing number of research groups.

The amide moiety is an essential functional group in organic chemistry. In fact, it is estimated that more than a quarter of main ingredients of all marketed drugs contain at least one amide group and are therefore found in all major therapeutic classes of pharmaceuticals. A selection of some drugs containing amide function that exhibit plethora of therapeutic indications drugs is depicted in Figure 1 (compounds **A-D** and idrocilamide **1**). For instance, lidocaïne **A** is a local anesthetic from the amino-amides series. Oseltamivir **B** bearing an acetamide function is an antiviral molecule and is used in the treatment and prevention of A and B influenzas. Another amide derivative with different biological activity is the third-generation cephalosporin antibiotic cefotiam **C**. Ranolazine **D**, mainly marketed under the brand name Ranexa®, is used to treat heart related chest pain. Idrocilamide (**1**) was firstly described as a precursor in the preparation of new penicillins.[1] The anti-inflammatory and myorelaxant properties of idrocilamide (**1**) have been described in the 2000s[2] and compound is being commercialized under different galenic forms and commercial names (Srilane®, Talval® or Relaxnova®). Other biological properties have been described in the literature for this compound, such as sedative effects, activity against depression, rosacea, migraines and convulsions.[3-7] The marketing of the topical cream Srilane® was stopped in France in December 2018, one of the causes being the mechanism of action of idrocilamide (**1**) that remains unresolved.

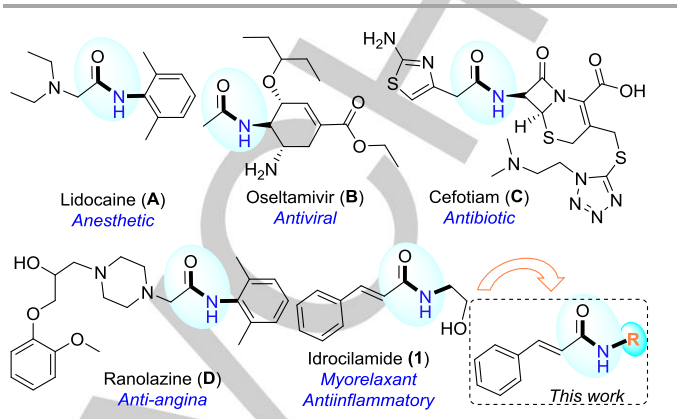
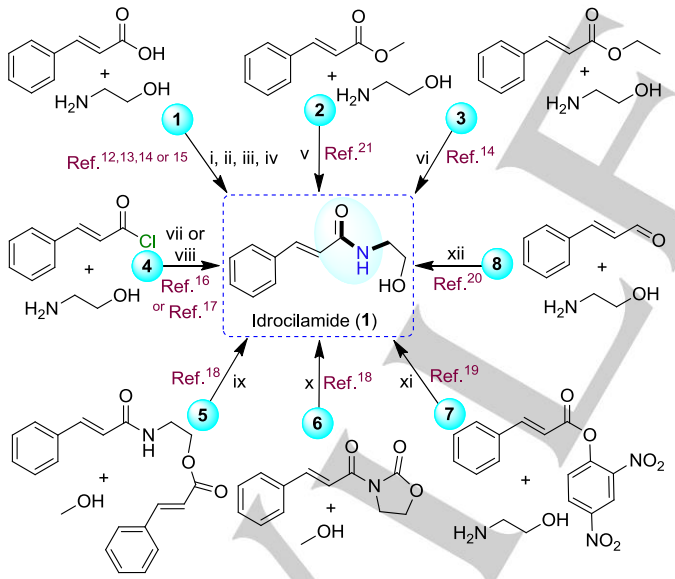



**Fig. 1** Structure of selected main ingredients of drugs bearing amide function **A**-**D**, idrocilamide (**1**) and targeted idrocilamide derivatives in the current study.

The formation of the amide function is extremely well-documented. More than forty research articles have been dedicated this year only to the synthesis of amides.[8,9] Classical synthetic pathway to access amides include the use of activated carboxylic acid derivatives such as activated esters, acyl halides or anhydrides in the presence of various amounts of coupling agents, generally expensive and/or toxic.[8,10] Recent developments in amide synthesis using nonactivated starting materials have been described.[10] These environmentally friendly methodologies mainly include: i) direct amidation of carboxylic acids with amines mediated by different catalysts, the most employed being boric acid derivatives under heating, or under microwave irradiation; ii) transamidation between amides and amines in presence of transition metals catalysts (iron, nickel and manganese derivatives being the most used); iii) aminolysis reaction of esters with amines under different catalytic conditions (*e.g.* transition metals derivatives[11]).

The reported strategies for the synthesis of idrocilamide (**1**) are depicted in Scheme 1. Eight different procedures were described.[12-21] The most documented is the treatment of cinnamic acid with ethanolamine in different conditions: 1-i) methylchloroformate, triethylamine in $CH_2Cl_2$ at room temperature to provide idrocilamide **1** in 82% yield;[12] 1-ii) similar conditions have been also reported by Xiu, J.-H. and co-workers[13] and allowed to obtain the target idrocilamide in 75% yield; 1-iii) the reaction between cinnamic acid and ethanolamine conducted in presence of sulfuric acid furnished 68% of idrocilamide;[14] 1-iv) the two-step procedure described by Zhang, J.-S.[15] started from cinnamic acid which, upon activation in presence of thionyl chloride to provide cinnamoyl chloride, was treated with ethanolamine to obtain final idrocilamide (**1**) without specifying the final yield. Two contributions describe the synthesis of compound **1** by direct treatment of cinnamoyl chloride with ethanolamine in $CH_2Cl_2$ followed by alkaline treatment by using aqueous sodium

carbonate (4-vii)[16] or triethylamine (4-viii)[17] to furnish the target amide in good yield. Another synthetic pathway (2) started from an α,β-unsaturated ester that underwent methanolysis in the presence of trimethylphosphine at room temperature and provided 49% of idrocilamide (**1**).[18] In the same report, when 3-(*trans*-cinnamoyl)-2-oxazolidinone (α,β-unsaturated imide) was employed as a substrate, four products including idrocilamide (**1**) (isolated as major product in 46% yield) were obtained (6).[18] The nucleophilic substitution reaction (7) between 2,4-dinitrophenyl cinnamate and ethanolamine in water containing 20 mol% of DMSO at 25°C was also reported to furnish idrocilamide without yield indication.[19] Another starting material used to provide idrocilamide was (*E*)-cinnamaldehyde as shown in pathway (8).[20] The reaction started by adding DBU to a solution of 1,3-dimethyltriazolium iodide and ethanolamine in THF under argon atmosphere (8-xii). Cinnamaldehyde and 3,3',5,5'-tetra-*tert*-butyldiphenoquinone were next added and the mixture was stirred at room temperature for 2 hours to obtain idrocilamide in 63% yield.[20] Two aminolysis reactions have been reported starting from ethyl[14] and methyl cinnamates[21] in presence of ethanolamine. The first (3) provided the amide in 53% yield. The second method (2) used methanol as solvent, large excess of aminoalcohol and an equivalent of $Na_2CO_3$ as a base and constitute the best transformation described in the literature to obtain idrocilamide (**1**) in terms of final yield (87%).[21]




