

Article

Toward a New Way for the Valorization of Miscanthus Biomass Produced on Metal-Contaminated Soils Part 2: Miscanthus-Based Biosourced Catalyst: Design, Preparation, and Catalytic Efficiency in the Synthesis of Moclobemide

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Abstract: The conception of two biosourced catalysts (biocatalysts) using stems of miscanthus from the first part of this study are described herein. The temperature and the process used to extract metals from plant as mixture of Lewis acids were investigated in detail and proved to be essential in the design of the biosourced catalysts and their catalytic efficiency. One part of the crude mixture of Lewis acids extracted from the aerial parts of miscanthus plants was used without further treatment as a homogeneous biocatalyst (M1), and the other part was supported on montmorillonite K10 to provide a heterogeneous biocatalyst (MM1). M1 and MM1 were next tested in the synthesis of moclobemide (main ingredient of a drug used to treat depression) and led to excellent yield. Additional comparative experiments with different commercial metallic salts (NaCl, KCl, CaCl₂, MgCl₂, CuCl₂, ZnCl₂, FeCl₂, FeCl₃, MnCl₂, and AlCl₃) and their mixtures were carried out and underlined the importance of the multimetallic synergy on catalytic activity. Finally, a comparison of this new synthetic method assisted by the biosourced catalyst with the previously described procedures to access moclobemide was realized by calculating their green chemistry metrics. This study revealed that the use of the biosourced catalyst led to one of the greenest synthetic methods described today to produce moclobemide.

Keywords: miscanthus; catalyst; moclobemide; green chemistry; metric



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1. Introduction

Nowadays, the practice of chemistry more respectful of human and the environment has become an essential axis of research. According to the 12 principles of green chemistry [1], there are many ways to reduce the environmental impact of organic synthesis. For instance, the use of biobased raw materials, limitation of the use of solvent, or the development of synthesis under reasonable pressure and temperature conditions. In this study, we will focus on the well-known concept in organic chemistry, which fits perfectly into this perspective of green chemistry: catalysis. Indeed, the main effect of catalysts is the reduction of the energy threshold necessary for the reaction progress, which generates a higher yield, shorter reaction time, or lower activation temperature. There are many families of chemical species capable of playing the role of catalyst [2]. Lewis acids are the most common and widely used in homogeneous and heterogeneous organic syntheses when they are supported on montmorillonite K10 [3–5].

Still in the context of green chemistry, the development of inexpensive catalysts from renewable sources is becoming a challenge for industrials and researchers. In this light, a decade ago, Pr. Grison and her team developed for the first time a new type of catalyst [6], called eco-catalyst or biosourced catalyst. These catalysts originated from hyperaccumulative biomasses grown on metal contaminated soils. Metal-uptake by selected plants then takes place, producing biomass enriched with metals. Biomasses are then recovered and after thermal and several chemical treatments, metals are extracted in the form of Lewis acids, thus constituting plant-based biocatalysts. As summarized by Helchelski et al. [5], this technology has proved effective in many different chemical reactions such as well-known Friedel–Crafts alkylation and acylation, Biginelli reaction, or Suzuki–Miyaura coupling. Nevertheless, the use of hyperaccumulating plants presents several drawbacks. Their size and therefore the amount of biomass ultimately generated is often small (e.g., *Anthyllis vulneraria* L.), requesting the use of specific tools for their harvesting. The plants are often endemics (i.e., *Grevillea exul* Lindley, [7]) and so, there are unusual plants in some regions (e.g., *Noccaea caerulescens* (J. Presl and C. Presl) F.K. Mey, *Bacopa monnieri* (L.) Wettst.) and finally not recommended for production in large-scale contaminated soils due to the lack of seeds. The use of so-called “tolerant” plants, which can grow on metal contaminated soils while concentrating a significant amount of metals [8] may therefore constitute a sustainable alternative. Indeed, in the first part of the current study [9], our group demonstrated that *Miscanthus × giganteus*, with the assistance of a monocalcium phosphate (MCP) amendment, accumulated, to a certain extent, metals of interest in the aerial parts.

In the incessant search for “tolerant” plants and their requalifying into bio-ore resources, the current study deals with (i) the conception of two biocatalysts using the stems of miscanthus from the first part of this study [9]; (ii) the evaluation of the catalytic activity of the biocatalysts prepared in the synthesis of moclobemide, a main ingredient of a marketed drug used to treat major depressive episodes and anxiety (marketed under different commercial names: Amira[®], Aurorix[®], Clobemix[®], Depnil[®], or Manerix[®]); (iii) additional comparative experiments with different commercial metallic salts in order to identify the real species responsible for the catalytic activity present in the biosourced catalysts; (iv) comparison of our method with the other described synthesis pathways to access moclobemide using green chemistry metrics.

2. Materials and Methods

2.1. Mineralization and Analysis

The mineralization method was based on the procedure described in literature [10,11]. The concentration of heavy (Cd, Pb, Zn, Cu, Mn, and Fe), alkali (Na and K), and alkaline earth (Ca and Mg) metals in ashes and as well as the HCl-extracted metals were determined by flame atomic absorption spectrometry (AA-6800, Shimadzu, Tokyo, Japan) following the recommendations described in the literature [11,12] to avoid potential spectra interferences. Details on characteristics of light source, limits of detection and quantification were given in Waterlot and Hechelski [11].

