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Biomass of ryegrass from field experiments: toward a cost-effective and efficient biosourced catalyst for the synthesis of Moclobemide

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ABSTRACT

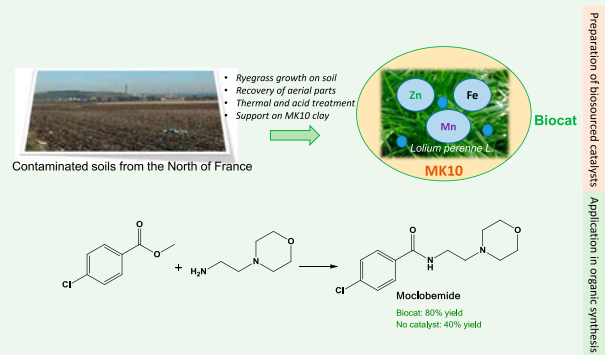
Lolium perenne L., a common plant perennial ryegrass from Europe, northern Africa and Asia, was selected to produce biomass under field conditions. The biomass of this nonfood crop was from a highly contaminated agricultural soil by potentially toxic metals (Cd, Pb and Zn) with the aim of maintaining the agricultural vocation of these soils. In this perspective and in view of the metal concentration (Cd, Pb, Zn, macro- and micro-nutrients), the biomass of ryegrass was considered as a bio 'ore' resource and was used as the starting material for the preparation of contemporary biosourced catalysts. The heterogeneous catalyst from the current work was successfully used in the synthesis of Moclobemide, used to treat anxiety and major depressive episodes. Through this original approach, Moclobemide was synthesized in one step, in 80% yield under solvent-free conditions.

ARTICLE HISTORY

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KEYWORDS



Field experiment; ryegrass; biosourced catalyst; moclobemide; aminolysis



Introduction

The design of chemicals and their processes represent a major global challenge in both economic and environmental terms. Limiting the use of hazardous products constitutes currently one of the main objectives when industrials develop innovative chemical processes to synthesize new organic or inorganic compounds. The major challenge for industrials is to avoid the use of hazardous products for cleaner chemistry. The term 'green chemistry' reflects this vocation to protect the environment but also to create economic benefits and to fit into a circular economy process (1). In this

regard, catalysis is one of the fundamental pillars of the 12 principles of green chemistry (2). Many reactions need to be catalyzed thanks to organic or inorganic catalysts to produce high added-value molecules with high selectivity while reducing the number of toxic compounds, steps as well as separating agents (2). To fit into green chemistry, these catalysts must be robust, cost-effective, non-toxic and if possible, re-usable. The main objective of the current study was to use a new generation of catalysts in order to synthesize formally the anti-depressant Moclobemide. This molecule, named (4-chloro-*N*-(2-morpholin-4-ylethyl)benzamide) constitutes

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the active ingredient of the marketed Amira[®], Aurorix[®], Clobemix[®], Depnil[®], Manerix[®] and Moclamide[®] drugs. The title amide is a reversible inhibitor of monoamine oxidase A (MAO) (3). The resulting inhibition has as consequence the increase of the cerebral concentration of the monoaminergic mediators. Indeed, according to the mechanism of action, Moclobemide decreases the catabolism of norepinephrine, serotonin and, to a lesser degree, dopamine. Moclobemide is used to treat major depressive episodes and anxiety.

Recently, new catalysts, called 'ecocatalysts', have been developed and are involved in many reactions (4). Taking advantage of the hyperaccumulating plants biomass, these ecocatalysts (Eco-Mn[®], Eco-Zn[®], Eco-Cu[®]) are produced from metals found in the biomass. This approach is very interesting since it affords good yields, high regio- and stereo-selectivity, low catalytic loading and the possibility of recycling these catalysts under mild conditions (5, 6). However, these hyperaccumulating plants are: (i) often small in size (e.g. *Anthyllis vulneraria* L.), which requires specific tools to harvest them, (ii) endemic to a specific geographical region (i.e. *Grevillea exul* Lindley) (7), (iii) unusual plants in some regions (e.g. *Noccaea caerulea* (J.Presl & C.Presl) F.K.Mey, *Bacopa monnieri* (L.) Wettst) and (iv) not recommended for a production in large-scale contaminated soils due to the lack of seeds.

