Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-018-1525-6

ORIGINAL PAPER

# An innovative and efficient method to synthesize meloxicam in one-step procedure with respect to the green chemistry

**Pierrick Dufrénoy[1,2,5] · Alina Ghinet[1,2,3] · Marie Hechelski[4] · Adam Daïch[5] · Christophe Waterlot[4]**

Received: 3 April 2018 / Accepted: 11 October 2018


**Abstract**
An improved procedure for the synthesis of meloxicam drug (methyl 4-hydroxy-2-methyl-*2H*-1,2-benzothiazol-2-amine-3-carboxylate 1,1-dioxide) was described in one-step using mainly impregnated montmorillonite K10 (MK10) with $ZnCl_2$ as a heterogeneous catalyst. This innovative method was compared to the last described procedure employed in the manufacture of this anti-inflammatory drug by means of some metrics used in a first step of the evaluation process of the environmental impact of a chemical transformation. Apart from the yield, which was 90%, atom economy, waste, environmental factor, reaction mass efficiency and stoichiometric factor were calculated as 91.6%, 8.4%, 0, 8.1% and 1%, respectively. Interpretation of these metrics was given and highlighted the fact that the strategy used in the current study may be considered as an environmental-friendly and sustainable method that fits well in the green chemistry concepts.

**Keywords** Meloxicam · Green chemistry · Metrics · Heterogeneous catalyst · Montmorillonite K10

## Introduction

Since two decades, the main concerns for chemistry researchers are to develop organic synthetic routes with the aim to find quicker, cleaner, cheaper synthesis process. In this way, many efforts have been made to avoid or to reduce the use of (1) certain catalysts considered as pollutants, (2) organic solvents and molecules that are able to cause problems for environment and human health but also (3) the generation of hazardous substances in the course of chemical reactions. This problem is not only a great interest for organic chemistry researchers. Indeed, since the Pollution Prevention Act of 1990, scientists, industrialists and operators have had to develop together methodologies encouraging the design of environmentally benign processes and products, including also the reduction of the cost of their production and the limitation of energy, to ensure constant improvement of the synthetic processes towards a concept of green chemistry. In that sense, new chemistry concepts using microwaves irradiation [1, 2] and ultrasounds [3–5] have been developed in research laboratory, as well as solvent-free reactions [6, 7], innovative supported reagents like alumina, aluminosilicates, amorphous silica-alumina ($SiO_2$–$Al_2O_3$), carbon, Celite, graphite, Kieselguhr, molecular sieves, oxides different than $SiO_2$–$Al_2O_3$, porous, mesoporous and microporous solid supports, silica-gel, clays and pillared clays [8–47].

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) of the oxicam family, with anti-inflammatory, analgesic and antipyretic properties largely used in human and veterinary medicine. The representative molecules of the family of oxicams are: tenoxicam **1**, piroxicam **2** and meloxicam **3** (Fig. 1). Meloxicam is the active pharmaceutical ingredient in the marketed drug Mobic® for human or Metacam® for veterinary use. This compound is used in short-term symptomatic treatment of acute attacks of

✉ Christophe Waterlot
christophe.waterlot@yncrea.fr

1 Laboratoire de chimie durable et santé, Yncrea Hauts-de-France, HEI, 13 rue de Toul, 59046 Lille Cedex, France

2 Faculté de médecine, Pôle recherche, Inserm U995, LIRIC, Université de Lille, CHU de Lille, Place Verdun, 59045 Lille Cedex, France

3 Faculty of Chemistry, 'Alexandru Ioan Cuza' University of Iasi, Bd. Carol I nr. 11, 700506 Iasi, Romania

4 Laboratoire Génie Civil et géoEnvironnement (LGCgE), Yncrea Hauts-de-France, 48 boulevard Vauban, 59046 Lille cedex, France

5 Normandie Univ., UNILEHAVRE, FR 3038 CNRS, URCOM EA 3221, UFR Sciences & Techniques, 25 rue Philipe Lebon, BP: 1123, F-76063 Le Havre Cedex, France

Published online: 22 October 2018

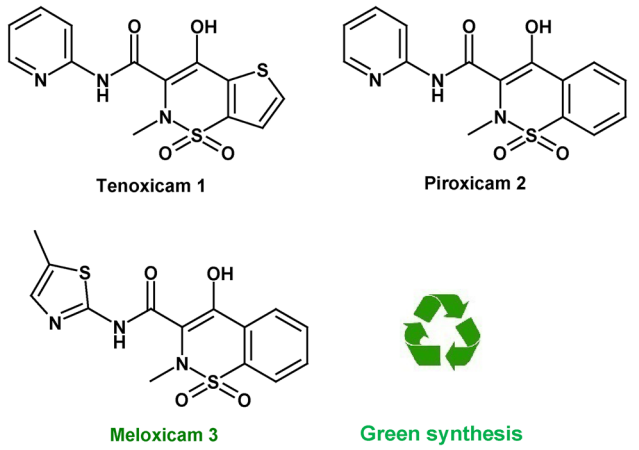



**Fig. 1** Structure of representative members of the oxicams family: tenoxicam **1**, piroxicam **2** and target meloxicam **3**

osteoarthritis and in long-term symptomatic treatment of rheumatoid arthritis and ankylosing spondylitis. Its mechanism of action involves the inhibition of cyclooxygenases (COX) with, however, an inhibition selectivity on COX-2 even if it only appears at the recommended minimum dosages. This inhibition results, as for the other NSAIDs, in the inhibition of the biosynthesis of prostaglandins, known mediators of the inflammation.