2.2. Conception of Biocatalysts

Stems of miscanthus (57 g) from mesocosm experiment using dicalcium phosphate (DCP) as amendments from the first part of this study [9] were transformed into ashes in a muffle furnace (Nabertherm P330, Lilienthal, Germany) under air flow using the following temperature program: (i) 20–250 °C in 30 min, (ii) 250 °C for 1 h, (iii) 250–500 °C in 2 h, and (iv) 500 °C for 8 h. The concentration of metal in ashes from the stem of miscanthus are summarized in Table 1. The resulting ashes were treated with HCl aqueous solution at different concentrations ranging from 0.5 to 6 M with a weight ratio ashes/HCl: 1/10 (Table 2). The best extraction rate of metallic species from ashes was obtained when a 2 M HCl aqueous solution was used and ranged from 80% (Cu) to 100% (Fe) (Table 2). The mixture was stirred at 70 °C for 2 h and the final suspension was poured through a filter paper in a Buchner funnel (Cloup, champigny-sur-Marne, France). After cooling, the mixture was filtered through

celite and the filtrate was evaporated to dryness. The resulting solid was dried at 80 °C for 12 h, to provide 1.9036 g of a white powder. From this, 0.5036 g were used as such and constituted the homogenous catalyst (M1) and the remaining 1.5 g were supported on montmorillonite K10 to obtain 1.22 mmol Zn per g of support in dry methanol to provide the heterogeneous catalyst (MM1) [13]. Upon concentration in vacuo, MM1 was finally activated at 120 °C overnight.

2.3. Organic Chemistry

2.3.1. Chemicals

Methyl 4-chlorobenzoate and 4-(2-aminoethyl)morpholine were purchased from TCI Europe N.V. (Zwijndrecht, Belgium). Iron (II and III) chlorides, calcium chloride, and copper chloride were purchased from Sigma-Aldrich (Saint-Quentin Fallavier, France). Manganese and magnesium chlorides were purchased from Fluka chemika (Illkirch, France). Sodium, potassium, and aluminum chlorides were purchased from Alfa Aesar. Zinc chloride was purchased from Acros Organics (Illkirch, France).

2.3.2. Synthesis of Moclobemide

Methyl 4-chlorobenzoate (0.5 g, 2.93 mmol, 1 eq.), 4-(2-aminoethyl)morpholine (0.38 g, 2.93 mmol, 1eq.), and the selected catalyst (0.05 eq., 0.02 g M1, 0.12 g MM1) were introduced in a 25 mL round-bottom flask without any solvent and were stirred for 18 h at 100 °C. The resulting crude was then analyzed by ¹H NMR (Varian 400-MR spectrometer) to determine the conversion rate of the reagents and the formation of moclobemide (Figure 1).

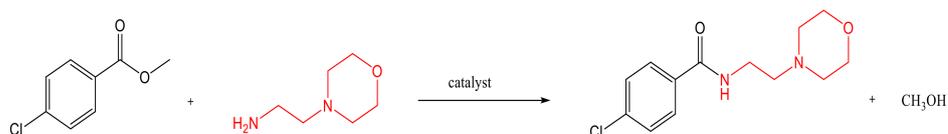


Figure 1. Synthesis of moclobemide from methyl-4-chlorobenzoate and 4-(2-aminoethyl)morpholine.

2.4. Green Chemistry Metrics

2.4.1. Atom Economy (AE) and Percentage of Waste

Atom economy is a theoretical value introduced by Trost et al. [14]. It represents the percentage of atoms from reactants which are involved in a reaction providing a product. It is defined as the ratio of the molar mass of the isolated product over the sum of the molar masses of all the products which appear in the stoichiometric equation (Equation (1)).

$$AE (\%) = \frac{\text{Molecular weight of the isolated product}}{\text{Sum of the Molecular weight of the reactants}} \times 100 \quad (1)$$

The percentage of atoms included in the waste resulting from the reaction (Equation (2)).

$$\text{Waste} (\%) = 100 - AE \quad (2)$$

Table 1. Metal concentrations (mean± standard deviation) of ashes from stems of miscanthus ($n = 6$).

Metal	Cd	Pb	Zn	Fe	Mn	Cu	Ca	Mg	Na	K
Concentration (mg kg ⁻¹)	110 ± 22	108 ± 21	2727 ± 342	1072 ± 291	265 ± 50	89 ± 6	59,710 ± 11,750	8186 ± 982	481 ± 94	237,193 ± 33,335

Table 2. Extraction rate of metallic species from miscanthus ashes according to the concentration of the HCl aqueous solution.

[HCl]	Extraction Rate of Metallic Species from Miscanthus Ashes (%)									
	Cd	Pb	Zn	Fe	Mn	Cu	Ca	Mg	Na	K
HCl 6M	68.5 ± 0.7	54.1 ± 4.5	100.0 ± 1.0	61.9 ± 1.3	98.6 ± 0.4	68.5 ± 0.2	83.2 ± 0.4	93.4 ± 1.8	86.8 ± 11.5	99.8 ± 0.2
HCl 5M	74.3 ± 0.2	53.7 ± 2.2	92.9 ± 1.4	88.4 ± 2.5	95.3 ± 0.5	64.8 ± 1.1	82.1 ± 0.1	89.5 ± 0.5	85.5 ± 12.4	94.9 ± 0.2
HCl 4M	82.8 ± 1.5	57.1 ± 3.4	94.6 ± 0.2	92.6 ± 1.3	100.0 ± 0.3	71.2 ± 0.2	87.9 ± 0.5	92.9 ± 0.1	84.9 ± 13.1	97.9 ± 0.8
HCl 3M	91.7 ± 0.2	56.6 ± 3.7	86.0 ± 0.1	100.0 ± 1.2	96.2 ± 1.9	74.5 ± 0.3	87.8 ± 0.2	91.5 ± 0.2	85.7 ± 14.2	98.4 ± 0.3
HCl 2M	96.5 ± 2.1	63.1 ± 2.8	94.0 ± 1.0	100.0 ± 2.7	99.2 ± 1.1	80.7 ± 0.7	92.1 ± 0.6	92.7 ± 0.9	97.3 ± 5.6	99.4 ± 0.7
HCl 1M	95.1 ± 0.4	59.1 ± 2.7	89.0 ± 0.9	93.3 ± 1.4	99.1 ± 0.5	82.7 ± 0.6	80.0 ± 0.1	89.1 ± 0.7	61.8 ± 9.6	86.2 ± 0.6
HCl 0.5M	100.0 ± 1.4	59.4 ± 1.1	86.4 ± 0.3	67.3 ± 0.2	91.6 ± 1.0	84.2 ± 0.5	95.5 ± 0.0	88.5 ± 2.1	78.5 ± 10.5	100.0 ± 0.5