**Scheme 1** Reported synthetic procedures to access idrocilamide **1**.[12-21] Reagents and conditions: i) $CH_2Cl_2$, $Et_3N$, $ClCO_2Me$, r.t, 2 h (82%); ii) $Et_3N$, $ClCO_2Me$, $CH_2Cl_2$, cooled to r.t, 1 h, then $CH_2Cl_2$, cooled, 2 h, r.t then aq. HCl (75%); iii) $SOCl_2$, THF, reflux, not indicated yield ; iv) $H_2SO_4$ r.t (68%); v) $Na_2CO_3$, MeOH, 2 h, 80°C (87%); vi) r.t (53%); vii) $CH_2Cl_2$, then aq. $Na_2CO_3$, r.t, 16 h (78%); viii) $CH_2Cl_2$, then $Et_3N$, $CH_2Cl_2$, r.t, 4 h (78%); ix) $Me_3P$, r.t (49%; x) $Me_3P$, 5 min, r.t (46%); xi) $H_2O$, DMSO, 25°C (not indicated yield); xii) 3,3',5,5'-tetra-*tert*-butyldiphenoquinone, dimethyltriazolium iodide, DBU, r.t, 2 h (63%).

Ultimately, from all these considerations, the major part of these methods led to modest conversions, were often realized in dichloromethane generating chlorinated effluents and used superficial reagents, which is problematic for industrial production.

In the current contribution, new supported catalysts on montmorillonite K-10 (MK10) have been conceived following the methodology described by Waterlot *et al.* (2000)[22] using $ZnCl_2$ as MK10-supported Lewis acid. To lead furthermore this project, new catalysts, called ecocatalysts have been prepared using aerial parts from *Lolium perenne* L. plants grown on contaminated soils from the North-region of France.[23] To test the performance of these new catalysts, the aminolysis reaction has been selected as a model transformation to provide the amide linkage. Chemical efforts were next directed on the synthesis of the bioactive idrocilamide (**1**) and derivatives.

In order to obtain more information on the biological activity of idrocilamide and seek derivatives with improved efficiency, the analysis of the effect of the molecules on reactive oxygen species (ROS) generation from macrophages and on macrophage migration between epithelial cells to *Candida albicans* have been conducted.

## Results and Discussion

### Chemistry

The study started with the evaluation of different catalysts, including classical catalysts for comparison reasons, supported catalysts and ecocatalysts on the synthesis of idrocilamide (**1**) and derivatives. Next, the efficiency and the recyclability in five successive aminolysis reactions of the newly produced supported catalysts and ecocatalysts after their first use were assessed.

**Table 1** Description of the catalysts used in the synthesis of idrocilamide (**1**).[a]

| Entry | Catalyst | Description |
|---|---|---|
| **1** | $Na_2CO_3$ | Catalyst described in the literature[21] |
| **2** | $ZnCl_2$ | Classical Lewis acid |
| **3** | Cat1 | $ZnCl_2$ supported on montmorillonite K10 without thermal activation |
| **4** | Cat2 | $ZnCl_2$ supported on montmorillonite K10 with thermal activation (120°C) |
| **5** | Ecocat1 | Metal salts contained in the aerial parts of plants grown on contaminated soils and MK-10-supported |
| **6** | Ecocat2 | Metal salts contained in the aerial parts of plants grown on contaminated soils and MK-10-supported |

[a] All the catalysts were used dry.

The synthesis of idrocilamide (**1**) has been realized by reacting methyl cinnamate and ethanolamine in the presence of six different catalysts described in the Table 1. These catalysts include the sodium carbonate ($Na_2CO_3$), classical catalyst mentioned in the literature for this reaction[21] (Table 1 – entry **1**), the commercial zinc (II) chloride ($ZnCl_2$) (Table 1 – entry **2**), two supported catalysts (Cat1 and Cat2, respectively without thermal activation and activation at 120°C – Table 1 – entries **3** and **4**). Two other new ecocatalysts produced from the aerial parts of ryegrass grown on contaminated soils and MK10-

supported (Ecocat1 and Ecocat2 – Table 1 – entries **5** and **6**) were tested.

The different steps necessary for the preparation of ecocatalysts Ecocat1 and Ecocat2 are presented in Figure 2. Briefly, the fresh biomass (aerial parts of *Lolium perenne* L.) was first dried, then mineralized at 500°C. The resulting ashes were treated with concentrated hydrochloric acid to transform the present metals into corresponding metal salts, which were finally supported on montmorillonite K10 and thermally activated at 120°C (Figure 2).[23]

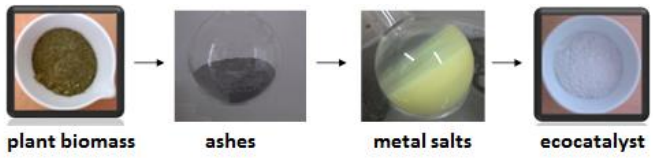
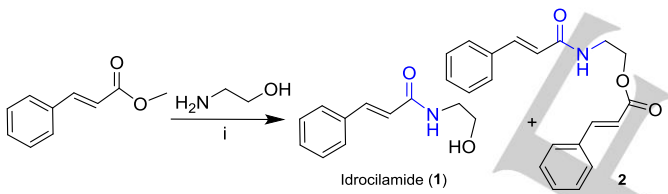



**Fig. 2** Schematization of the main steps to obtain ecocatalysts Ecocat1 and Ecocat2.

The reaction performed in different catalytic conditions is illustrated in Scheme 2 and the results of the catalytic study reported in Figure 3. Idrocilamide (**1**) was obtained as the major reaction product along with a by-product (compound **2**, Scheme 2) obtained from the double reaction of methyl cinnamate on ethanolamine that was isolated in 5-15% yield, depending on the nature of the catalyst (Scheme 2).