New therapeutic approaches are currently investigated for the use of meloxicam alone or in combination. Eight clinical trials are currently under way: four phase II, three phase III studies and one unspecified phase study using meloxicam are in progress [48]. Phase II studies are focused on: (1) meloxicam in association with filgrastim to assess the safety and efficacy of mobilizing autologous peripheral blood stem cells (PBSCs) from multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL) patients planning to undergo high-dose chemotherapy with stem cell support; (2) the evaluation of meloxicam on the mobilization of hematopoietic stem cells to see if it provides a benefit to people receiving Autologous Hematopoietic Stem Cell Transplantation (AHSCT); (3) the efficacy of meloxicam on knee osteoarthritis (KOA) and (4) association of meloxicam and sulfasalazine coupled with TNF-α treatment on patients with ankylosing spondylitis. The phase III clinical trials in progress on meloxicam alone or in combination study: (1) the comparison lidocaine–prilocaine vs. meloxicam in the treatment of postpartum perineal pain; (2) the evaluation of the safety and tolerability of preoperative dosing of meloxicam in subjects undergoing colorectal surgery; (3) the combination of meloxicam and traditional Chinese medicine Fangji Huangqi pill on KOA.

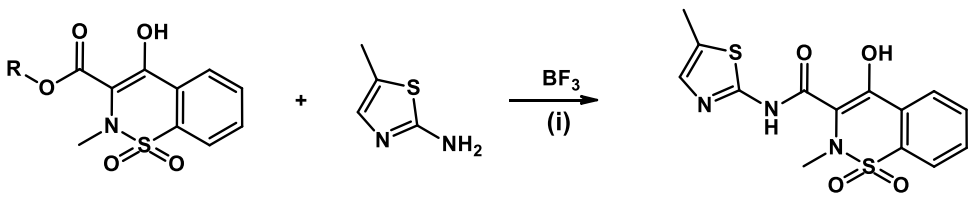
Meloxicam **3** is the most studied representative of the oxicam family. In the current work, we investigated a clean and efficient synthesis of this molecule and compared it to the other procedures described in the literature to propose the simplest synthetic pathway to this active pharmaceutical ingredient from a green chemistry perspective.

## Screening of reaction conditions

The first innovative route was proposed by Zia-ur-Rehman et al. (2005) in which *N*-methyl benzothiazine alkyl (methyl, ethyl or *iso*propyl) carboxylate (**4a–c**) and 5-methyl-1,3-thiazol-2-amine (or 5-methyl-2-aminothiazole) (**5**) were condensed together under an inert medium in presence of boron trifluoride ($BF_3.Et_2O$), used as Lewis acid catalyst, to give meloxicam **3** in good yield (Scheme 1) [49].

In more recent days, Mezei et al. have proposed an original approach (Scheme 2) [50]. The authors produced crude meloxicam **3a** starting from methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazol-2-amine-3-carboxylate 1,1-dioxide **4a** and 5-methyl-2-aminothiazole **5** under argon atmosphere and in the presence of charcoal. Due to the presence of charcoal in the crude meloxicam along with by-product **6** (12% yield), the authors decided to produce meloxicam potassium salt monohydrate **7** by adding a KOH solution in the crude mixture to discard the charcoal and the undissolved residues. The solution was further treated with a KOH solution and the compound **7** was filtered and washed with water. This precipitate was dissolved again in a KOH solution in presence of charcoal under stirring. The mixture was filtered off and the solution was acidified with HCl under stirring.

**Scheme 1** Condensation of substituted alkyl carboxylate and 5-methyl-2-aminothiazole (Route 1; [49]). Reagents and conditions: (i) 1.2 equiv. of amine, 0.02 equiv. of boron trifluoride, xylene, nitrogen atmosphere, reflux, 16 h, 76%