Other plants, called 'metal tolerant plants' can also grow on metal contaminated soils while concentrating significant amount of metals (8). Among these, *Lolium perenne* L., ubiquitous plant easy to grow, harvest and spread throughout Europe, Asia and northern Africa, is known for its phytomanagement ability in field-experiments (9). An original transformation of the ryegrass biomass into biosourced catalyst was thus investigated in the current work and a green, solventless and ecocatalyzed synthesis of Moclobemide via aminolysis reaction was conducted. To the best of our knowledge, only one similar amidation reaction was tested to obtain this target drug (10).

Material and methods

Study site and plant cultivation

The study site (latitude: N 50° 26' 18"; longitude: E 3° 0' 53") is located near the former Metaleurop Nord plant, a lead smelter which ceased operations in October 2003 after 110 years of industrial activity. This site was contaminated by potentially toxic metals (PTMs) due to the past atmospheric deposition of contaminated dusts. Nevertheless, the main contamination is limited to the ploughed layer (0-25 cm) of the agricultural

soils. Seeds of *Lolium perenne* L. (Seed company: Carneau; variety: Cantalou) were sown on the soil surface. For this preliminary study, quadrats (40 × 40 cm; n=9) were established regularly within the study site. The growth period lasted 8 weeks in the summer period (May-June 2018).

Digestion of plant and soil sample analyses

Plant digestion

0.3 g of dry plant samples (crushed and sieved to < 315 μm) were put into a 50-mL digestion tube and 5 mL of HNO₃ (69%) were added. In a first step, the reaction medium was heated at 65 ± 5°C in a hot block digester (DigiPREP MS, SCP Science) for 20 min and then, at 90 ± 5°C for 45 min. After heating, 1.2 mL of deionized water and 1.8 mL of H₂O₂ (30%) were slowly added in the cooled solution and the mixture was heated at 90 ± 5°C for 45 min. Finally, the mixture was cooled at room temperature and the volume was adjusted to 25 mL with deionized water. Each digested-solution was filtered over an acetate Millipore membrane (0.45 μm porosity) and stored in acid-washed plastic bottles at 4 °C prior to analysis.

Each plant sample was dried at 105°C in a muffle oven (P 330, Nabertherm) till a constant mass in order to determine the residual moisture content. A correction to dry mass was obtained and was thus applied to the reported metal concentrations (Cd, Pb, Zn, Cu, Mn, Fe, Ca, Mg, Na and K). A calcination of plant samples was then conducted at 500°C for 8 h to obtain ashes. The metal concentrations in ashes were then expressed at 500°C.

Soil digestion

0.3 g of dry soil sample (dried at 40 °C, crushed and sieved at <250 μm) was placed in a digestion tube with 3 mL of HNO₃ (69%) following the USEPA 3050 B method. The mixture was first heated at 95 ± 5°C for 2 h and 45 min in the hot block digester. After cooling, 0.9 mL of H₂O₂ (30%) and 0.6 mL of deionized water were slowly added to the solution and the reaction medium was heated for 15 min. Then, 3 mL of HCl (37%) were added in the cooled solution and the mixture was heated again for 15 min. After cooling, the volume was adjusted to 25 mL with deionized water and the mixture was filtered over an acetate Millipore membrane (0.45 μm porosity). Samples were then stored at 4°C before analysis.

Metal analysis

The concentration of PTMs (Cd, Pb, Zn, Cu, Mn and Fe), alkali (Na and K) and alkali earth metals (Ca and Mg) in

soil and plant digests were determined by flame atomic absorption spectrometry (AA-6800, Shimadzu, Tokyo, Japan) following the recommendations described in the literature. High-intensity boosted-discharge hollow-cathode Cd, Pb and Zn lamps (Hamamatsu, Iwata, Japan) were used to avoid spectral interferences (11, 12). For Cu, Mn, Fe, Na, K, Ca and Mg, lamps were operated between 6 and 12 mA and a deuterium lamp (D2 lamp) was used for the background correction.

Determination of soil parameters

Soil pH was measured according to the NF ISO 10390 method (13) and total carbonates were determined by measuring the release of CO₂ by means of a Bernard calcimeter and resulting from the reaction between HCl and carbonates (14).