**Scheme 2** Reaction conditions: i) Neat or catalyst 5 w%, solvent free, 70°C, 24 h.

The most efficient catalyst for the studied transformation proved to be the commercial zinc chloride ($ZnCl_2$), which provided idrocilamide (**1**) in 75% yield (red, Figure 3). The sodium carbonate ($Na_2CO_3$) displayed slight decreased efficiency and allowed to obtain the title molecule **1** in near 70% yield (yellow, Figure 3). The same conversion was also induced by the Ecocat2 (green, Figure 3). The $ZnCl_2$-supported catalysts on MK10 (Cat1 and Cat2) were less efficient and provided target idrocilamide (**1**) in moderate yields of 52 and 56%, respectively (Figure 3). Neat conditions for the studied synthesis furnished target compound in 54% yield (Figure 3). The less efficient catalyst was the Ecocat1, which seemed to inhibit the conversion of the reaction (45% yield) compared to the reaction conducted in the absence of catalyst (54% yield). Interestingly, the catalytic performance of Ecocat2 was the best since idrocilamide (**1**) was obtained in 70% middle yield (Figure 3) and up to 78% yield (Figure 4). From our point of view the difference in the concentration of Zn in ashes used to prepare Ecocat1 and Ecocat2 cannot explain the different efficiencies of both catalysts since their conception was based on the same Zn/MK10 ratio.[23] So even if we cannot exclude the effects of other cations (*e.g.* Fe, Al, Mn), the great difference in catalyst's efficiency may be explained by the thermal activation at 120°C applied during the conception of Ecocat2.

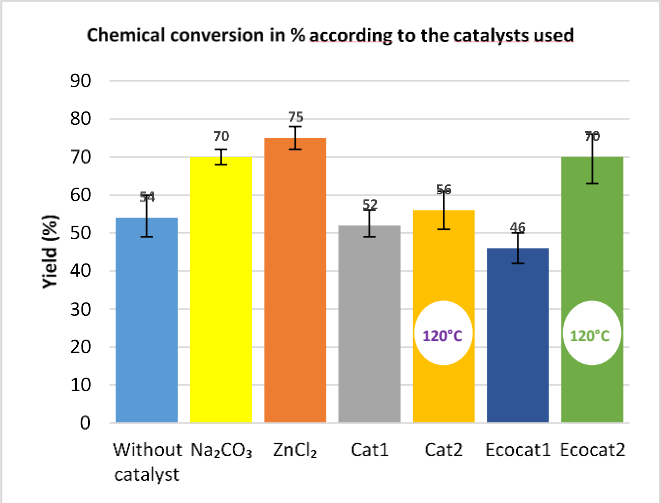



**Fig. 3** Results obtained in the synthesis of idrocilamide (**1**) in different catalytic conditions. Results represent mean and standard deviation of three independent experiments.

Indeed, differential calorimetric scanning of these ecocatalysts showed two endothermic and exothermic pics between 100 and 130°C in relation to the release of water, HCl and physisorbed water[23] which will contribute to decrease the catalyst's efficiency as it was highlighted in other study.[24]

The recyclability of the supported catalysts (Cat1 and Cat2) and the ecocatalysts (Ecocat1 and Ecocat2) has been investigated. For this purpose, the synthesis of idrocilamide was realized in duplicate by repeating the operation five times by using the same catalyst isolated from the previous reaction. The results of the recyclability study have been illustrated on the Figure 4.

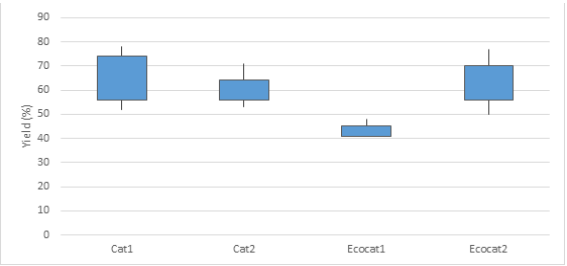
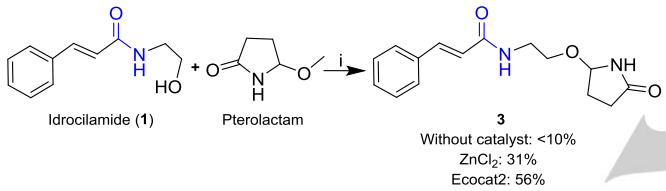



**Fig. 4** Chemical conversion according to the catalysts used: mean yields in presence of different catalysts over 5 distinctive runs (experiences realized in duplicate).

The best supported catalyst in the current study for the synthesis of idrocilamide (**1**), Ecocat2, proved to be reusable conserving catalytic power and inducing 50% to 77% yield over the 5 distinctive runs (Figure 4). The absence of the catalytic activity of Ecocat1 has been proved again, the maximum yield provided being 48% in the second and third run (Figure 4). In

comparative manner, the recyclability of supported catalysts (Cat1 and Cat2) was also improved. Indeed, in comparison with the efficiency and the recyclability of the ecocatalyst1, the synthesis of idrocilamide (**1**) in presence of these catalysts is operative with yields ranging from 52% up to 78% in presence of Cat1 (Figure 4) and from 53% up to 71% in the presence of Cat2 (Figure 4), respectively.

Next, after having demonstrated the reactivity of the terminal alcohol of idrocilamide (**1**) to obtain molecule **3**, the reaction between idrocilamide (**1**) and the natural 5-methoxy-pyrrolidone (pterolactam) using three different reaction conditions (without catalyst, $ZnCl_2$ and Ecocat2) was tested to provide a new potential prodrug of idrocilamide (compound **3**) but also compare the catalytic activity between $ZnCl_2$ and Ecocat2, the best catalysts in the current study (Scheme 3). It is interesting to note that neat conditions allowed to obtain very low transformation of starting reagents (yield inferior to 10%), while the zinc chloride improved the condensation to 31% yield. Finally, Ecocat2 proved to possess the best catalytic activity and allowed to isolate compound **3** in 56% yield (Scheme 3).