4a-c

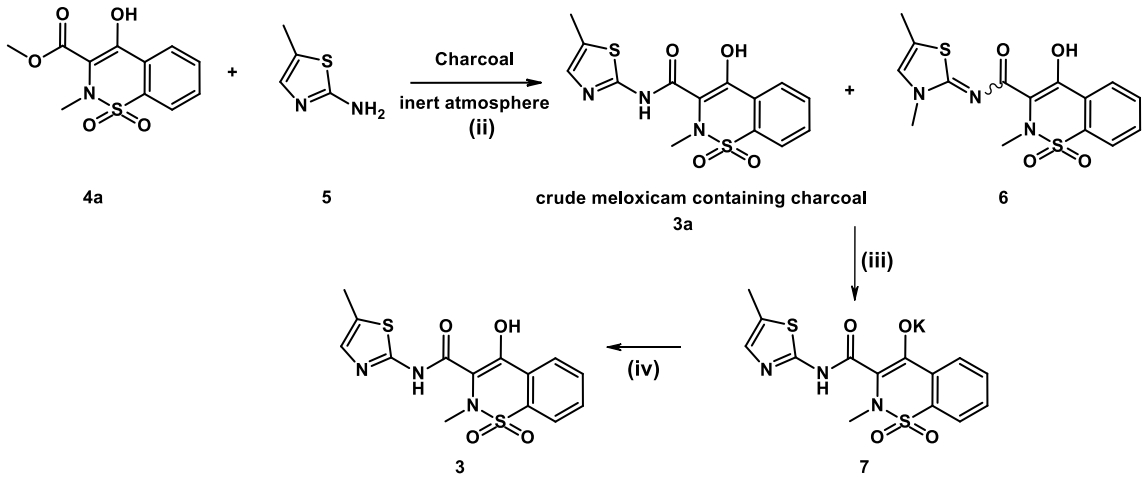
4a: R = $CH_3$

4b: R = $C_2H_5$

4c: R = $CH(CH_3)_2$

5

3




**Scheme 2** Condensation of substituted methyl carboxylate and 5-methyl-2-aminothiazole in presence of charcoal (Route 2; [50]); reagents and conditions: (ii) charcoal, xylene, reflux, 24 h; (iii) 0.82 equiv. of KOH (0.5 w/w% aqueous solution), 50 °C, 1 h, then 4.12 equiv. of KOH (23 w/w% aqueous solution), 10 °C, 2 h; (iv) 1.6 equiv. of KOH (0.5 w/w% aqueous solution), EtOH, 40–45 °C, 0.5 h, charcoal, HCl aqueous solution, 30 °C, 0.5 h, then stirring at 10 °C, 2 h

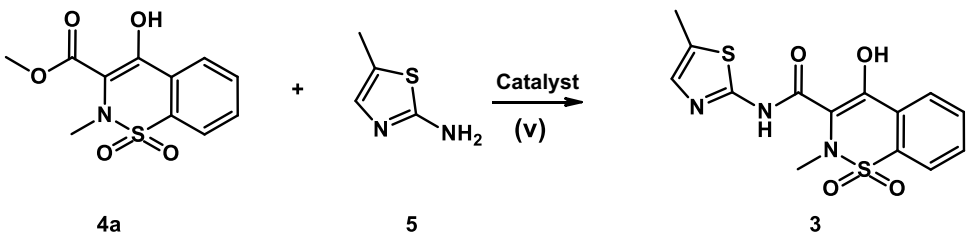
The precipitate was filtered, washed with water and dried in vacuo to obtain purified meloxicam **3** [50].

For the current study, our objective was to highlight innovative and green synthetic pathway to produce meloxicam **3** and to compare our results with the most recent effective pathway described in the literature [50]. In this way, we studied alternative methods with the aim of (i) improving the reaction yield, (ii) reducing the cost of the reaction and its time-consuming and (iii) limiting the waste production compared to the most recent described methodology. Our first procedure was conducted by mixing 1 equivalent of methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazol-2-amine-3-carboxylate 1,1-dioxide **4a** and 1 equivalent of 5-methyl-2-aminothiazole **5** in the presence of 0.05 equivalents of $ZnCl_2$ (Scheme 3, Route 3a). The mixture was refluxed for 24 h in *o*-xylene. After the reaction, the solvent was evaporated and the mixture was washed with water to destroy the Lewis acid $ZnCl_2$. The crude organic product was extracted by $CH_2Cl_2$ and the mixture was purified by flash chromatography (EtOAc:*n*-Heptane, 00:100 to 50:50).

Innovative synthesis methods were developed to produce meloxicam **3** under cleaner and cheaper conditions. These methods were based on the use of heterogeneous catalysts, which were prepared using MK10 as a solid support, instead of $ZnCl_2$. The syntheses of meloxicam **3** were performed following the procedure described above with 0.05 equivalents of (1) commercial MK10 (Fig. 3, Route 3b), (2) catalyst 1 (Cat 1) constituted by MK10 impregnated with $ZnCl_2$ and prepared according to the procedure described by Waterlot et al. (Scheme 3, Route 3c) [37].

## Green chemistry metrics: results and discussion

The efficiency of chemical processes is evaluated by metrics to quantify technical and environmental improvements that can be made when new synthetic pathways and new technologies are proposed. In the concept of sustainable chemistry, the green chemistry metrics facilitate the adoption of the innovative process by the scientific community and industrialists. It




**Scheme 3** Condensation of substituted methyl carboxylate and 5-methyl-2-aminothiazole in presence of $ZnCl_2$ or heterogeneous catalysts. Reagents and conditions: (v) Route 3a: 0.05 equiv. of $ZnCl_2$; Route 3b: 0.05 equiv. of MK10; Route 3c: 0.05 equiv. of Cat 1, *o*-xylene, reflux, 24 h

is well adopted that yield is the most common parameter to evaluate the efficiency of a chemical process. However, even if this parameter is the most simple, it is not always the most appropriate in green chemistry since the operator cannot evaluate changes in relation with the utilization, the modification or the formation of toxic compounds as well as process hazards. Some associated metrics, developed in this sense, are the atom economy, the carbon efficiency, the reaction mass efficiency, the environmental factor and the stoichiometric factor.

## Yield

The mass, the molar mass and the number of mole of reactants and products involved in the three steps described in Scheme 2 are summarised in Table 1. From these data, it was established that yields of potassium salt **7** and meloxicam **3** were 80.9% and 97%, respectively. The overall yield of this multistep synthesis was obtained by multiplying yields from each step and was 78.5%. In practice, this result is considered as a good yield. However, taking into account the general procedure, this value may be different due to the fact that the yield of individual step depends on the experimental conditions and the operators.