2.4.2. Environmental Factor (E-Factor)

The environmental factor is an indicator very representative of the waste generated during a reaction [15]. It is calculated by dividing the mass of waste by the mass of product (Equation (3)), giving a value representing the mass of waste generated by mass of products.

$$E - Factor = \frac{Mass\ of\ waste}{Mass\ of\ product} \times 100 \quad (3)$$

2.4.3. Reaction Mass Efficiency (RME)

Reaction mass efficiency allows to calculate the mass conservation of a reaction [16]. It is defined as the ratio of the weight of the isolated product over the sum of the weight of the reactants (Equation (4)).

$$RME = \frac{Weight\ of\ the\ isolated\ product}{Sum\ of\ weight\ of\ the\ reactants} \times 100 \quad (4)$$

3. Results and Discussion

3.1. Application of the Biosourced Catalysts in the Synthesis of Moclobemide and Additional Experiments with Different Commercial Metal Salts

The extracted Lewis acids obtained from miscanthus stems led to the conception of two biosourced catalysts (M1 and MM1) which were involved in the synthesis of moclobemide. The conversion rates generated by the biosourced catalysts were first compared with that obtained in the absence of catalyst. From Table 3, we can observe that without any catalytic system, at 100 °C for 18 h, the conversion rate was 25%, while the use of M1 and MM1 increased the conversion rate to 90% and 79%, respectively. These first results clearly proved the catalytic activity of the biosourced catalysts. Moreover, the different efficiencies between M1 and MM1 can be explained by the nature of the catalyst. Indeed, M1 was composed of crude extracted Lewis acids without further workup or purification, while in MM1, extracted crude Lewis acids were supported on MK-10 clay. The same Zn/reagents ratio was conserved during the chemical syntheses of moclobemide using M1 or MM1 catalysts. However, it is important to note that even if MM1 showed slightly reduced catalytic activity compared to M1, thanks to its heterogeneous nature, it was recovered and reused at the end of the reaction. The catalyst MM1 showed good catalytic performance for up to five cycles of utilization. We tested it only on five runs of the same chemical transformation. At the end of the 5th run, reused MM1 still induced moclobemide formation (56%), which was much higher compared to the reaction carried out without catalyst (25%) (Table 3). From a global point of view, the use of the two biosourced catalysts led to a very clean process proceeding in solvent-free conditions, without the need of specific atmosphere conditions (e.g., argon, nitrogen), large excess of reactant, or the use of expensive and/or exotic catalyst or ligand, while preserving very good performance. As detailed in Table 1, the Cd and Pb concentrations are two of the three lowest concentrations. Taking into account the percentage of extracted metal using 2 M HCl, the percentage of Cd and Pb are 0.035% and 0.022%, respectively. Considering the general procedure, this means that 7 µg Cd and 4.5 µg Pb were introduced in the mixture. After purification of moclobemide, it was analyzed by ETAAS to highlight possible metallic traces due to the catalysts. The concentrations of Cd and Pb were below the limit of detection ($LD_{Cd} = 0.02 \mu\text{g/L}$; $LD_{Pb} = 0.06 \mu\text{g/L}$).

Table 3. Conversion rate according to the catalyst.

Catalyst	Conversion Rate (%) *
Without catalyst	25
M1	90
MM1	79

* 100 °C, 18 h, 0.05 eq. cat. Reactions were performed in duplicate.

After having proved the effectiveness of the designed miscanthus-based catalysts M1 and MM1, additional chemical efforts were undertaken to try to identify the real species responsible for the catalytic activity. In this perspective, we evaluated the catalytic activity of all commercial metal chloride versions of the metals contained in miscanthus stems. The results are presented in Table 4. A different catalytic behavior was observed for the salts tested. Some metallic salts provided better conversion rate (MnCl₂, FeCl₂, AlCl₃ with, respectively, 56%, 53%, and 54%) compared to others (FeCl₃, ZnCl₂, and CuCl₂, respectively, 41%, 36%, and 39%). However, none of the investigated pure metal chloride provided a conversion rate equivalent to that obtained with the biosourced catalysts M1 and MM1. These results corroborated well with the statement that the catalytic activity does not come from a single metal but is probably due to a multimetallic synergy, in accordance with the work of Professor Grison's team related by Hechelski et al. [5].

Table 4. Conversion rate according to the commercial pure metal chloride.

Catalyst	ZnCl ₂	CaCl ₂	NaCl	KCl	MnCl ₂	CuCl ₂	FeCl ₂	AlCl ₃	MgCl ₂	FeCl ₃
Conversion rate (%) *	36	42	43	43	56	39	53	54	44	41

* 100 °C, 18 h, 0.05 eq. cat. Reactions were performed in duplicate.

The investigation of binary equimolar mixtures of commercial metal chlorides was next envisaged. Fourteen mixtures of six metal chlorides (CaCl₂, ZnCl₂, AlCl₃, MnCl₂, FeCl₂, and FeCl₃) were thus tested in the same synthetic procedure to access moclobemide. The choice of the metal salts for the tests in mixture was dictated by the results obtained with the pure salts used alone (Table 4). Indeed, since CaCl₂, MgCl₂, NaCl, and KCl provided similar yields (42–44% yields), only CaCl₂ was retained for binary mixture investigation. CuCl₂ was also excluded since its efficiency proved to be limited (only 39% yield). Results obtained with selected mixtures of metal chlorides are reported in Table 5. Again, the equimolar mixtures of the metal salts tested did not allow to achieve the same yields as those obtained with the biobased catalysts M1 or MM1. The most efficient tested binary mixture was the one composed of MnCl₂ and FeCl₂ and provided moclobemide in 54% yield not exceeding the performance of these same species used alone. The conclusions which emerged from this study were threefold: (i) the equimolar mixture was not representative of the chemical composition of the biosourced salts; then, (ii) the counterion of the metal had an importance on the catalytic activity; finally, (iii) in investigated mixtures, the metal salts seemed to be in competition which resulted in situ in a decrease in catalytic activity in the most cases (see ZnCl₂ and AlCl₃ alone (36% and 54% yield, respectively) in Table 4 compared to ZnCl₂/AlCl₃ mixture (30% yield) in Table 5).

