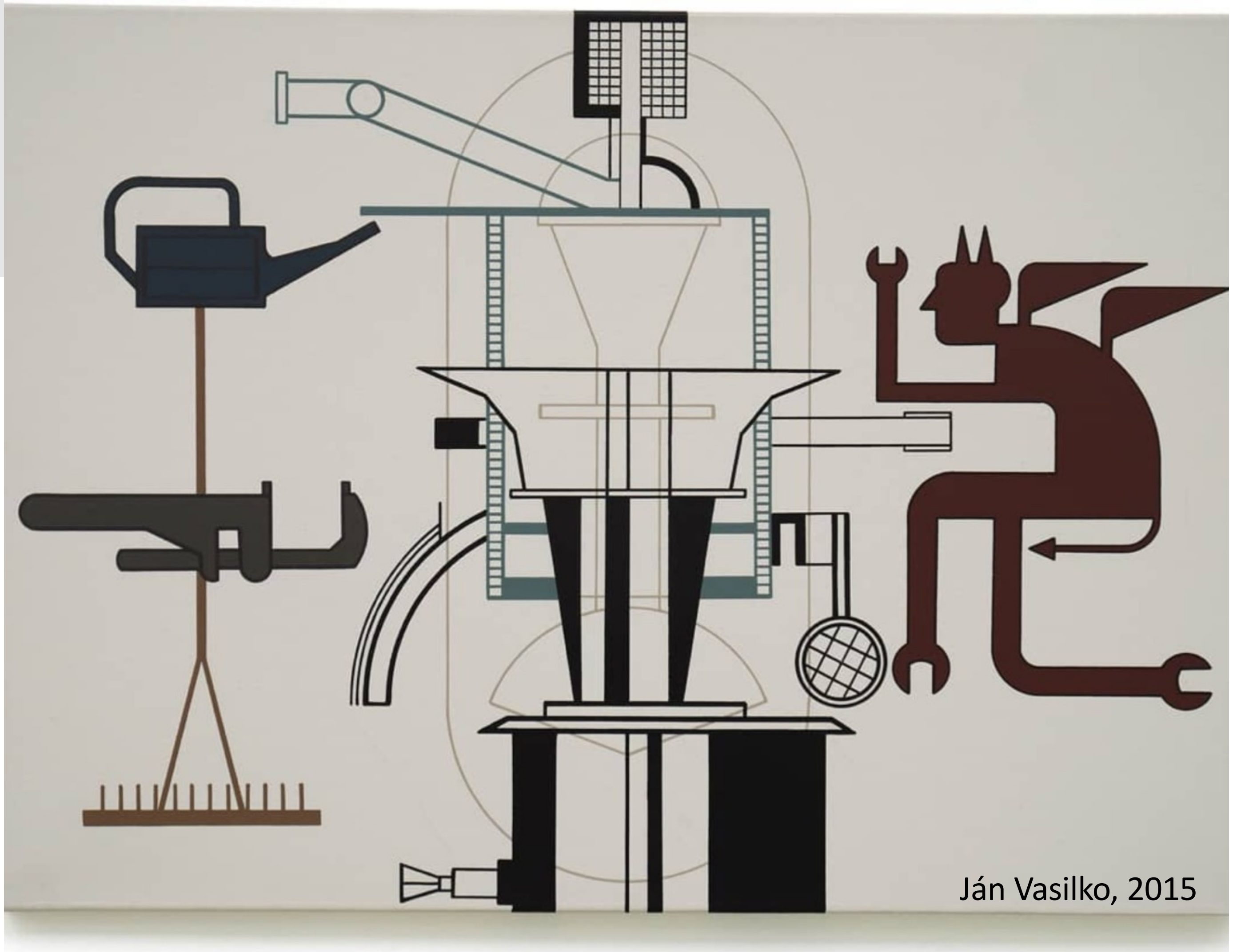
Malmener les molécules pour

le bien de la planète et de l'humanité

Dr Frédéric Lamaty
Chimie Verte et Technologies Innovantes
Institut des Biomolécules Max Mousseron
Montpellier, France