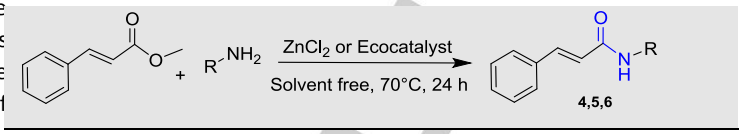



**Scheme 3** Reagents and conditions: i) neat or catalyst 5 w%, solvent free, 80°C, 24 h.

New idrocilamide derivatives have been next synthesized in the presence of the previously identified efficient catalysts ($ZnCl_2$ and Ecocat2) in order to compare their anti-inflammatory properties with those of the parent compound **1**. Methyl cinnamate was submitted to aminolysis reaction with three different amines (Scheme of Table 2). Selected amines except less nucleophile aniline reacted with the methyl ester and provided the expected amides **4** and **6**. Interestingly, Ecocat2 displayed in all cases an improved catalytic power compared to commercial Lewis acid (entries 1, 3 in Table 2).

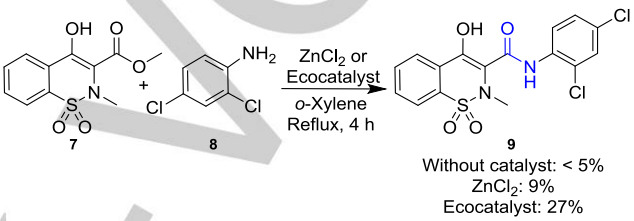
In order to test the efficiency of Ecocat2 on the construction of the amide bond in a different family of molecules with potential anti-inflammatory activity, the reaction of an ester function from the oxicam family (methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide) with 2,4-dichloroaniline was performed (Scheme 4). Solventless conditions were not adapted for this transformation since methyl ester was not soluble in the medium. For this reason, the reaction has been conducted in refluxing *o*-xylene. Of interest, in the absence of catalysts, only traces of final product have been detected. The zinc chloride catalysis was slightly more efficient and Ecocat2 permitted the obtention of oxicam derivative **9** in 27% yield. The latter molecule has been previously identified as anti-inflammatory agent in animals.[25]

**Table 2** Results obtained for the synthesis of amides **4, 5** and **6** using methyl cinnamate and selected amines.




| Entry | *Amine* | Product | Catalyst (Yield %) | |
|---|---|---|---|---|
| | | | $ZnCl_2$ | Ecocat2 |
| 1 | *n-Propylamine* | **4** | 22 | 48 |
| 2 | Aniline | **5** | NR[b] | NR |
| 3 | *(R)-(+)-Methylbenzylamine* | **6** | 11 | 40 |

[a] Isolated yield in %. [b] Not determined.




**Scheme 4** Synthesis of amide **9** bearing an oxicam moiety.

## Biological evaluation

### Analysis of the effect of the molecules 1-4, 6, and 9 on ROS generation from macrophages

Reactive oxygen species (ROS) are involved in the pathogenesis of cardiovascular disease, and clinically related to pathologies manifested by obesity, diabetes, and metabolic syndrome.[26-28] Increased levels of ROS generation cause disruption of tissue homeostasis leading to increased morbidity and risk of mortality.[29] To analyze the effect of newly synthesized molecules on the ROS generation, macrophages were pretreated with the synthesized molecules (**1**, **2**, **3**, **4**, **6**, and **9**) and then exposed to LPS in order to induce ROS production.

The percentage of ROS significantly increased in the macrophages exposed to LPS (10 µmol/L) and analyzed with a kinetic chemiluminescent assay for 4 hours. In contrary the pretreatment of macrophages with these molecules at a concentration of $10^{-5}$ mol/L, and exposed to LPS, significantly reduced the ROS production (Fig. 5A). We next used a decreasing concentration of these molecules and observed that molecules **2**-**4**, **6** and **9** at a concentration of $10^{-6}$ mol/L significantly reduced ROS production. In contrast, the pretreatment of macrophages with the reference idrocilamide (**1**) did not inhibit the ROS production (Fig. 5B). This finding indicates clearly that the tested molecules show antioxidant properties in preventing ROS generation and that newly synthesized derivatives **2**-**4**, **6, 9** are more active than parent idrocilamide (**1**).

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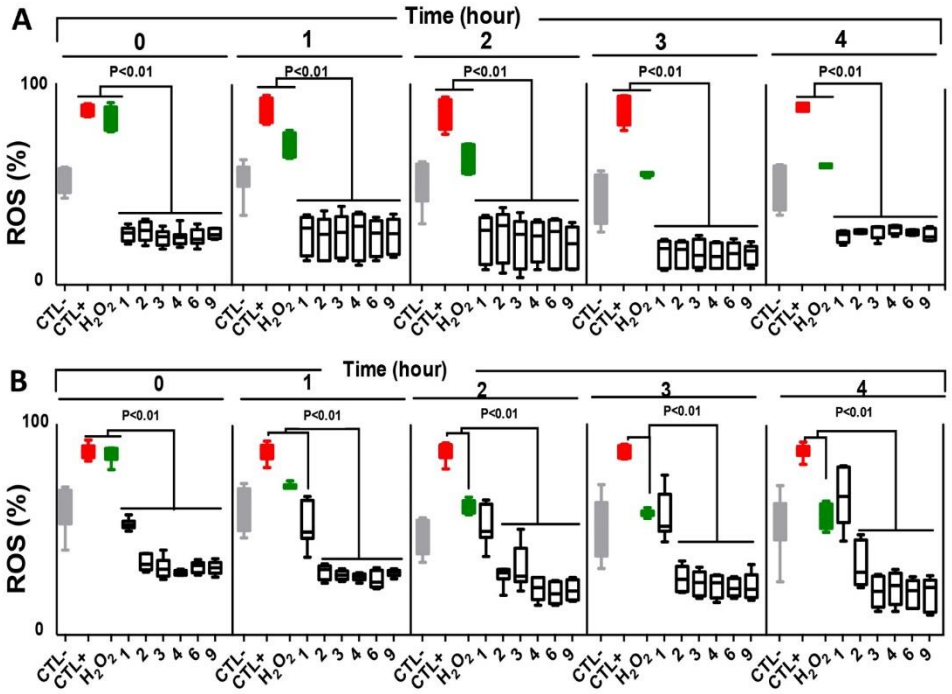


**Fig. 5** Effect of compounds **1-4, 6, 9** on the ROS generation from macrophages in a kinetic chemiluminescent assay. **A,** Analysis of ROS generation in the supernatant of macrophages pretreated with molecules at a concentration $10^{-5}$ mol/L. **B,** Analysis of ROS generation in the supernatant of macrophages pretreated with molecules at a concentration $10^{-6}$ mol/L. CTL- corresponds to macrophages alone. CTL+ corresponds to macrophages + LPS. $H_2O_2$ alone without macrophages at a concentration of 1.7 mol/L was used as a positive control.