Table 5. Conversion rate according to the mixture of two different commercial metal chlorides (salt 1/salt 2).

Catalyst	Conversion Rate (%) *
ZnCl ₂ /AlCl ₃	30
ZnCl ₂ /MnCl ₂	44
ZnCl ₂ /FeCl ₂	33
ZnCl ₂ /CaCl ₂	40
AlCl ₃ /MnCl ₂	35
AlCl ₃ /FeCl ₂	27
AlCl ₃ /CaCl ₂	53
MnCl ₂ /FeCl ₂	54
MnCl ₂ /CaCl ₂	46
FeCl ₂ /CaCl ₂	45
FeCl ₃ /AlCl ₃	40
FeCl ₃ /CaCl ₂	30
FeCl ₃ /ZnCl ₂	20
FeCl ₃ /MnCl ₂	42

* 100 °C, 18 h, 0.025 eq. salt 1 and 0.025 eq. salt 2. Reactions were performed in duplicate.

Table 6. Conversion rate according to the proportion of FeCl₂ and MnCl₂.

Eq. FeCl ₂	Eq. MnCl ₂	Conversion Rate (%) *
0.045	0.005	48
0.040	0.010	38
0.035	0.015	41
0.030	0.020	78
0.025	0.025	54
0.020	0.030	20
0.015	0.035	45
0.010	0.040	48
0.005	0.045	40

* Reactions were performed in duplicate.

3.2. Comparison with the Other Described Synthesis Pathways of Moclobemide by Green Chemistry Metrics Calculation

Many syntheses of moclobemide were previously reported but most have different drawbacks: use of toxic solvents, numerous reagents, exotic and/or expensive catalysts and/or ligands, excess of reagents, requirement of operating temperatures up to 160 °C, or generating large volumes of waste. All the methods described in the literature leading to a yield higher than 75% are presented in Figure 2. From these methods, we calculated the value of the main green chemistry metrics, which are atom economy (AE), waste, reaction mass efficiency (RME), and environmental factor (E-Factor) (Table 7). First, yields ranged from 77% to 100%, with an average of 90.3%. The M1 catalyst provided a yield of 90%, which therefore places our method among the most effective syntheses described to date. However, our method was the second-best regarding the AE. Indeed, values ranged from 8.88% to 93.7% with an average of 45%, while the use of M1 led to an AE of 89.3%, right behind the methods described by Allen et al. [17] and Li et al. [18] (respectively, 90.0% and 93.7%). As waste is directly connected with AE (Equation (2)), our method was also the third to generate the least amount of waste. Next, the RME (an indicator which considers both the AE and yield), ranged from 8.76% to 80.4% with an average of all methods of 40.5%. The best RME value of 80.4% was obtained by using M1, showing that our method presents the best compromise between yield and AE. Finally, the E-Factor was calculated and values ranged from 0.188 to 10.5 with an average of 2.52. The use of M1 led to an E-Factor of 0.243, which denoted that 0.243 g of waste were generated per gram of

moclobemide produced. This E-factor value is consequently promising. Indeed, among all the other methods, only the synthesis of Allen et al. [17] and Li et al. [18] presented a lower E-Factor (respectively, 0.240 and 0.188). By considering the values of these different green chemistry metrics of our method and by comparison with the others, our biosourced catalysts, especially M1, led to one of the greenest synthetic routes described to date to produce moclobemide.

A similar efficient synthetic pathway was described by Riant et al. [43] but was applied to access the nonchlorinated analogue of moclobemide. For this reason, it was not considered for comparison in terms of green metrics in this study. The method used vinyl benzoate (3 eq.) and amine at room temperature in solvent-less conditions and quantitatively yielded the target amide. Since moclobemide is *para*-chloro substituted, we can assume that the same methodology applied with vinyl 4-chlorobenzoate, more reactive than vinyl benzoate in this amidation reaction thanks to the chloro substituent, should also provide quantitatively the title compound. This method deserves further investigation in due course.

Table 7. Calculated main green chemistry metrics of all efficient (yield > 75%) synthetic pathways described to produce moclobemide.

Entry	Reference	Yield (%)	AE (%)	Waste (%)	RME (%)	E-Factor
1	[18]	85	93.7	6.30	79.7	0.19
2	[19]	90	28.8	71.2	25.9	2.86
3	[20]	89	55.6	44.4	49.5	1.02
4	[21]	94	17.3	82.7	16.5	5.16
5	[22]	80	26.4	73.6	30.5	2.26
6	[23]	90	51.3	48.7	46.1	1.10
7	[24]	98	33.6	66.4	34.1	2.03
8	[25]	97	8.88	91.2	8.76	10.50
9	[26]	85	52.8	47.2	44.9	1.21
10	[27]	88	36.8	63.2	32.4	2.09
11	[28]	85	13.2	86.8	11.5	7.84
12	[29]	100	45.5	54.5	45.5	1.13
13	[30]	90	44.3	55.7	41.7	1.51
14	[31]	98	55.0	45.0	53.9	0.79
15	[32]	97	22.7	77.2	22.0	3.65
16	[33]	77	31.2	68.8	24.1	3.15
17	[34]	99	11.6	88.4	11.5	7.79
18	[35]	76	35.8	64.2	28.2	2.68
19	[36]	99	18.7	81.3	18.5	4.51
20	[37]	90	64.6	35.4	58.1	0.72
21	[38]	96	43.1	56.9	43.2	1.42
22	[39]	80	59.9	40.1	47.9	1.19
23	[40]	95	66.1	33.9	62.8	0.59
24	[41]	96	40.2	59.8	40.2	1.59
25	[17]	85	90.0	10.0	76.5	0.24
26	[42]	100	36.4	63.6	36.4	1.68
27	This study (M1)	90	89.3	10.7	80.4	0.24
28	This study (MM1)	79	89.3	10.7	70.6	0.42