Aminolysis reactions may be performed without any catalyst. The direct condensation between methyl ester **4a** and amine **5** without using any catalyst was much less effective and provided the target product **3** in only 34% yield. That explains why we decided to use $ZnCl_2$ as Lewis acid in a first step and then, we attempted to replace this homogeneous catalyst by heterogeneous catalysts. Meloxicam **3** was produced in only one step whatever the catalyst chosen (Scheme 3) and the global results are presented in Table 2. As shown in this table, meloxicam **3** was produced using $ZnCl_2$ (Route 3a) and was isolated in good yield (81.7%). Due to (1) the release of HCl vapours resulting from the reaction between $ZnCl_2$ and water molecules in the atmosphere and (2) the final workup to destroy this catalyst, heterogeneous catalysts were further tested. The first was MK10, a well-known clay belonging to the smectite group, which presents Bronsted and Lewis acid sites (Route 3b). Unfortunately, meloxicam **3** was obtained in a very low yield (29%). We decided to increase the number of Lewis acid's sites of the MK10 by synthesizing impregnated MK10 with $ZnCl_2$ (Zn-MK10) following the procedure described by Waterlot et al. [37]. The yield of the reaction reached 90%, which is considered in practice as an excellent yield.

In view of the low meloxicam's yield via the Route 3b (Scheme 3), this synthetic pathway was not considered in the following part of the current study.

## Atom economy (AE) and Sheldon's E-factor

The atom economy is a theoretical value described in the literature [51] and was expressed in percentage by Eq. 1. From this metric, it may be defined the percentage of reactants engaged in the reaction process that may be considered as waste materials.

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

From the atom economy, and therefore, the waste materials, the E-factor, introduced by Sheldon [52], may be calculated following Eq. 2. For researchers and industrials, this metric may measure how much material enters

**Table 1** Molar mass, mass of reactants and products, mol number and yield associated with the manufacturing of meloxicam according to Mezei et al. [50]

| Chemical formula of reactants and products | $C_{11}H_{11}NO_5S$ **(6)** | $C_4H_6N_2S$ **(5)** | Crude $C_{14}H_{13}N_3O_4S_2$ **(3a)** | KOH $C_{14}H_{12}KNO_4S_2{\cdot}H_2O$ **(8)** | KOH | HCl | $C_{14}H_{13}N_3O_4S_2$ **(3)** | |
|---|---|---|---|---|---|---|---|---|
| Molar mass of reactants and products (g $mol^{-1}$) | 269 | 114 | | 56 | 407.52 | 56 | 36.5 | 351 |
| Mass of reactants and products (g): step (ii) | 35 | 15 | 43 | | | | | |
| Mol number of reactants and products: step (ii) | 0.130 | 0.132 | | | | | | |
| Mass of reactants and products (g): step (iii) | | | 43 | 36 | 42.9 | | | |
| Mol number of reactants and products: step (iii) | | | | 0.643 | 0.105 | | | |
| Mass of reactants and products (g): step (iv) | | | | | 34.1 | 7.5 | 8.8 | 28.5 |
| Mol number of reactants and products: step (iv) | | | | | 0.084 | 0.134 | 0.241 | 0.081 |
| Yield (%) | | | | | 80.9 | | | 97.0 |

**Table 2** Molar mass, mass of reactants and products, mol number and yield associated with the synthesis of meloxicam described in the current study

| Chemical formula of reactants and products | Route 3a | | | | Route 3b | | Route 3c | |
|---|---|---|---|---|---|---|---|---|
| | $C_{11}H_{11}NO_5S$ **(6)** | $C_4H_6N_2S$ **(5)** | $ZnCl_2$ | $C_{14}H_{13}N_3O_4S_2$ **(3)** | MK10 | $C_{14}H_{13}N_3O_4S_2$ **(3)** | Zn-MK10 | $C_{14}H_{13}N_3O_4S_2$ **(3)** |
| Molar mass of reactants and products (g $mol^{-1}$) | 269 | 114 | 136.39 | 351 | | 351 | | 351 |
| Mass of reactants and products (mg) | 200 | 87 | 5 | 213.21 | 30 | 75.8 | 30 | 235 |
| Mol number of reactants and products | 7.43E − 04 | 7.63E − 04 | 3.67E − 05 | 6.07E − 04 | | 2.16E − 04 | | 6.70E − 04 |
| Yield (%) | | | | 81.7 | | 29.0 | | 90.0 |

**Table 3** Metrics associated to the determination of the environmental factor (E-factor)

| | Atom economy (%) | Waste (%) | E-factor |
|---|---|---|---|
| Route 2 | 36.4 | 63.6 | 2.1 |
| Route 3a | 67.6 | 32.4 | 2.4E − 02 |
| Route 3c | 91.6 | 8.4 | 0.0 |

the production site and how much leaves as product and/or waste materials.

$$\text{E-factor} = \frac{\text{Mass of waste}}{\text{Mass of product}}. \quad (2)$$

The three metrics were calculated from the Routes 2, 3a and 3c and the results are presented in Table 3. Compared to the multistep synthesis described in Mezei et al. [50], the atom economy related to synthesis of meloxicam **3** using $ZnCl_2$ was 1.86-fold higher (67.6% vs. 36.4%). The best AE was obtained using the impregnated Zn-MK10 (91.6%) and was 2.5-fold higher than the AE obtained by Mezei et al. [50]. For the Route 3c, this result means that only 8.4% of the atomic mass of the reactants used in the reaction will constitute waste, whereas in Mezei et al. [50], 63.6% of the engaged reactants may be considered as waste. Although the E-factor values were very low for each route, the best E-factor was obtained for the Route 3c. This result may be explained by the properties of the heterogeneous catalyst Zn-MK10. This catalyst was recovered after solid–liquid filtration and it was reused five times without significant loss of activity.