**Analysis of the effect of the molecules 1-4, 6, and 9 on macrophage migration between epithelia cells to *Candida albicans***

A reduction of the intestinal epithelial barrier function is observed during the intestinal inflammation that would promote the migration of the immune cells including macrophages.

The effect of molecules **1-4, 6, 9** on the migration of macrophages between Caco-2 cells to human opportunistic fungus *Candida albicans* was assessed (Figure 6). A significant decrease in the migration of macrophages pre-treated with molecules (**2**, **3**, **4**, **6**, and **9**) at a concentration of $10^{-5}$ mol/L is observed when compared to those untreated with the molecules (Fig. 6A). In contrast, no effect was detected for these molecules on macrophage migration at a concentration of $10^{-6}$ mol/L (Fig. 6B).

The reference idrocilamide (**1**) did not show any significant effect on macrophage migration. Overall, the present findings suggest that idrocilamide derivatives (**2, 3, 4, 6,** and **9**) exert anti-inflammatory properties via reducing ROS production and macrophage migration.

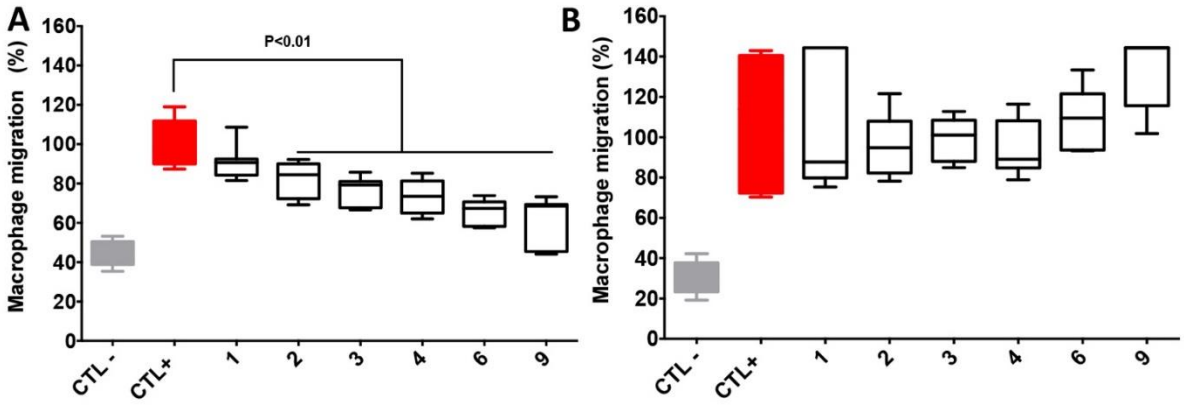


**Fig. 6** Effects of the compounds **1-4, 6, 9** on macrophage migration between epithelial cells to *C. albicans*. **A.** Analysis of macrophage migration pre-treated with molecules at a concentration of $10^{-5}$ mol/L. **B.** Analysis of macrophage migration pre-treated with molecules at a concentration of $10^{-6}$ mol/L. CTL- corresponds to macrophages alone. CTL+ corresponds to macrophage migration between epithelial cells to *C. albicans* without treatment with molecules.

## Conclusions

In summary, zinc-containing catalysts (zinc chloride, montmorillonite K10 impregnated with zinc (II) chloride-Cat1 and Cat2 and ecocatalysts Ecocat1 and Ecocat2) have been identified for efficient green synthesis of idrocilamide (**1**), marketed myorelaxant and anti-inflamatory agent. Ecocat2 was found to possess the best catalytic activity for the aminolysis reaction between methyl cinnamate and ethanolamine and provided the target molecule in 70% yield in solventless conditions. In addition, the recyclability of supported catalysts (Cat1, Cat2, Ecocat1 and Ecocat2) has been investigated in the synthesis of idrocilamide (**1**) over five distinctive runs.

Ecocat 2 has been further selected as privileged catalyst in additional aminolysis reactions to produce amides **4**, **6**, and **9** and in condensation of 5-methoxypyrrolidin-2-one with idrocilamide (**1**). The catalytic activity was systematically compared to that of commercial zinc chloride and highlighted the excellent catalytic power of ecocatalysts for amide linkage construction.

Synthesized molecules **1**-**4**, **6** and **9** have been submitted to biological evaluation of their antioxidant and anti-inflammatory potential *in vitro* in two assays: ROS generation from macrophages and macrophage migration between epithelia cells to *Candida albicans*. Interestingly, all molecules displayed improved activity compared to parent idrocilamide (**1**). The latter inhibited the ROS production at a concentration of 10µM but lost the activity at a concentration of 1µM while all other molecules **2**-**4, 6** and **9** conserved the inhibitory potential on ROS generation even at 1µM concentration. The same tendency was observed also in the macrophage migration between epithelial cells to *C. albicans*. Parent idrocilamide did not display any inhibitory potential at tested concentrations while molecules **2**-**4, 6** and **9** decreased the migration of macrophages when applied at a 10µM concentration.

Ultimately, this work provides new environmentally friendly methodology for the amide bond formation in organic chemistry and opens the way for the discovery of new analogues of marketed controversial idrocilamide (**1**) with improved antioxidant and anti-inflammatory activity.