Preparation of the biosourced catalyst (Biocat)

Ashes from ryegrass biomass were mixed in 2M HCl (ratio solid:liquid 1:10) for 2 h at 70°C. After cooling, the mixture was filtered on celite and the filtrate was evaporated to dryness. The residue was dried at 80°C for 12 h and then mixed with montmorillonite K10 in dry methanol to obtain 1.22 mmol Zn per g of support (15). Activation of this catalyst was performed at 120°C overnight (15).

Synthesis of Moclobemide by aminolysis reaction and physico-chemical characterization

Starting materials were commercially available and were used without further purification (suppliers: Carlo Erba Reagents S.A.S., and Fisher Scientific). Moclobemide was obtained by simple aminolysis reaction between a methyl ester, here methyl 4-chlorobenzoate **1** (1 g, 5.86 mmol) and corresponding amine, the 4-(2-aminoethyl)morpholine **2** (0.77 mL, 5.86 mmol), in equimolar ratio, under magnetic stirring and heating for 24 h at 40°C or at 100°C. Target product has been isolated in 40% (0.63 g) and 80% yield (1.26 g), respectively after flash liquid chromatography purification on Combiflash Companion RF200 (Serlabo Technologies, Entraigues) equipped with prepacked silica column (CHROMABOND column Flash RS 25 SiOH, 25 g of adsorbant) purchased from Macherey-Nagel using a gradient of *n*-heptane/ethyl acetate 100/0–0/100 as the mobile phase.

Melting point was measured on an MPA 100 Opti-Melt® apparatus. Thin layer chromatography (TLC) was performed on Macherey Nagel silica gel plates with fluorescent indicator and was visualized under a UV-lamp at 254 and 365 nm. The retention factor (R_f) of Moclobemide was determined using a mixture of

dichloromethane and methanol (97:3) as mobile phase. IR spectrum was recorded on a Varian 640-IR FT-IR Spectrometer. Nuclear Magnetic Resonance (NMR) spectra were acquired at 400 MHz for ¹H NMR and at 100 MHz for ¹³C NMR, on a Varian 400-MR spectrometer at 25°C with tetramethylsilane (TMS) as internal standard, at 25°C and in CDCl₃. Chemical shifts (δ) are expressed in ppm relative to TMS. Splitting patterns are designed: s, singlet; d, doublet; t, triplet; q, quadruplet. Coupling constants (J) are reported in Hertz (Hz).

Results and discussion

Soil properties and concentration of metals in plant samples

The agricultural soils around the former Metaleurop Nord smelter develop mainly on loessic materials (16). The studied soil is silt loam. The pH of this soil was slightly alkaline (7.86 ± 0.04), the soil was poorly calcareous (16.6 ± 3.3 g kg⁻¹) and the organic matter contents were relatively high (6.18 ± 0.32%) probably due to the agricultural history of the soil. The average concentration of PTMs in the soil samples were 11.0 ± 0.4 mg Cd kg⁻¹, 486 ± 18 mg Pb kg⁻¹ and 815 ± 67 mg Zn kg⁻¹.

The concentrations of PTMs, alkali and alkali earth metals were summarized in Table 1. The results showed that the most phytoavailable metals were Fe (296 ± 120 mg kg⁻¹) and Zn (147 ± 43 mg kg⁻¹) whereas the least were Cd (2.60 ± 0.45 mg kg⁻¹) and Pb (14.2 ± 3.9 mg kg⁻¹), both of them being known as carcinogenic, mutagenic and reprotoxic substances. As reported in Table 1, the concentrations of alkali and alkali earth metals are greater than PTMs. The concentrations of these metals in the shoots of ryegrass were in the following order K > Ca > Mg > Na (Table 1). This ranking may be explained by the fact that K is a primary nutrient and was defined as the most important element for plant nutrition whereas Na is a non-essential metal for plants (17). The concentration of Ca is lesser than that of K but higher than Mg. Interestingly, the ratio K/(Ca + Mg) was higher than 1 for all plant samples, indicating a higher absorption of monovalent over divalent cations (18).

In view of our objectives, Lewis acids (LA) from Zn, Cu, Mn and Fe are of great interest in organic synthesis. The ratios LA/Cd and LA/Pb were 200 ± 65 and 36 ± 8, respectively. On the other hand, the average concentrations of Ca and Mg in ashes at 5.4% and 2.2%, respectively, should contribute to the reactivity of the biosourced catalyst since Ca and Mg derivatives are also important catalysts in organic synthesis.