## Reaction mass efficiency (RME)

The reaction mass efficiency was based on the Curzons's definition [53] and was calculated from Eq. 3.

$$\text{RME} = \frac{\text{Isolated weight of the isolated product}}{\text{Sum of the weights of the reactants}} \times 100. \quad (3)$$

Although Mezei et al. [50] produced meloxicam **3** via a multistep synthesis, they presented their results from crude meloxicam product. This point is very important since this Curzons's metric requires the assumption that 100% of the product in a reaction is engaged in the subsequent reaction. The reaction mass efficiency of the Mezei's reaction was 20.9%. This value means that 79.1% of the weights of the reactants used in the reaction Scheme 2 is not inserted in the meloxicam **3**. This result correlated well with the high percentage of waste (63.6%; Table 3). In contrast, RME values were 73.1% and 81.9% for the routes 3a and 3c, respectively. Once again, the best result was obtained using the impregnated Zn-MK10 catalyst and highlighted that only 8.1% of the weights of the reactants engaged in the reaction was not inserted in the meloxicam **3**, reflecting the very low quantity of waste (8.4%, Table 3).

## Stoichiometric factor (SF)

The stoichiometric factor highlights the difference between the reaction conducted in the process studied and this reaction when the reactants should be used in stoichiometric condition [53].

$$\text{SF} = 1 + \frac{\text{Sum of the weights of the reactants} - \text{ sum of the weights of the reactants in a stoichiometric process}}{\text{Sum of the weights of the reactants in a stoichiometric process}} \times 100. \quad (4)$$

The SF metric was calculated for the reaction described in Scheme 2. The value of 1.29 indicated that 29% of the weight of the reactants in the process described by Mezei et al. [50] were used in excess. This result is in relation with the use of KOH to produce the meloxicam potassium salt and the treatment of this salt by KOH and HCl to obtain meloxicam **3**. In view of our both processes, $ZnCl_2$ was used under catalytic conditions (1:10; Route 3a) and the impregnated Zn-MK10 was a reusable catalyst used under catalytic conditions too (Route 3c). Consequently, the SF values were 1 for both syntheses ways indicating that no limiting and excess reactants were used in our innovative process.

## Conclusion

Since the 12 principles of the green chemistry are known by researchers and industrials, many efforts have been made to develop economical, ecological and safe syntheses. The current study reported the most recent and innovative syntheses of meloxicam, a non-steroidal anti-inflammatory drug, the first based on the use of $ZnCl_2$ and the second using impregnated MK10 (Zn-MK10). Apart from the fact that meloxicam was synthesized in one step using this heterogeneous catalyst with the best yield (90%), some quantitative tools used as metrics were used to evaluate the performance of our synthesis. For this pathway, atom economy waste and E-factor were 91.6%, 8.4% and 0, respectively. The reaction mass efficiency highlighted that only 8.1% of the weights of the reactants engaged in the reaction was not inserted in the meloxicam **3** produced under a perfect stoichiometric conditions (stoichiometric factor = 1).

## Experimental

Starting materials are commercially available and were used without further purification (suppliers: Carlo Erba Reagents S.A.S., Tokyo Chemical Industry Co. Ltd., Fluorochem Ltd., and Fisher Scientific). Melting point was measured on a MPA 100 OptiMelt® apparatus and is uncorrected. Nuclear magnetic resonance (NMR) spectra 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 ($\delta$) are expressed in ppm relative to TMS. Splitting patterns are designed: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; sym m, symmetric multiplet; br s, broaden singlet; br t, broaden triplet. Coupling constants (*J*) are reported in Hertz (Hz). Thin layer chromatographies (TLC) were realized on Macherey Nagel silica gel plates with fluorescent indicator and were visualized under a UV-lamp at 254 nm and 365 nm. Column chromatographies were 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.

### Synthesis of 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carbox-amide-1,1-dioxyde (3) without catalyst

2-Amino-5-methylthiazole (85 mg, 0.7 mmol) was added to a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **4a** (200 mg, 0.7 mmol) in *o*-xylene (3 mL) and the mixture was stirred at reflux during 24 h. After cooling to room temperature, the xylene was evaporated and $CH_2Cl_2$ (10 mL) was further added to the crude. The compound was then purified on flash chromatography (EtOAc:*n*-Heptane, 00:100 to 50:50) to provide the 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxyde (**3**) in 34% yield.

### Synthesis of 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carbox-amide-1,1-dioxyde (3) with $ZnCl_2$ as catalyst

2-Amino-5-methylthiazole (85 mg, 0.7 mmol) and zinc chloride (5 mg, 0.037 mmol) were added to a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **4a** (200 mg, 0.7 mmol) in *o*-xylene (3 mL) and the mixture was stirred at reflux during 24 h. After cooling to room temperature, the xylene was evaporated and $CH_2Cl_2$ (10 mL) was further added to the crude and washed with distilled water (2 × 10 mL). The organic layer was dried on $Na_2SO_4$, filtered, concentrated in vacuo and the residue was then purified on flash chromatography (EtOAc:*n*-heptane, 00:100 to 50:50) to provide the 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxyde (**3**) in 82% yield.