## Experimental Section

### Materials and methods

Starting materials are commercially available and were used without further purification (suppliers: Carlo Erba Reagents S.A.S., Tokyo Chemical Industry Co. Ltd. and Acros Organics). Melting points were measured on a MPA 100 OptiMelt® apparatus and are uncorrected. Nuclear Resonance Magnetic (NMR) were acquired at 400 MHz for $^{1}$H NMR and at 100 MHz for $^{13}$C NMR, on a Varian 400-MR spectrometer with tetramethylsilane (TMS) as internal standard, at 25°C. Chemical shifts (δ) are expressed in ppm relative to TMS. Splitting patterns are designed: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; quint, quintuplet; br s, broaden singlet; br t, broaden triplet. Coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatography (TLC) was realized on Macherey Nagel silica gel plates with fluorescent indicator and were visualized under a UV-lamp at 254 nm and 365 nm. Column chromatography was performed with a CombiFlash R*f* Companion (Teledyne-Isco System) using RediSep packed columns. IR spectra were recorded on a Varian 640-IR FT-IR Spectrometer. Elemental analyses (C, H, N) of new compounds were determined on a Thermo Electron apparatus by "Pôle Chimie Moléculaire-Welience", Faculté des Sciences Mirande, Dijon, France.

**Synthesis of *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide (Idrocilamide, 1) without catalyst.** A mixture of methyl cinnamate (0.5 g, 3 mmol) and ethanolamine (0.19 mL, 3 mmol) was stirred at 70°C during 24h. After cooling to room temperature, the crude was purified by flash chromatography (EtOAc:*n*-heptane; 6:4) to provide pure *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide 1 as a white solid in 54% yield; mp 101-102°C (EtOAc); $R_f$ = 0.30 (EtOAc:*n*-Hept; 9:1); IR *v* (cm$^{-1}$): 3295, 1649, 1595, 1556, 1344, 1229. $^{1}$H NMR (400MHz, $CDCl_3$) *δ* (ppm): 3.55 (q, *J* = 5.7 Hz, 2H, $CH_2CH_2$), 3.78 (dd, *J* = 5.3, 4.9 Hz, 2H, $CH_2CH_2$), 6.46 (d, *J* = 15.7 Hz, 1H, CHCHCO), 6.59 (br t, *J* = 6.2 Hz, 1H, $NHCH_2$), 7.32-7.34 (m, 3H, Ar*H*), 7.46-7.48 (m, 2H, Ar*H*), 7.63 (d, *J* = 15.7 Hz, 1H, CHCHCO). $^{13}$C NMR (100 MHz, $CDCl_3$) *δ* (ppm): 42.8 ($CH_2$), 62.4 ($CH_2$), 120.4 (CH), 128.0 (CHx2), 129.0 (CHx2), 129.9 (CH), 134.8 (C), 141.7 (CH), 167.3 (C).

**Synthesis of *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide (Idrocilamide, 1) in presence of $ZnCl_2$ as catalyst.** A catalytic amount of $ZnCl_2$ (21 mg, 0.15 mmol) was added to a mixture of methyl cinnamate (0.5 g, 3 mmol) and ethanolamine (0.19 g, 3 mmol) is added. The mixture was stirred at 70°C during 24h. After cooling to room temperature, the crude was solved in $CH_2Cl_2$ (25mL) and washed with water (3x20mL). The organic layers were concentrated under vacuum and the resulting crude was purified by flash chromatography (EtOAc:*n*-heptane; 6:4) to provide pure *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide (**1**) in 75% yield.

**Synthesis of *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide (Idrocilamide, 1) in presence of $ZnCl_2$-impregnated MK10 (Zn-MK10, Cat 1 and Cat2) or Ecocatalysts (Ecocat 1 and Ecocat 2) as catalysts.** A catalytic amount of catalyst (216 mg, 0.15 mmol) was added to a mixture of methyl cinnamate (0.5 g, 3 mmol) and ethanolamine (0.19 mL, 3 mmol). The medium was stirred at 70°C during 24h. After cooling to room temperature, the crude was solved in ethyl acetate (25mL) and filtered to recover the supported catalyst. The filtrate was concentrated under vacuum and the resulting crude was purified on flash chromatography (EtOAc:*n*-heptane; 6:4) to provide pure *N*-(2-hydroxyethyl)-3-phenyl-2-propenamide (**1**) in 46 to 70% yield.

**Ethyl 3-phenyl-2-[(1-oxo-3-phenyl-2-propen-1-yl)amino]-2-propenoate 2**. By-product from the synthesis of idrocilamide (**1**); 5% yield; white solid; mp 80-84°C (EtOAc); $R_f$ = 0.88 (EtOAc:*n*-Hept; 9:1); IR *v* (cm$^{-1}$): 3371, 3288, 3026, 2953, 1708, 1622, 1532, 1165. $^{1}$H NMR (400MHz, $CDCl_3$) *δ* (ppm): 3.75 (q, *J*

= 5.6 Hz, 2H, NHC$H_2$C$H_2$), 4.39 (t, *J* = 5.2 Hz, 2H, NHCH$_2$C$H_2$O), 6.09 (br t, *J* = 5.2 Hz, 1H, N*H*CH$_2$CH$_2$O), 6.42 (d, *J* = 15.6 Hz, 1H, C*H*CHCOO), 6.47 (d, *J* = 15.6 Hz, 1H, C*H*CHCONH), 7.29-7.43 (m, 6H, Ar*H*), 7.49-7.54 (m, 4H, Ar*H*), 7.65 (d, *J* = 15.6 Hz, 1H, CHC*H*COO), 7.73 (d, *J* = 15.6 Hz, 1H, CHC*H*CONH). $^{13}$C NMR (100 MHz, CDCl$_3$) *δ* (ppm): 39.4 (CH$_2$), 63.6 (CH$_2$), 117.5 (CH), 120.4 (CH), 128.0 (CHx2), 128.3 (CHx2), 129.0 (CHx2), 129.1 (CHx2), 129.9 (CH), 130.7 (CH), 134.3 (C), 134.9 (C), 141.6 (CH), 145.8 (CH), 166.1 (C), 167.3 (C). Anal. Calcd. For $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.58; H, 6.08; N, 4.54%.