Application of the biosourced catalyst in the synthesis of Moclobemide

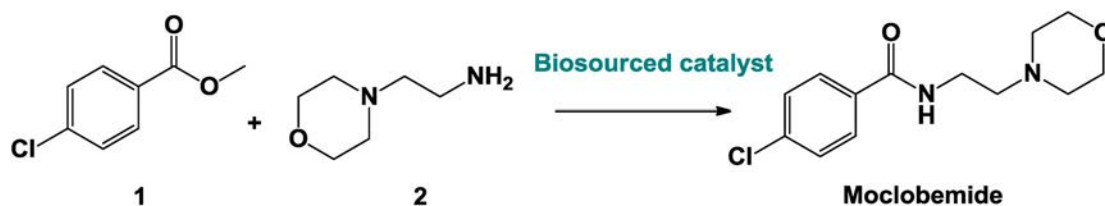
Five main synthetic strategies have been applied to synthesize this molecule. The most studied was the reaction between 4-chlorobenzoic acid and 2-morpholin-4-ylethanamine in the presence of various catalysts as tetramethyl orthosilicate (TMOS) (19), diphenylphosphoryl azide (DPPA)/Et₃N (20), bis(pentamethylcyclopentadienyl) zirconium perfluorooctanesulfonate (21) or zirconocene dichloride (ZrCp₂Cl₂) (22) in different solvents such as toluene, dichloromethane or tetrahydrofurane to provide target molecule in 85–100% yield. The second synthetic pathway used 4-chlorobenzoic acid chloride and 2-morpholin-4-ylethanamine in the presence of triethylamine (3 eq.) in dichloromethane (23), disodium carbonate or sodium hydroxide (24) to provide Moclobemide in 35–95% yield. The third strategy was a transamidation of 4-chlorobenzoic amide in presence of 2-morpholin-4-ylethanamine catalyzed by mesoporous niobium oxide spheres (Nb₂O₅) at 160°C under argon atmosphere and allowed the synthesis of Moclobemide in 90% yield (25). The fourth method was based on the reaction between *p*-chlorobenzonitrile (1 eq.) and 2-morpholin-4-ylethanamine (8 eq.) with 10% mol of iron nitrate nonahydrate (Fe(NO₃)₃·9H₂O) as catalyst under heating (125°C) for 24 h. The conversion was 71% and Moclobemide was isolated in 54% yield (26). Finally, a recent procedure reported the synthesis of the title compound in 90% yield using methyl 4-chlorobenzoate (1 eq.) and 2-morpholin-4-ylethanamine (2 eq.) and necessitating an excess of strong base LiHMDS (3 eq.) in THF (10). In the current study, Moclobemide was obtained from an equimolar mixture of methyl 4-chlorobenzoate **1** and 2-morpholin-4-ylethanamine **2** in the presence of the biosourced catalyst (Scheme 1). The reaction was conducted under two temperature conditions (40°C and 100°C) and blank was made to evaluate the effect of our biosourced catalyst on the reaction rate and yield. For the four conditions, an equilibrium was reached 24 h after the beginning of the reaction. The reaction yields at 40°C were below 5% in the absence of catalyst and 40% in the presence of biocatalyst whereas they were 25% and up to 80% at 100°C, respectively. The melting point of Moclobemide was 141°C and the retention factor (Rf) was 0.31. The characteristic infrared bands were 3276, 2969, 2943, 2812, 1634, 1541, 1486, 1310, 1116 cm⁻¹ (Figure 1) and the nuclear magnetic resonance (NMR) of the nuclei ¹H and ¹³C (Figures 2A and B) were described hereafter.

¹H NMR (CDCl₃) δ (ppm): 2.50 (t, *J* = 4.4 Hz, 4H, O(CH₂)₂), 2.60 (t, *J* = 6.0 Hz, 2H, NHCH₂CH₂), 3.54 (q, *J* = 6.0 Hz, 2H, NHCH₂CH₂), 3.73 (t, *J* = 4.8 Hz, 4H, N(CH₂)₂),

Table 1. Concentrations of metals in the shoots of ryegrass (dry weight) and in ashes^a (*n*=9).