### Synthesis of 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carbox-amide-1,1-dioxyde (3) with MK10 as catalyst

2-Amino-5-methylthiazole (85 mg, 0.7 mmol) and MK10 (30 mg, 0.037 mmol) were added to a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **4a** (200 mg, 0.7 mmol) in *o*-xylene (3 mL) and the mixture was stirred at reflux during 24 h. After cooling to room temperature, the mixture was filtered to recover the MK10, the xylene was evaporated and $CH_2Cl_2$ (10 mL) was added to the crude. The compound was then purified on flash chromatography (EtOAc:*n*-heptane, 00:100 to 50:50) to provide the 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxyde (**3**) in 29% yield.

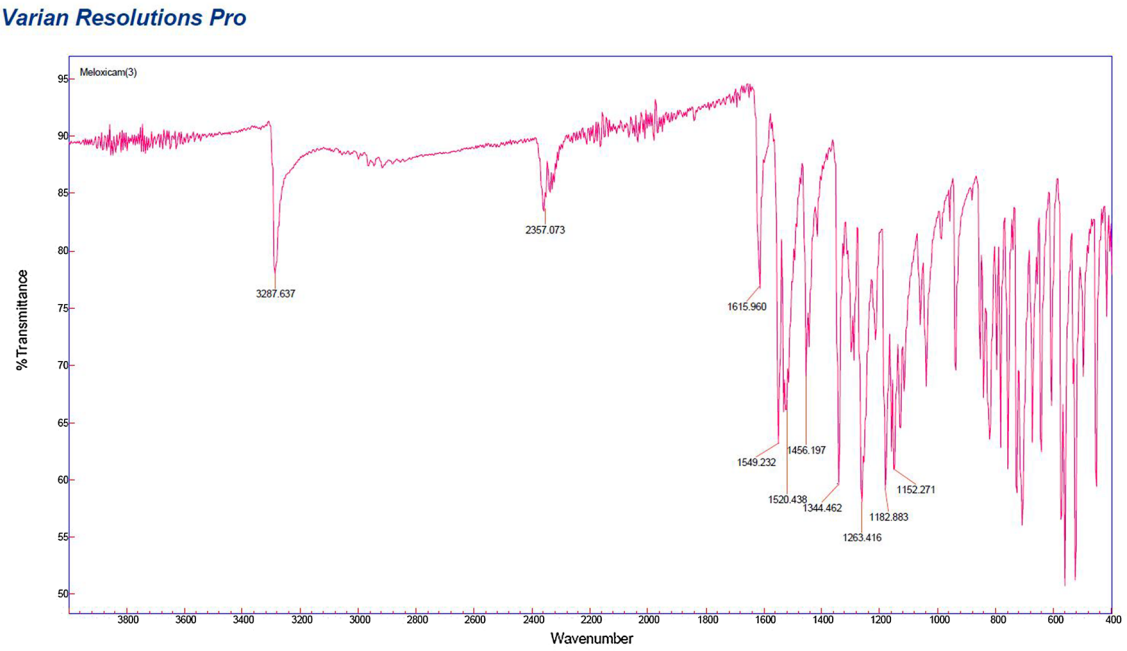



**Fig. 2** Infrared spectrum of meloxicam **3**

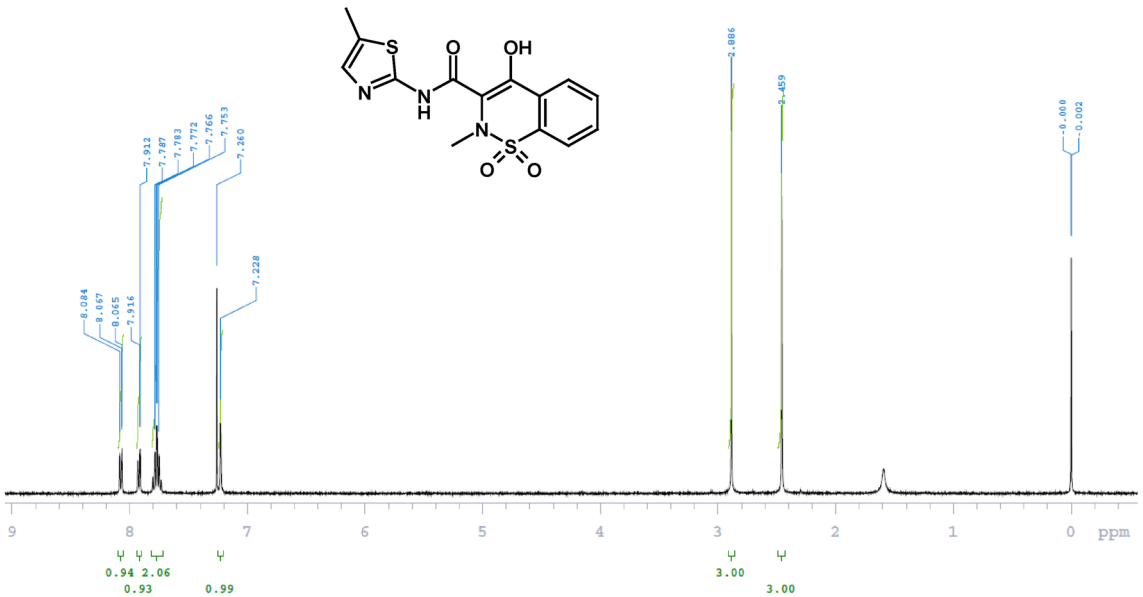



**Fig. 3** $^{1}$H RMN of meloxicam **3**

## Synthesis of 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carbox-amide-1,1-dioxyde (3) with impregnated MK10 (Zn-MK10) as catalyst