***N*-(2-((5-Oxopyrrolidin-2-yl)oxy)ethyl)cinnamamide (3)**. 5-Methoxypyrrolidine (0.45 g, 4 mmol) was added to a mixture of idrocilamide (**1**) (0.75 g, 4 mmol) and zinc (II) chloride (26.7 mg, 0.20 mmol) and the resulting mixture was stirred at 80°C during 24h. After cooling to room temperature, the crude was solved in $CH_2Cl_2$ (25mL) and washed with water (3x20mL). The organic layers were concentrated under vacuum and the resulting crude was purified by flash chromatography (EtOAc:*n*-heptane; 5:5 to 100:0) to provide pure *N*-(2-((5-oxopyrrolidin-2-yl)oxy)ethyl)cinnamamide (**3**) in 31% yield; white solid; mp 113-116°C (EtOAc); $R_f$ = 0.09 (EtOAc:*n*-Hept; 9:1); IR *ν* (cm$^{-1}$): 3304, 3184, 2902, 1702, 1662, 1630, 1531, 1284, 1213. $^1$H NMR (400MHz, CDCl$_3$) *δ* (ppm): 1.99-2.07 (m, 1H, CH$_2$C$H_2$CH), 2.18-2.31 (m, 2H, C$H_2$CH$_2$CH), 2.45-2.55 (m, 1H, CH$_2$C$H_2$CH), 3.51-3.66 (m, 4H, NHC$H_2$C$H_2$O), 4.99 (d, *J* = 5.8 Hz, 1H, CONHC*H*), 6.50 (d, *J* = 15.4 Hz, 1H, C*H*CHCO), 6.72 (br t, *J* = 4.8 Hz, 1H, CHCON*H*CH$_2$), 7.32-7.34 (m, 3H, Ar*H*), 7.47-7.50 (m, 2H, Ar*H*), 7.63 (d, *J* = 15.4 Hz, 1H, CHC*H*CO), 8.06 (br s, 1H, CON*H*CHCO). $^{13}$C NMR (100 MHz, CDCl$_3$) *δ* (ppm): 28.0 (CH$_2$), 28.5 (CH$_2$), 39.6 (CH$_2$), 66.0 (CH$_2$), 86.5 (CH), 120.1 (CH), 127.9 (CHx2), 128.9 (CHx2), 129.8 (CH), 134.9 (C), 141.1 (CH), 166.4 (C), 179.5 (C). Anal. Calcd. For $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.73; H, 6.70; N, 10.90%.

***N*-Propyl-3-phenyl-2-propenamide (4)**. A catalytic amount of Ecocat2 (252 mg, 0.3 mmol) was added to a mixture of methyl cinnamate (1.0 g, 6 mmol) and propylamine (0.36 g, 6 mmol). The mixture was stirred at 70°C during 24h. After cooling to room temperature, the crude was solved in ethyl acetate (50 mL) and filtered to recover the ecocatalyst. The filtrate was concentrated under vacuum and the resulting crude was purified by flash chromatography (EtOAc:*n*-heptane, 5:5 to 100:0) to provide pure *N*-propyl-3-phenyl-2-propenamide **(4)** in 48% yield; brown solid; mp 75-78°C (EtOAc); $R_f$ = 0.61 (EtOAc:*n*-Hept; 6:4); IR *ν* (cm$^{-1}$): 3262, 2968, 2361, 1652, 1610, 1548, 1341, 1221. $^1$H NMR (400MHz, CDCl$_3$) *δ* (ppm): 0.96 (t, *J* = 7.2 Hz, 3H, CH$_2$CH$_2$C$H_3$), 1.60 (sext, *J* = 6.8 Hz, 2H, CH$_2$C$H_2$CH$_3$), 3.36 (q, *J* = 7.2 Hz, 2H, C$H_2$CH$_2$CH$_3$), 5.81 (br s, 1H, CON*H*CH$_2$), 6.41 (d, *J* = 15.6 Hz, 1H, ArC*H*CHCO), 7.34-7.35 (m, 3H, Ar*H*), 7.48-7.50 (m, 2H, Ar*H*), 7.62 (d, *J* = 15.6 Hz, 1H, ArCHC*H*CO). $^{13}$C NMR (100 MHz, CDCl$_3$) *δ* (ppm): 11.6 (CH$_3$), 23.1 (CH$_2$), 41.6 (CH$_2$), 121.0 (CH), 127.9 (CHx2), 128.9 (CHx2), 129.7 (CH), 135.0 (C), 140.9 (CH), 166.0 (C). The physico-chemical properties correspond to those described in the literature.[30]

**(2*E*)-3-Phenyl-*N*-[(1*R*)-1-phenylethyl]-2-propenamide (6)**. A catalytic amount of Ecocat2 (126 mg, 0.15 mmol) was added to a mixture of methyl cinnamate (0.5 g, 3 mmol) and (*R*)-(+)-methylbenzylamine (0.39 mL, 3 mmol). The mixture was stirred at 70°C during 24h. After cooling to room temperature, the crude was solved in ethyl acetate (50 mL) and filtered to recover the ecocatalyst. The filtrate was concentrated under vacuum and the resulting crude was purified by flash chromatography (EtOAc:*n*-heptane, 50:50 to 100:0) to provide pure (2*E*)-3-Phenyl-*N*-[(1*R*)-1-phenylethyl]-2-propenamide **(6)** in 40% yield; white solid; mp 139-141°C (CH$_2$Cl$_2$); $R_f$ = 0.57 (EtOAc:*n*-Hept; 5:5); IR *ν* (cm$^{-1}$): 3306, 1652, 1620, 1541, 1224. $^1$H NMR (400MHz, CDCl$_3$) *δ* (ppm): 1.41 (d, *J* = 6.8 Hz, 3H, CHC$H_3$), 5.05 (quint, *J* = 7.8 Hz, 1H, C*H*CH$_3$), 6.71 (d, *J* = 15.6 Hz, 1H, C*H*CHCO), 7.21-7.26 (m, 1H, Ar*H*), 7.33 (d, *J* = 3.1 Hz, 2H, Ar*H*), 7.37-7.43 (m, 5H, Ar*H*), 7.42 (d, *J* = 15.6 Hz, 1H, CHC*H*CO), 7.55 (d, *J* = 7.1 Hz, 2H, Ar*H*), 8.55 (d, *J* = 8.4 Hz, 1H, CON*H*CH). $^{13}$C NMR (100 MHz, DMSO-$d_6$) *δ* (ppm): 22.5 (CH$_3$), 48.0 (CH), 122.3 (CH), 126.0 (CHx2), 126.7 (CH), 127.5 (CHx2), 128.3 (CHx2), 128.9 (CHx2), 129.4 (CH), 134.9 (C), 128.8 (CH), 144.5 (C), 164.0 (C). The physico-chemical properties correspond to those described in the literature.[31]