	Cd (mg kg ⁻¹)	Pb (mg kg ⁻¹)	Zn (mg kg ⁻¹)	Cu (mg kg ⁻¹)	Mn (mg kg ⁻¹)	Fe (mg kg ⁻¹)	Na (g kg ⁻¹)	Mg (g kg ⁻¹)	Ca (g kg ⁻¹)	K (g kg ⁻¹)
<i>L. perenne</i> at 105 °C	2.60 ± 0.45	14.2 ± 3.9	147 ± 44	13.5 ± 1.0	43 ± 9	296 ± 120	1.0 ± 0.3	3.1 ± 0.6	7.5 ± 1.3	33.2 ± 4.5
Ashes	18.2 ± 2.46	150 ± 87	955 ± 277	103 ± 9	324 ± 51	2280 ± 936	7.2 ± 2.1	22.1 ± 5.9	53.9 ± 13.9	238.4 ± 54.9

^aAshes were obtained after heating the dry plant samples at 500 °C for 8 h.



Scheme 1. Synthesis of Moclobemide from methyl-4-chlorobenzoate (1) and 4-(2-aminoethyl)morpholine (2).

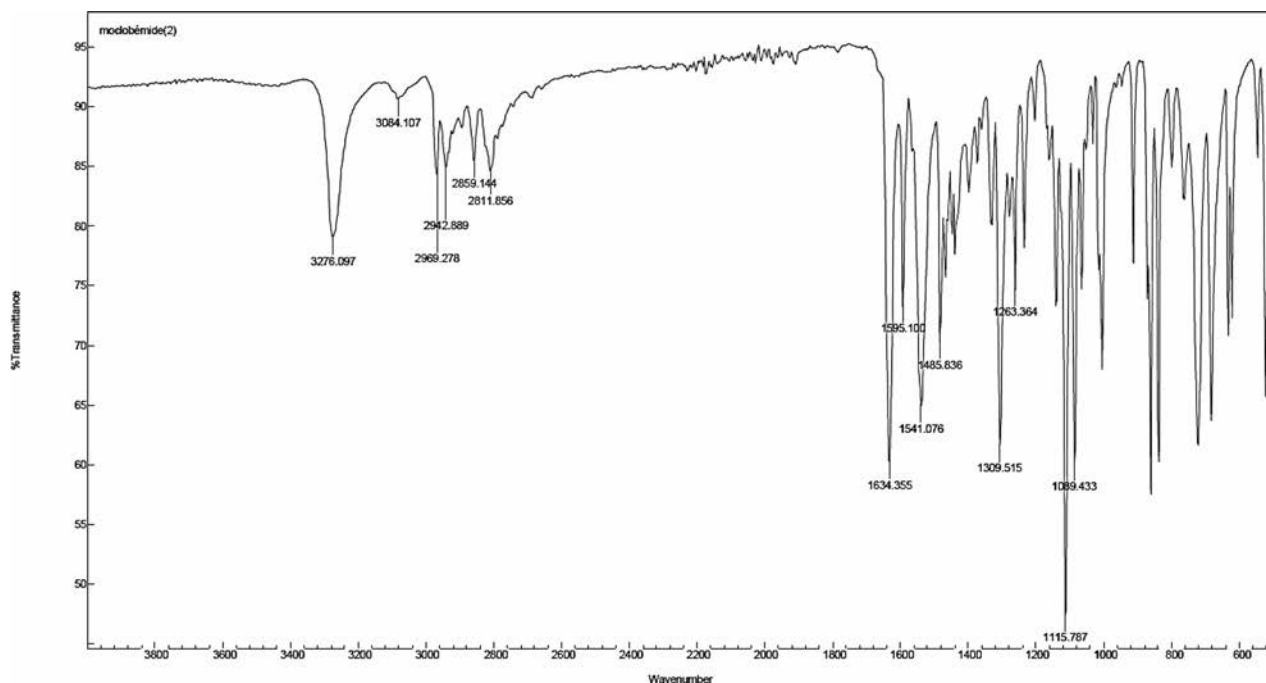


Figure 1. Infrared spectrum of Moclobemide.

6.78 (br s, 1H, CONH), 7.41 (d, $J = 8.4$ Hz, 2H, ArH), 7.71 (d, $J = 8.4$ Hz, 2H, ArH).

^{13}C NMR (CDCl_3) δ (ppm): 36.2 (CH_2), 53.4 ($\text{CH}_2 \times 2$), 56.9 (CH_2), 67.1 ($\text{CH}_2 \times 2$), 128.5 ($\text{CH} \times 2$), 128.9 ($\text{CH} \times 2$), 133.1, 137.7 (C), 166.4 (CO).