2-Amino-5-methylthiazole (85 mg, 0.7 mmol) and Zn-MK10 (30 mg, 0.037 mmol) were added to a solution of methyl 2-methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **4a** (200 mg, 0.7 mmol) in *o*-xylene (3 mL) and the mixture was stirred at reflux during 24 h. After cooling to room temperature, the mixture was filtered to recover the supported catalyst, the xylene was evaporated and $CH_2Cl_2$ (10 mL) was added to the crude. The mixture was then purified on flash chromatography (EtOAc:*n*-heptane, 00:100 to 50:50) to provide the

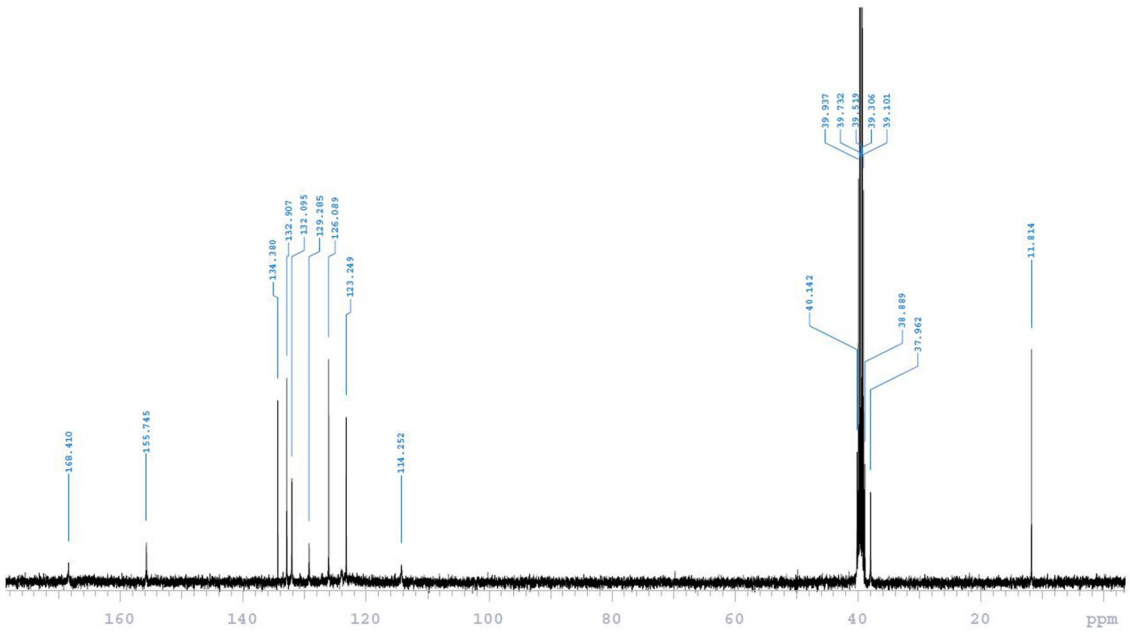



**Fig. 4** $^{13}$C RMN of meloxicam **3**

4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxyde (**3**) in 90% yield.

White solid; mp 245–246 °C ($CH_2Cl_2$); Rf 0.62 (EtOAc:*n*-Heptane, 60:40), IR $\nu$ cm$^{-1}$: 3288, 1549, 1344, 1264, 1183 (Fig. 2). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ (ppm): 2.46 (s, 3H, C*H*$_3$), 2.89 (s, 3H, C*H*$_3$), 7.23 (s, 1H, thiazolyl-*H*), 7.75 (dquint, $J$ = 7.2, 1.6 Hz, 2H, Ar*H*), 7.91 (dd, $J$ = 7.4, 2.0 Hz, 1H, Ar*H*), 8.06 (dd, $J$ = 8.2, 1.6 Hz, 1H, Ar*H*) (Fig. 3). $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm): 11.8 ($CH_3$), 38.0 ($CH_3$), 114.3 (C), 123.3 (CH; C), 126.1 (CH), 129.3 (CH), 132.1 (CH), 132.9 (CH; C), 134.4 (2C), 155.7 (C), 168.4 (C) (Fig. 4).

**Acknowledgements** The authors warmly thank Yncréa Hauts-de-France and the "Fondation de La Catho de Lille" for their financial support of this study in the frame of « Matériaux Verts Fonctionnels » program (P.D.'s and M. H.'s PhD scholarships). The authors are also grateful to the "Université Le Havre Normandie" for technical help.