***N*-(2,4-dichlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (9).** A catalytic amount of Ecocat2 (45 mg, 0.055 mmol) and 2,4-dichloroaniline (178 mg, 1.1 mmol) were added to a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (300 mg, 1.1 mmol) in *o*-xylene (5 mL). The mixture was stirred at reflux for 47h. After cooling to room temperature, the crude was filtered to recover the ecocatalyst. The filtrate was concentrated under vacuum and the resulting crude was purified by flash chromatography (CH$_2$Cl$_2$:MeOH, 100:0 to 90:10) to provide pure *N*-(2,4-dichlorophenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (**9**) in 27% yield; orange solid; mp 232-234°C (CH$_2$Cl$_2$); $R_f$ = 0.53 (EtOAc:*n*-Hept; 65:35); IR *ν* (cm$^{-1}$): 3365, 1633, 1580, 1520, 1344, 1178. $^1$H NMR (400MHz, CDCl$_3$) *δ* (ppm): 2.92 (s, 3H, NC$H_3$), 3.42 (br s, 1H, O*H*), 7.51 (dd, *J* = 8.4, 2.2 Hz, 1H, Ar*H*), 7.65 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.78 (d, *J* = 2.3 Hz, 1H, Ar*H*), 7.87-7.95 (m, 3H, Ar*H*), 8.04 (d, *J* = 6.5 Hz, 1H, Ar*H*), 10.41 (br s, 1H, N*H*Ar). $^{13}$C NMR (100 MHz, DMSO-$d_6$) *δ* (ppm): 40.2 (CH$_3$), 111.4 (CH), 124.2 (CH), 126.3 (CH), 127.8 (CH), 127.8 (C), 129.1 (CH), 129.9 (C), 130.9 (C), 131.8 (C), 132.7 (C), 133.2 (CH), 133.6 (CH), 134.2 (C), 157.2 (C), 167.3 (C).

**Cell lines and yeast culture.**

The human monocytic THP-1 cells were incubated in RPMI 1640 medium (Gibco by LifeTechnologies™, France) supplemented with 10% fetal bovine serum (FBS; Gibco, France), 50 IU/mL penicillin, and 50 IU/mL streptomycin. THP-1 cells were differentiated into macrophages in the presence of phorbol-12-myristate 13-acetate (PMA, 25 nmol/L, Sigma-Aldrich, France) at 37°C and 5% $CO_2$. Caco-2 cells were grown in Dulbecco's modified Eagle medium (DMEM) (Sigma-Aldrich, France), supplemented with 20% FBS, 50 IU/mL penicillin and 50 IU/mL streptomycin at 37 °C and 5% $CO_2$. *C. albicans* strain SC5314 was used in this study and maintained at 4 °C in yeast peptone dextrose broth (YPD; 1% yeast extract, 2% peptone, 2% dextrose). To prepare the yeast suspension, *C. albicans*

cells were cultured in Sabouraud dextrose broth (Sigma-Aldrich, St. Quentin Fallavier, France) for 24 h at 37°C in a rotary shaker.[32]

**Migration assay.**

A migration assay was performed as described previously.[33,34] Caco-2 cells were grown to confluence at a cell density of 200,000 cells/mL in upper chamber of the transwell devices (Costar Transwell inserts in a 96-well plate format) for 48 h in DMEM (Sigma-Aldrich, France) and 20% FBS. After 48h incubation, DMEM was removed, and 150 µL containing 5x105 calcein-labeled washed PMA-differentiated THP-1 macrophage cells and pre-treated with the molecules (at concentration of $10^{-5}$ or $10^{-6}$ mol/L) were added to Caco-2 cells in the upper chamber of the transwell devices. A volume of 150 µL RPMI containing $10^5$ *C. albicans* yeast cells was added to the lower chamber. Plates were placed in a humidified incubator at 37°C and 5% $CO_2$ for 8h. After migration, non-migrated cells were removed from upper chamber of transwell inserts, and the migrated macrophages present on *C. albicans* strains were assessed by measuring fluorescence using a fluorometer (FLUOstar® Omega (BMG Labtech).

**ROS Assay.**

Macrophages ($5x10^5$ cells) were plated in 96-well plates, pretreated with molecules **1**-**4,6,** and **9** at concentration $10^{-5}$ or $10^{-6}$ mol/L and exposed to 10 µmol/L of LPS recruiting a signaling pathways through TLR4 to induce ROS (Sigma-Aldrich, France), incubated at 37°C and 5% $CO_2$ in 100 µL RPMI 1640 medium supplemented with 10% fetal bovine serum. A volume of 50 µL of a mixture of 50 µg/mL horseradish peroxidase and 50 µM luminol were added to each well. The chemiluminescence was measured at different incubation times, 0h, 1h, 2h, 3h, and 4h in a FLUOstar Omega Fluorometer (BMG Labtech). $H_2O_2$ alone without macrophages at a low concentration 1.7 mol/L was used as a positive control.

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## Conflict of Interest

The authors declare no conflict of interest.

**Keywords:** ecocatalyst • idrocilamide • amide • antioxidant • green chemistry

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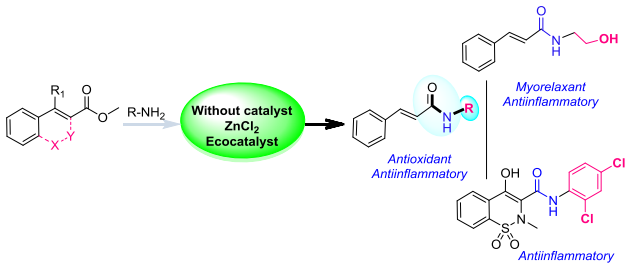


The work given herein involves new environmental eco-friendly approach for the synthesis of amide function tethered to idrocilamide and derivatives with improved antioxidant and anti-inflammatory activity. Interesting idrocilamide prodrug was also explored under these greener conditions using intramolecular trapping of the *N*-acyliminium species.

**Green amidation**

*P. Dufrénoy, R. Charlet, M. Hechelski, A. Daïch, C. Waterlot, S. Jawhara and A. Ghinet**

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***New efficient eco-friendly supported catalysts for the synthesis of amides with antioxidant and anti-inflammatory properties***