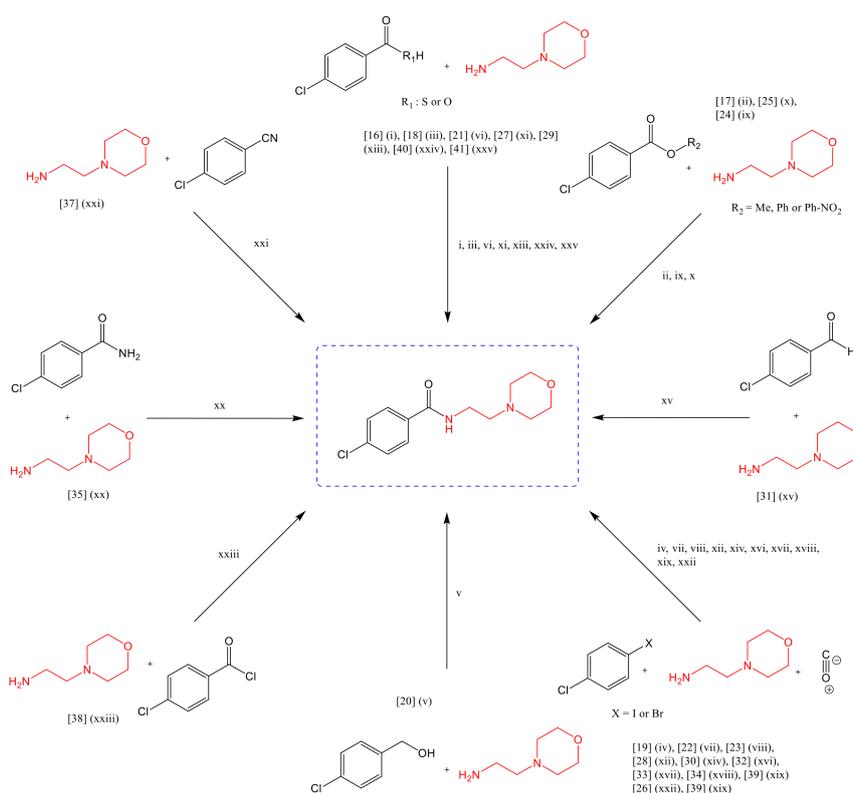


Figure 2. Reported efficient synthetic procedures (yield > 75%) to access moclobemide. Reagents and reactional conditions: (i) 4-chlorobenzoic acid (1 eq.); amine (1 eq.); bis(pentamethylcyclopentadienyl) zirconium perfluorooctanesulfonate (5 mol%); THF; 100 °C; 12 h; 85% yield. (ii) methyl 4-chlorobenzoate (1 eq.); amine (2 eq.); LiHMDS (3 eq.); THF; r.t.; 15 h; 90% yield. (iii) 4-chlorobenzenecarbothioic acid (2 eq.); amine (1 eq.); Mes-Acr-MeBF₄ (2 mol%); MeCN; r.t.; 5 h; 89% yield. (iv) 1-chloro-4-iodobenzene (1 eq.); amine (2 eq.); Pd(OAc)₂ (2 mol%); PTABS ligand (4 mol%); Et₃N (2 eq.); DMF; CO atmosphere; 60 °C; 24 h; 94% yield. (v) 4-chlorobenzyl alcohol (1 eq.); *N*-hydroxyphthalimide (1 eq.); amine (3 eq.); TBHP (2 eq.); MeCN; r.t.; 20 h; 80% yield. (vi) 4-chlorobenzoic acid (1 eq.); amine (1.2 eq.); TCT (0.38 eq.); FPyr (0.1 eq.); NMM (1.3 eq.); MeCN; 80 °C; 9 h; 90% yield. (vii) 1-chloro-4-iodobenzene (1 eq.); amine (2 eq.); xantphos Pd G4 (0.05 eq.); DABCO (2 eq.); CO (1 eq.); THF; r.t.; 16 h; 98% yield. (viii) 1-chloro-4-iodobenzene (1 eq.); amine (2 eq.); xantphos Pd G4 (0.05 eq.); DABCO (2 eq.); FeTPP (0.13 eq.); TBABF₄ (6.68 eq.); THF; CO₂ atmosphere; r.t.; 36 h; 85% yield. (ix) (4-nitrophenyl) 4-chlorobenzoate (1 eq.); amine (1.2 eq.); NHC (0.2 eq.); DBU (0.2 eq.); THF; r.t.; 30 min; 85% yield. (x) phenyl 4-chlorobenzoate (1 eq.); amine (1 eq.); NaHMDS (2 eq.); toluene; r.t.; 15 h; 88% yield. (xi) 4-chlorobenzoic acid (1 eq.); amine (1 eq.); TMSO (2 eq.); toluene; N₂ atmosphere; 110 °C; 1 h; 100% yield. (xii) 1-chloro-4-iodobenzene (1 eq.); amine (2.5 eq.); DABCO (1.25 eq.); supported Pd(OAc)₂ (0.07 eq.); CO atmosphere (5 bar); 120 °C; 3 h; 100% yield. (xiii) 4-chlorobenzoic acid (1 eq.); amine (1.1 eq.); MYTsA (1 eq.); CH₂Cl₂; r.t.; 9 h; 98% yield. (xiv) 1-bromo-4-chlorobenzene (1 eq.); amine (1.5 eq.); Na₂CO₃ (3 eq.); Pd(OAc)₂ (0.01 eq.); xantphos (0.01 eq.); HCOOH (1.3 eq.); MsCl (1.3 eq.); Et₃N (2.6 eq.); toluene; 100 °C; 2 h; 97% yield. (xv) 4-chlorobenzaldehyde (1 eq.); amine (1.5 eq.); Ru(bpy)₃Cl₂ (0.01 eq.); ^tBuOOH (1.3 eq.); NCS (3 eq.); MeCN; blue LEDs (7 W); r.t.; 24 h; 77% yield. (xvi) 1-chloro-4-iodobenzene (1 eq.); amine (1.2 eq.); Pd(OAc)₂ (0.025 eq.); DPEphos (0.1 eq.); CsOH.H₂O (10 eq.); CHCl₃ (3 eq.); toluene; 80 °C; 24 h; 99% yield. (xvii) 1-chloro-4-iodobenzene (1 eq.); amine (2 eq.); DABCO (2 eq.); Pd-AmP-MCF (0.02 eq.); toluene; CO atmosphere; 105 °C; 20 h; 76% yield. (xviii) 4-chlorobenzaldehyde (1 eq.); amine (2 eq.); CsF (0.1 eq.); Pd(dba)₂ (0.05 eq.); PPh₃ (0.1 eq.); Et₃N (2 eq.); (Ph₂MeSi)₂ (0.75 eq.); dioxane; CO₂ atmosphere; 80 °C; 18 h; 99% yield. (xix) 1-bromo-4-chlorobenzene (1 eq.); amine (1.5 eq.); K₂CO₃ (1.5 eq.); Pd/ZIF-8 (0.21 eq.); dppePhos (0.01 eq.); toluene; CO atmosphere (4 bar); 105 °C; 12 h; 96% yield. (xx) 4-chlorobenzamide (1 eq.); amine (2 eq.); Nb₂O₅ (0.05 eq.); 160 °C; 16 h; 90% yield. (xxi) 4-chlorobenzonitrile (2 eq.); amine (1 eq.); Zn(OTf)₂ (0.1 eq.); NH₂OH.HCl (0.1 eq.); *p*-xylene; 150 °C; 8 h; 80% yield. (xxii) 1-chloro-4-iodobenzene (1 eq.); amine (3 eq.); Ph₃SiH (4 eq.); CsF (0.4 eq.); Pd(dba)₂ (0.05 eq.); PPh₃ (0.1 eq.); Et₃N (2 eq.); dioxane; CO₂ atmosphere; 80 °C; 24 h; 85% yield. (xxiii) 4-chlorobenzoyl chloride (1 eq.); amine (1 eq.); Et₃N (1 eq.); THF; r.t.; 12 h; 95% yield. (xxiv) 4-chlorobenzoic acid (1 eq.); amine (1 eq.); ZrCl₄ (0.05 eq.); toluene; 110 °C; 24 h; 85% yield. (xxv) 4-chlorobenzoic acid (1 eq.); amine (1 eq.); TEA (1 eq.); DPPA (0.85 eq.); CH₂Cl₂; r.t.; 16 h; 100% yield.