From a thermodynamic point of view, these results highlighted the necessity of our biosourced catalyst to displace the reaction equilibrium toward the formation of Moclobemide under the studied conditions. On the other hand, they revealed that this reaction was an endothermic reaction since the temperature had a positive effect on the reaction yield. It is worth mentioning that this reaction was (i) conducted in one-step, (ii) solventless, (iii) under non-specific atmosphere conditions (e.g. argon, nitrogen), and so, was in line with the principles of green chemistry. These advantages may have substantial impacts to industrial processes while being part of an active environmental approach. Additional studies must be investigated to evaluate the recyclability of biosourced catalyst.

Next, the green metrics of the current eco-catalyzed synthetic route were calculated and compared to those of previously reported procedures. Results of the main green metrics (yield, Atom Economy (AE), Waste, Reaction Mass Efficiency (RME) and Environmental Factor (E -Factor)) for all syntheses discussed in this manuscript are presented in Table 2. AE defines the percentage of reactants engaged in the reaction process that may be considered as waste materials. Reaction Mass Efficiency (RME) measures how efficiently the mass of reactant ends up in the desired product and does not include catalysts, solvents, or other reactants not specifically in the balanced chemical equations of the process. The E -Factor shows how effective the overall production capability is by comparing the amount of waste generated by the process with the amount of desirable product that is created. The lower E -Factor, the more efficient and greener the process is (27).