## References

1. R.S. Varma, Green Chem. **313**, 43 (1999)
2. P. Lidström, J. Tierney, B. Wathey, J. Westman, Tetrahedron **57**, 9225 (2001)
3. T.J. Mason, Chem. Soc. Rev. **26**, 443 (1997)
4. B. Banerjee, Ultrason. Sonochem. **35**, 1 (2017)
5. B. Banerjee, Ultrason. Sonochem. **35**, 15 (2017)
6. S.L. Barbosa, M.J. Dabdoub, G.R. Hurtado, S.I. Klein, A.C.M. Baroni, C. Cunha, Appl. Catal. A Gen.l **313**, 146 (2006)
7. H.M. Marvaniya, K.N. Modi, D.J. Sen, Int. J. Drug. Dev. Res. **3**, 34 (2011)
8. A. McKillop, D.W. Young, Synthesis **6**, 401 (1979)
9. A. McKillop, D.W. Young, Synthesis **7**, 481 (1979)
10. B.M. Khadilkar, S.D. Borkar, Tetrahedron Lett. **38**, 1641 (1997)
11. M. Nikoorazm, Sci. Iran. **20**, 603 (2013)
12. N.A. Noureldin, D.G. Lee, Tetrahedron Lett. **22**, 4889 (1981)
13. B. Chiche, A. Finiels, C. Gauthier, P. Geneste, J. Org. Chem. **51**, 2128 (1986)
14. V. Paul, A. Sudalai, T. Daniel, K.V. Srinivasan, Tetrahedron Lett. **35**, 2601 (1994)
15. B.M. Choudary, M.L. Kantam, M. Sateesh, K.K. Rao, P.L. Santhi, Appl. Catal. A Gen. **149**, 257 (1997)
16. V.R. Choudhary, S.K. Jana, N.S. Patil, Tetrahedron Lett. **43**, 1105 (2002)
17. K. Bachari, O. Cherifi, Appl. Catal. A Gen. **319**, 259 (2007)
18. S. Horike, M. Dincâ, K. Tamaki, J.R. Long, J. Am. Chem. Soc. **130**, 5854 (2008)
19. D.J. Upadhyaya, S.D. Samant, Appl. Catal. A Gen. **340**, 42 (2008)
20. N.T.S. Phan, K.K.A. Ly, T.D. Phan, Appl. Catal. A: Gen. **382**, 246 (2010)
21. X. Chagjiu, L. Min, Z. Bin, S. Xingtian, Sci. Res. **14**, 7 (2012)
22. S.S. Patil, S.D. Jadhav, M.B. Deshmukh, Indian J. Chem. **52B**, 1172 (2013)
23. T. Ennaert, J. Van Aelst, J. Dijkmans, R. De Clercq, W. Schutyser, M. Dusselier, D. Verboekend, B.F. Sels, Chem. Soc. Rev. **45**, 584 (2016)
24. O. Sieskind, P. Albrecht, Tetrahedron Lett. **34**, 1197 (1993)
25. Z.H. Zhang, T.S. Li, F. Yang, G.G. Fu, Synth. Commun. **28**, 3105 (1998)
26. T.S. Li, Z.H. Zhang, T.S. Jin, Synth. Commun. **29**, 181 (1999)
27. S.A.E. Ayoubi, F. Texier-Boullet, J. Chem. Res. (S) 1, 208 (1995)
28. R.S. Varma, Tetrahedron **58**, 1235 (2002)
29. G. Song, B. Wang, X. Bu, Y. Kang, Y.L. Yang, Synth. Commun. **35**, 2875 (2005)
30. S. Dasgupta, B Török, Org. Prep. Proced. Int. **40**, 1 (2008)
31. G. Nagendrappa, Appl. Clay Sci. **53**, 106 (2011)
32. M. Balogh, I. Hermecz, Z. Meszaros, P. Laszlo, Helv. Chim. Acta **27**, 2270 (1984)

33. A. Maquestiau, A. Mayence, J.J. Vanden, Eynde, Tetrahedron Lett. **32**, 3839 (1991)
34. P. Laszlo, P. Pennetreau, A. Krief, Tetrahedron Lett. **27**, 3153 (1986)
35. S. Chalais, A. Cornelis, P. Laszlo, A. Mathy, Tetrahedron Lett. **26**, 2327 (1985)
36. M. Balogh, A. Cornéli, P. Laszlo, Tetrahedron Lett. **25**, 3313 (1984)
37. C. Waterlot, D. Couturier, B. Hasiak, J. Chem. Res. 0417 (2000)
38. A. Cornelis, P. Laszlo, P. Pennetreau, Clay Miner. **18**, 437 (1983)
39. A. Cornelis, P. Laszlo, Synthesis **10**, 849 (1980)
40. A. Cornélis, A. Gerstmans, P. Laszlo, A. Mathy, I. Zieba, Catal. Lett. **6**, 103 (1990)
41. P.D. Clark, A. Kirk, R.A. Kydd, Catal. Lett. **25**, 163 (1994)
42. J.J. Vanden Eynde, A. Mayence, Y.V. Haverbecke, Tetrahedron Lett. **36**, 3133 (1995)
43. R. Varala, R. Enugala, S.R. Adapa, Arkivoc **13**, 171 (2006)
44. G.D. Yadav, K.P. Pimparkar, J. Mol. Catal. A Chem **264**, 179 (2007)
45. A. Cornélis, P. Laszlo, S. Wang, Tetrahedron Lett. **34**, 3849 (1993)
46. C. Waterlot, D. Couturier, B. Rigo, A. Ghinet, M. De Backer, Chem. Pap. **6**, 873 (2011)
47. A. Dhakshinamoorthy, K. Knagaraj, K. Pitchumani, Tetrahedron Lett. **52**, 69 (2011)
48. https://clinicaltrials.gov. Accessed 15 Nov 2017
49. M. Zia-ur-Rehman, J.A. Choudary, S. Ahmad, Bull. Korean Chem. Soc. **26**, 1771 (2005)
50. T. Mezei, N. Mesterházy, T. Bakó, M. Porcs-Makkay, G. Simig, B. Volk, Org. Proc. Res. Dev. **13**, 567 (2009)
51. B.M. Trost, Science **254**, 1471 (1991)
52. R.A. Sheldon, Green Chem. **9**, 1273 (2007)
53. A.D. Curzons, D.J.C. Constable, D.N. Mortimer, V.L. Cunningham, Green Chem. **3**, 1 (2001)