4. Conclusions

Two biosourced catalysts (M1 and MM1) were successfully obtained from miscanthus biomass cultivated on metal-contaminated soils and were investigated in the synthesis of moclobemide.

Since many syntheses of moclobemide previously described have drawbacks, a review of all the procedures that allowed to obtain moclobemide with a yield greater than 75% was carried out (Figure 2). From this review, the test of the newly obtained biosourced catalysts demonstrated interesting catalytic activity and allowed to obtain moclobemide in good (79% for MM1) to excellent yield (90% for M1). The reaction proceeded in solvent-less conditions under heating at 100 °C for 18 h and needed 0.05 equiv of catalyst only. Of interest, even if the catalyst MM1 induced decreased catalytic activity compared to M1, it had the advantage of being regenerable at the end of the reaction and was reused for up to five runs.

Encouraged by the catalytic activity of M1 and MM1, additional studies to find the metal species responsible for their catalytic activity were carried out. Among the tested pure commercial metal chlorides, some of them resulted in better conversion rate (MnCl₂, FeCl₂, and AlCl₃ induced, respectively, 56%, 53%, and 54% yield) compared to others (ZnCl₂, CuCl₂, NaCl, KCl, CaCl₂, and MgCl₂ providing, respectively, 36%, 39%, 43%, 43%, 42%, and 44% yield). No pure species equaled the performance of biobased catalysts M1 or MM1 and highlighted the importance of the synergy of metallic species. Binary equimolar mixtures of commercial metal chlorides were also tested in the same synthesis to obtain moclobemide. The best efficiency was obtained with a mixture of MnCl₂ and FeCl₂ but did not exceed the performance induced by M1 or MM1 (54% versus 90% and 79%, respectively). This allowed to conclude that the equimolar mixture is not representative of the composition of the biosourced salts. Different ratios of MnCl₂ and FeCl₂ were finally studied and highlighted the importance of the proportion of MnCl₂ compared to that of FeCl₂. While a small excess of FeCl₂ compared to MnCl₂ (0.03:0.02 eq.) allowed to reach 78% yield equivalent to that of MM1, the reverse ratio FeCl₂:MnCl₂ 0.02/0.03 eq. considerably inhibited the chemical transformation and provided moclobemide in only 20% yield. This corroborated well with the composition of the biosourced catalyst, iron being detected in a greater concentration than that of manganese. Therefore, iron and manganese species proved their important role to the catalytic activity induced by the biosourced catalysts M1 and MM1 in the synthesis of moclobemide.

Finally, previously and newly described procedures to access moclobemide were all compared in terms of green chemistry metrics (AE, RME, and E-Factor) to evaluate their environmental impact. The biosourced catalysts, especially M1 (AE of 89.3%, RME of 80.4%, and E-Factor of 0.243), led to one of the greenest synthetic routes described to date to produce moclobemide. This study, therefore, opens new perspectives for the use of biobased catalysts obtained from plants as substitutes for products from the petrochemical industry. Moreover, their use can be further considered in various chemical transformations using Lewis acids and consequently contribute to the circular economy.