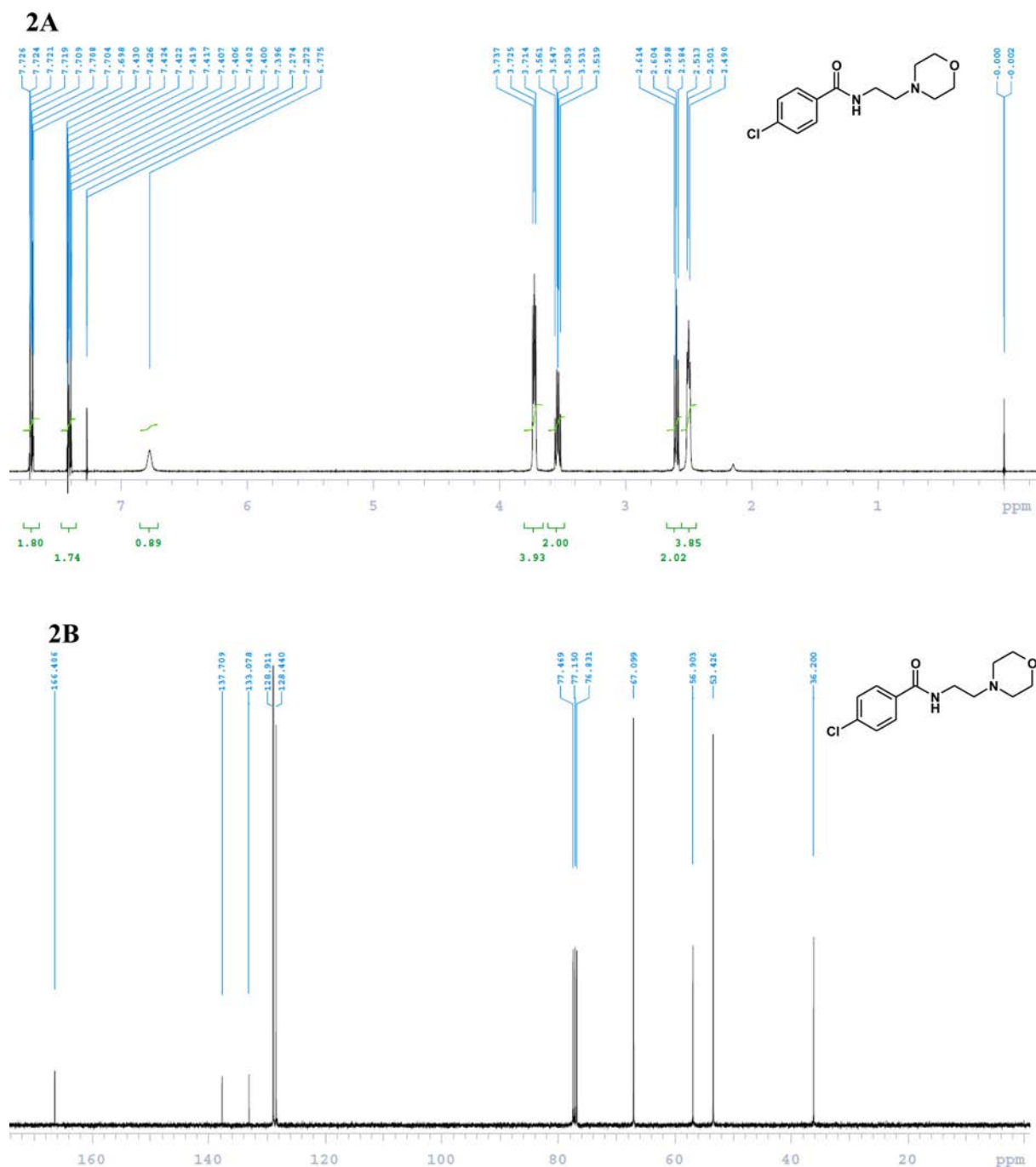


Figure 2. Nuclear magnetic resonance (NMR) spectrum of Moclobemide: 2A: ^1H NMR, 2B: ^{13}C NMR.

The analysis of these parameters calculated for different reported procedures and for the current eco-catalyzed process highlighted the fact that the high yield of moclobemide did not imply favorable green metrics and was insufficient to conclude on the environmental aspect of the processes. The most eco-friendly procedures proved to be those described in entries 3 (21), 4 (22) and 10 (this study) (Table 2). Our method was the third-best regarding the AE, waste, RME and *E*-Factor. However, it is important to note that even if

the biosourced catalyst showed slightly reduced catalytic activity, thanks to its heterogeneous nature, it was recovered and reused at the end of the reaction. The biosourced ryegrass catalyst showed good catalytic performance up to 5 cycles of utilization. It was tested only on 5 runs of the same chemical transformation. At the end of the 5th run, re-used biosourced catalyst still allowed moclobemide formation (47%), which was much higher compared to the reaction carried out without catalyst (25%).

Table 2. Calculated main green chemistry metrics of representative synthetic pathways described to produce moclobemide and of current ecocatalyzed procedure.

Entry	Reference	Yield (%)	AE (%)	Waste (%)	RME (%)	E-Factor
1	Braddock <i>et al.</i> 2018 (19)	100	45.5	54.5	45.5	1.13
2	Bodnar <i>et al.</i> 2015 (20)	100	27.0	73.0	27.0	2.63
3	Li <i>et al.</i> 2018 (21)	85	93.7	6.30	79.7	0.19
4	Allen <i>et al.</i> 2012 (22)	85	90.0	10.0	76.5	0.24
5	Donnier-Maréchal <i>et al.</i> 2017 (23)	35	93.7	6.28	32.8	1.98
6	Dascalov <i>et al.</i> 2000 (24)	99	18.7	81.3	18.5	4.51
7	Ghosh <i>et al.</i> 2014 (25)	90	64.6	35.4	58.1	0.72
8	Allen <i>et al.</i> 2009 (26)	54	22.2	77.8	12.0	7.4
9	Li <i>et al.</i> 2019 (10)	90	28.8	71.20	25.9	2.85
10	This study (biosourced catalyst)	80	89.3	10.7	71.5	0.52

Conclusion

Production of ryegrass shoots on a contaminated agricultural soil was conducted to evaluate: (i) the application of this biomass in metal uptake and (ii) the ability of the transformed biomass to catalyze an amidification reaction. Moclobemide was the product of interest since (i) it is a biologically active molecule used as the main ingredient of antidepressant commonly used in medicine and (ii) only one amidification reaction starting from methyl 4-chlorobenzoate and 4-(2-aminoethyl)morpholine was previously investigated to obtain this target drug and was characterized by poor green metrics. Characteristics of biomass and transformed-biomass allowed the synthesis of Moclobemide in 80% yield under environmentally friendly conditions (100°C, 24 h, atmospheric pressure, solvent-free, one-step). This transformation integrates several of the 12 principles of the green chemistry and falls within a phytomanagement technique of contaminated soils, the whole of the procedure being a part of the circular economy process. The green metrics of this transformation was calculated and compared to a major part of previously reported procedures. The values of AE, waste, RME and E-factor placed the current procedure in the top of the three greenest syntheses described to date to access moclobemide. Moreover, the biosourced catalyst proved to be recyclable and was successfully used for 5 runs of the same chemical transformation. For all these motives, the production of the target biosourced catalyst is attractive for both producers and chemical industry, whereas the prospect of a generation of green synthetic transformations comes at a key moment for the sustainability of agriculture on contaminated soils.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

Notes on contributors



Marie Hechelski, After attending university studies in the field of ecosystem biology, I continued training courses in plants ecotoxicology. My current research, part of my PhD., focuses on the management of contaminated soils by metals using phytostabilisation techniques and on the valorization of the plant biomass via the production of heterogeneous green catalysts.



Dr. Christophe Waterlot has obtained his PhD in organic and macromolecular chemistry in 1999 and his HDR (High Degree by Research) in Environmental Chemistry in 2015 at Lille 1 University. His research interests include the synthesis and properties of redox polymer using heterogeneous catalysts, the environmental availability of metals and metalloids in contaminated soils and the mobilization of these pollutants using mineral/or organic amendments to produce ecocatalysts. He has supervised 11 graduation courses MASTER and 6 PhD Thesis. He is author and co-author of 86 publications in refereed journals and author of one book in chemistry. He is member of editorial board of several scientific journals and reviewer for more than 60 journals of relevance in environmental and soil science, organic chemistry and polymer.



Pierrick Dufrénoy, After attending university studies in the field of organic chemistry and pharmacology, Pierrick Dufrénoy continued training courses in the synthesis of new compounds with biological effect and obtained his PhD in December 2018. His current research focuses on the synthesis of new potential therapeutic compounds via the valorization of new heterogeneous green supported Lewis acids.



Dr. Brice Louvel has obtained his PhD in environmental chemistry in 2009 at the LIMOS laboratory (CNRS UMR 7137). His research activities focused on the degradation of polycyclic aromatic hydrocarbons in the rhizosphere environment and on the monitoring of soil microbial communities. Then, he was assistant lecturer at Amiens University for one year. Since 2011, his fields of expertise are the monitoring of biological quality in uncontaminated and contaminated soils and sediments, the degradation of organic matter and the management of

contaminated soils by metals. He is author and co-author of 5 publications in refereed journals.



Adam Daïch was born in Aït Ouribel, Morocco. He received his B.S. degree on chemistry and applied industrial process engineering in 1987 from Pierre & Marie Curie University (UPMC) and ENSCP high school at Paris, France. He then obtained his PhD diploma in 1991 working on fused aza-polyheterocyclic systems with CNS activities under the guidance of Prof. B. Decroix at the University of Le Havre. Following two post-doctoral stints (1992–1993) as a associate with Dr F. Považanec at the Technical University of Slovakia of Bratislava and ATER at the University of Le Havre, respectively, he joined the laboratory of the Prof. J. Morel at the same University in 1993 as an Assistant Professor. He did his ‘habilitation’ in 2000 and promoted to the rank of full professor in 2004 at the University of Le Havre Normandy. Professor Daïch’s current research interests cover many topics including, 1)- Chemistry of N-acyliminium salts associated to tandem and/or cascade process, 2°)- Synthesis of natural and unnatural bioactive azaheterocycles and spiroindole-azaheterocycles, and 3°)- Valorisation of the bio-sourced materials derived from industries and agriculture. The synthesis based on the use of cost-effective reagents in association with new activating mode including supported eco-friendly Lewis Acids is also a part of his research work.



Dr. Alina Ghinet was born in Romania. She has obtained her PhD in medicinal chemistry in 2010 and her HDR (High Degree by Research) in Medicinal Chemistry in 2014 at Lille 2 University of Health and Law. Dr. A. Ghinet is associate professor and the head of the Sustainable Chemistry and Health Laboratory in JUNIA, HEI Lille, France. Her research is based on the design, organic synthesis and biological evaluation of new heterocyclic systems for therapeutic applications. She is interested in developing sustainable chemistry and sustainable pharmacy including the circular economy in order to be able to evaluate and act on the impacts of the drug production process. In the anticancer field, her researches are focused on inhibitors of tubulin polymerization and of protein farnesyltransferase. In the inflammatory diseases field, she is interested in P2X7-purinergic receptor or RAGE ligands and polo-like kinase 1 inhibitors.

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