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References

1. Anastas, P.; Warner, J. *Green Chemistry: Theory and Practice*; Oxford University Press: Oxford, UK, 2000.
2. Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. Catalytic Organic Reactions in Water toward Sustainable Society. *Chem. Rev.* **2018**, *118*, 679–746. [[CrossRef](#)] [[PubMed](#)]

3. Kobayashi, S.; Manabe, K. Lewis Acid Catalysis in Clean Solvents, Water, and Supercritical Carbon Dioxide, in: Clean Solvents, ACS Symposium Series. *Am. Chem. Soc.* **2002**, 151–165. [[CrossRef](#)]
4. Corma, A.; García, H. Lewis Acids: From conventional homogeneous to green homogeneous and heterogeneous catalysis. *Chem. Rev.* **2003**, *103*, 4307–4366. [[CrossRef](#)] [[PubMed](#)]
5. Hechelski, M.; Ghinet, A.; Louvel, B.; Dufrenoy, P.; Rigo, B.; Daïch, A.; Waterlot, C. From conventional Lewis Acids to heterogeneous Montmorillonite K10: Eco-friendly plant-based catalysts used as green Lewis Acids. *ChemSusChem* **2018**, *11*, 1249–1277. [[CrossRef](#)] [[PubMed](#)]
6. Grison, C.; Escande, V.; Biton, J. *Ecocatalysis: A New Integrated Approach to Scientific Ecology*; Elsevier: Amsterdam, The Netherlands; ISTE Press: London, UK, 2015; 100p. [[CrossRef](#)]
7. Escande, V.; Renard, B.-L.; Grison, C. Lewis acid catalysis and Green oxidations: Sequential tandem oxidation processes induced by Mn-hyperaccumulating plants. *Environ. Sci. Pollut. Res.* **2015**, *22*, 5633–5652. [[CrossRef](#)]
8. Conesa, H.M.; García, G.; Faz, Á.; Arnaldos, R. Dynamics of metal tolerant plant communities' development in mine tailings from the Cartagena-La Unión Mining District (SE Spain) and their interest for further revegetation purposes. *Chemosphere* **2007**, *68*, 1180–1185. [[CrossRef](#)]
9. Hechelski, M.; Louvel, B.; Dufrenoy, P.; Ghinet, A.; Waterlot, C. Toward a new way for miscanthus biomass valorization produced on metal-contaminated soils PART 1—Mesocosm and field experiments. *Sustainability* **2020**, *12*, 9370. [[CrossRef](#)]
10. U.S. EPA. *EPA Method 3050B: Acid Digestion of Sediments, Sludges, and Soils*, 2nd ed.; U.S. EPA: Washington, DC, USA, 1996.
11. Waterlot, C.; Hechelski, M. Benefits of Ryegrass on multicontaminated soils PART 1—Effects of fertilizers on bioavailability and accumulation of metals. *Sustainability* **2019**, *11*, 5093. [[CrossRef](#)]
12. Waterlot, C.; Pelfrène, A.; Douay, F. Effects of iron concentration level in extracting solutions from contaminated soils on the determination of zinc by flame atomic absorption spectrometry with two background correctors. *J. Anal. Methods Chem.* **2012**. [[CrossRef](#)]
13. Waterlot, C.; Couturier, D.; Hasiak, B. Friedel-Crafts Benzoylation of 1,4-dialkoxybenzenes—Cleavage and Rearrangement of Esters and Methoxymethyl Ethers in ZnCl₂ Montmorillonite K10 Clay. *J. Chem. Res.* **2000**, *2000*, 100–101. [[CrossRef](#)]
14. Trost, B.M. The atom economy—A search for synthetic efficiency. *Science* **1991**, *254*, 1471–1477. [[CrossRef](#)] [[PubMed](#)]
15. Sheldon, R.A. The E factor 25 years on: The rise of green chemistry and sustainability. *Green Chem.* **2017**, *19*, 18–43. [[CrossRef](#)]
16. Curzons, A.D.; Constable, D.J.C.; Mortimer, D.N.; Cunningham, V.L. So you think your process is green, how do you know?—Using principles of sustainability to determine what is green—A corporate perspective. *Green Chem.* **2001**, *3*, 1–6. [[CrossRef](#)]
17. Allen, C.L.; Chhatwal, A.R.; Williams, J.M.J. Direct amide formation from unactivated carboxylic acids and amines. *Chem. Commun.* **2011**, *48*, 666–668. [[CrossRef](#)] [[PubMed](#)]
18. Li, N.; Wang, L.; Zhang, L.; Zhao, W.; Qiao, J.; Xu, X.; Liang, Z. Air-stable Bis(pentamethylcyclopentadienyl) Zirconium Perfluorooctanesulfonate as an Efficient and Recyclable Catalyst for the Synthesis of N-substituted Amides. *ChemCatChem* **2018**, *10*, 3532–3538. [[CrossRef](#)]
19. Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N–C/O–C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161–11172. [[CrossRef](#)]
20. Song, W.; Dong, K.; Li, M. Visible Light-Induced Amide Bond Formation. *Org. Lett.* **2020**, *22*, 371–375. [[CrossRef](#)]
21. Bhilare, S.; Shah, J.; Gaikwad, V.; Gupta, G.; Sanghvi, Y.S.; Bhanage, B.M.; Kapdi, A.R. Pd/PTABS: An Efficient Catalytic System for the Aminocarbonylation of a Sugar-Protected Nucleoside. *Synthesis* **2019**, *51*, 4239–4248. [[CrossRef](#)]
22. Singha, K.; Ghosh, S.C.; Panda, A.B. N-Doped Yellow TiO₂ Hollow Sphere-Mediated Visible-Light-Driven Efficient Esterification of Alcohol and N-Hydroxyimides to Active Esters. *Chem. Asian J.* **2019**, *14*, 3205–3212. [[CrossRef](#)]
23. Huy, P.H.; Mbouhom, C. Formamide catalyzed activation of carboxylic acids—Versatile and cost-efficient amidation and esterification. *Chem. Sci.* **2019**, *10*, 7399–7406. [[CrossRef](#)]
24. Collin, H.P.; Reis, W.J.; Nielsen, D.U.; Lindhardt, A.T.; Valle, M.S.; Freitas, R.P.; Skrydstrup, T. COtab: Expedient and Safe Setup for Pd-Catalyzed Carbonylation Chemistry. *Org. Lett.* **2019**, *21*, 5775–5778. [[CrossRef](#)] [[PubMed](#)]
25. Jensen, M.T.; Rønne, M.H.; Ravn, A.K.; Juhl, R.W.; Nielsen, D.U.; Hu, X.-M.; Pedersen, S.U.; Daasbjerg, K.; Skrydstrup, T. Scalable carbon dioxide electroreduction coupled to carbonylation chemistry. *Nat. Commun.* **2017**, *8*, 489. [[CrossRef](#)] [[PubMed](#)]
26. Chen, L.-Y.; Wu, M.-F. An Efficient Catalytic Amidation of Esters Promoted by N-Heterocyclic Carbenes. *Synthesis* **2019**, *51*, 1595–1602. [[CrossRef](#)]
27. Li, G.; Szostak, M. Highly selective transition-metal-free transamidation of amides and amidation of esters at room temperature. *Nat. Commun.* **2018**, *9*, 4165. [[CrossRef](#)] [[PubMed](#)]
28. Lang, X.-D.; He, L.-N. Integration of CO₂ reduction with subsequent carbonylation: Towards extending chemical utilization of CO₂. *ChemSusChem* **2018**, *11*, 2062–2067. [[CrossRef](#)]
29. Braddock, D.C.; Lickiss, P.D.; Rowley, B.C.; Pugh, D.; Purnomo, T.; Santhakumar, G.; Fussell, S.J. Tetramethyl Orthosilicate (TMOS) as a reagent for direct amidation of carboxylic acids. *Org. Lett.* **2018**, *20*, 950–953. [[CrossRef](#)]
30. Papp, M.; Szabó, P.; Srankó, D.; Sáfrán, G.; Kollár, L.; Skoda-Földes, R. Mono- and double carbonylation of aryl iodides with amine nucleophiles in the presence of recyclable palladium catalysts immobilised on a supported dicationic ionic liquid phase. *RSC Adv.* **2017**, *7*, 44587–44597. [[CrossRef](#)]
31. Hu, L.; Xu, S.; Zhao, Z.; Yang, Y.; Peng, Z.; Yang, M.; Wang, C.; Zhao, J. Ynamides as racemization-free coupling reagents for amide and peptide synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13135–13138. [[CrossRef](#)]

32. Veryser, C.; Mileghem, S.V.; Egle, B.; Gilles, P.; Borggraeve, W.M.D. Low-cost instant CO generation at room temperature using formic acid, mesyl chloride and triethylamine. *React. Chem. Eng.* **2016**, *1*, 142–146. [[CrossRef](#)]
33. Iqbal, N.; Cho, E.J. Visible-light-mediated synthesis of amides from aldehydes and amines via in situ acid chloride formation. *J. Org. Chem.* **2016**, *81*, 1905–1911. [[CrossRef](#)]
34. Gockel, S.N.; Hull, K.L. Chloroform as a carbon monoxide precursor: In or ex situ generation of CO for Pd-catalyzed aminocarbonylations. *Org. Lett.* **2015**, *17*, 3236–3239. [[CrossRef](#)] [[PubMed](#)]
35. Tinnis, F.; Verho, O.; Gustafson, K.P.J.; Tai, C.-W.; Bäckvall, J.-E.; Adolffson, H. Efficient palladium-catalyzed aminocarbonylation of aryl iodides using palladium nanoparticles dispersed on siliceous mesocellular foam. *Chem. Eur. J.* **2014**, *20*, 5885–5889. [[CrossRef](#)] [[PubMed](#)]
36. Lescot, C.; Nielsen, D.U.; Makarov, I.S.; Lindhardt, A.T.; Daasbjerg, K.; Skrydstrup, T. Efficient fluoride-catalyzed conversion of CO₂ to CO at room temperature. *J. Am. Chem. Soc.* **2014**, *136*, 6142–6147. [[CrossRef](#)] [[PubMed](#)]
37. Ghosh, S.C.; Li, C.C.; Zeng, H.C.; Ngiam, J.S.Y.; Seayad, A.M.; Chen, A. Mesoporous niobium oxide spheres as an effective catalyst for the transamidation of primary amides with amines. *Adv. Synth. Catal.* **2014**, *356*, 475–484. [[CrossRef](#)]
38. Dang, T.T.; Zhu, Y.; Ngiam, J.S.Y.; Ghosh, S.C.; Chen, A.; Seayad, A.M. Palladium nanoparticles supported on ZIF-8 as an efficient heterogeneous catalyst for aminocarbonylation. *ACS Catal.* **2013**, *3*, 1406–1410. [[CrossRef](#)]
39. Davulcu, S.; Allen, C.L.; Milne, K.; Williams, J.M.J. Catalytic Conversion of Nitriles into Secondary- and Tertiary Amides. *ChemCatChem* **2013**, *5*, 435–438. [[CrossRef](#)]
40. Kim, D.; Sambasivan, S.; Nam, H.; Kim, K.H.; Kim, J.Y.; Joo, T.; Lee, K.-H.; Kim, K.-T.; Ahn, K.H. Reaction-based two-photon probes for in vitro analysis and cellular imaging of monoamine oxidase activity. *Chem. Commun.* **2012**, *48*, 6833–6835. [[CrossRef](#)]
41. Dang, T.T.; Zhu, Y.; Ghosh, S.C.; Chen, A.; Chai, C.L.L.; Seayad, A.M. Atmospheric pressure aminocarbonylation of aryl iodides using palladium nanoparticles supported on MOF-5. *Chem. Commun.* **2012**, *48*, 1805–1807. [[CrossRef](#)]
42. Bodnar, A.L.; Cortes-Burgos, L.A.; Cook, K.K.; Dinh, D.M.; Groppi, V.E.; Hajos, M.; Higdon, N.R.; Hoffmann, W.E.; Hurst, R.S.; Myers, J.K.; et al. Discovery and structure–activity relationship of quinuclidine benzamides as agonists of $\alpha 7$ nicotinic acetylcholine receptors. *J. Med. Chem.* **2005**, *48*, 905–908. [[CrossRef](#)]
43. Alalla, A.; Merabet-Khelassi, M.; Aribi-Zouiouche, L.; Riant, O. Green synthesis of benzamides in solvent and activation-free conditions. *Synth. Commun.* **2014**, *44*, 2364–2376. [[CrossRef](#)]