frederic.lamaty@umontpellier.fr
https://greenchem.cnrs.fr/

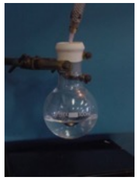


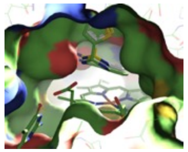
Ján Vasilko, 2015

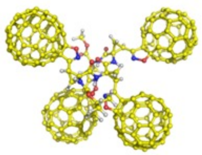
Biomolecules and Green Chemistry

IBMM
Institut des
Biomolécules
Max Mousseron

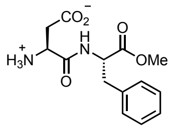
Institut des Biomolécules Max Mousseron

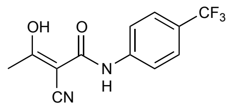


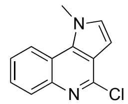


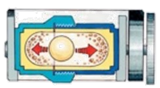


Green Chemistry and Enabling Technologies



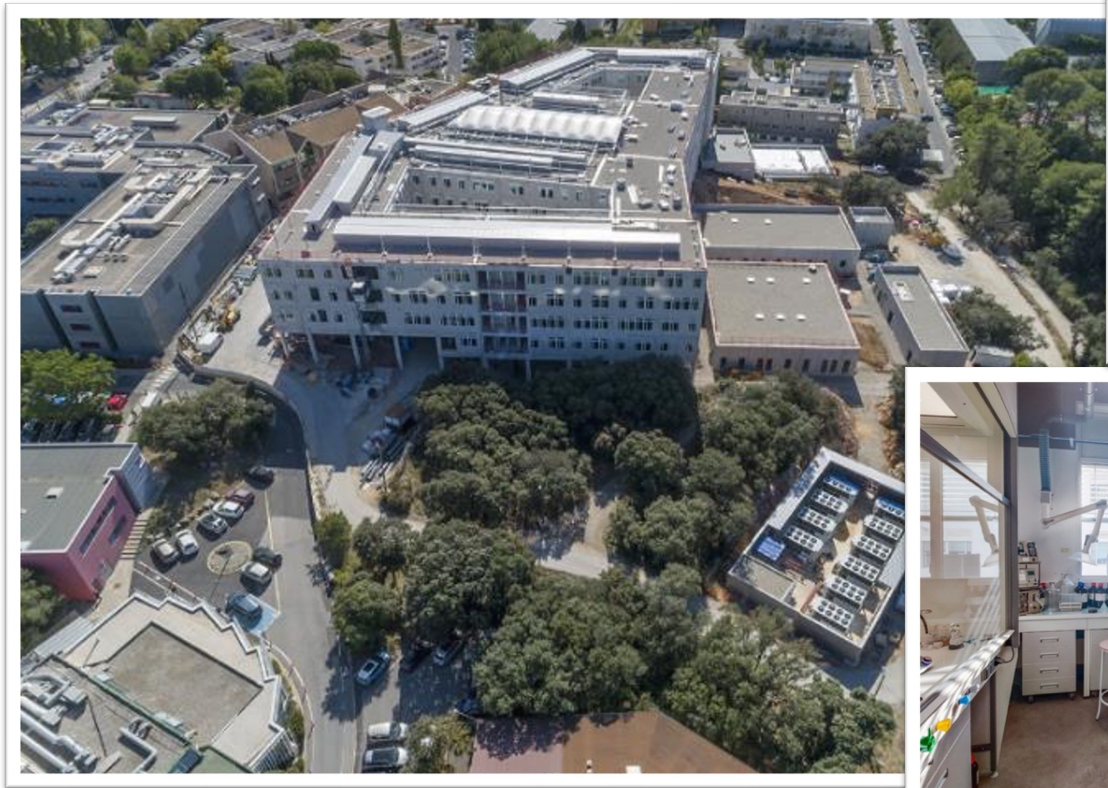






IBMM
Institut des
Biomolécules
Max Mousseron

Pôle Chimie Balard



IBMM
Institut des
Biomolécules
Max Mousseron

Produits de la chimie

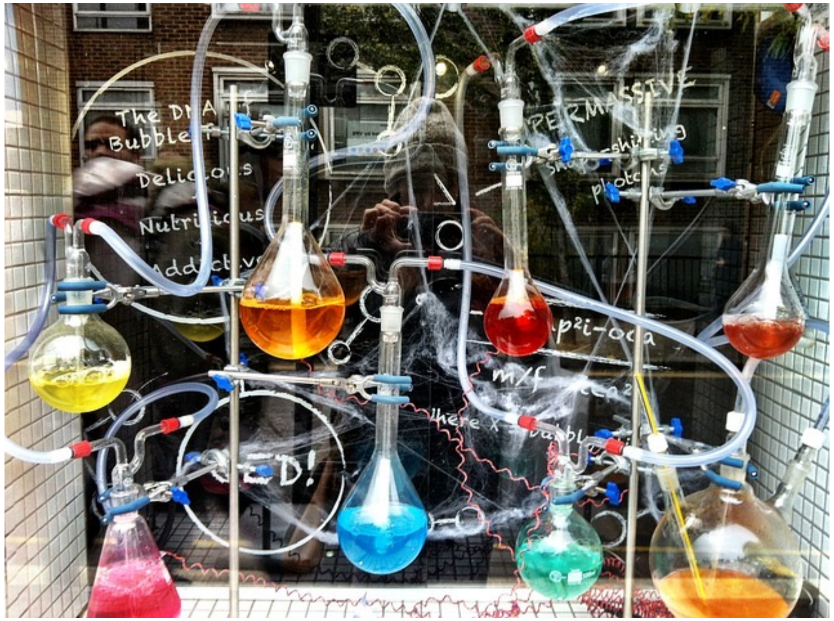
Chimie et pollution

Chimie verte

12 principes de la Chimie Verte
Paul Anastas & John Warner
1998

IBMM Institut des Biomolécules Max Mousseron

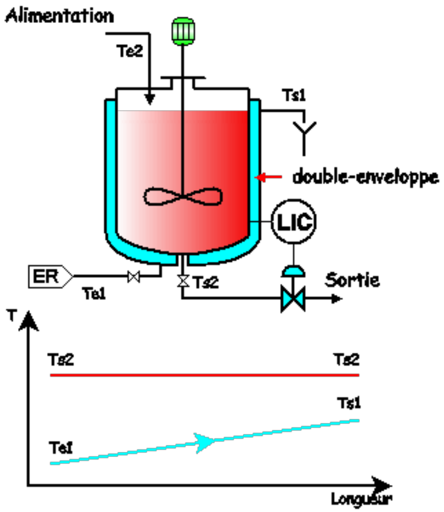
Chimie en solution



Quand les molécules se rencontrent…

Chimie en solution

Le solvant en chimie:
- Synthèse
- Purification
- Nettoyage
- Formulation du produit

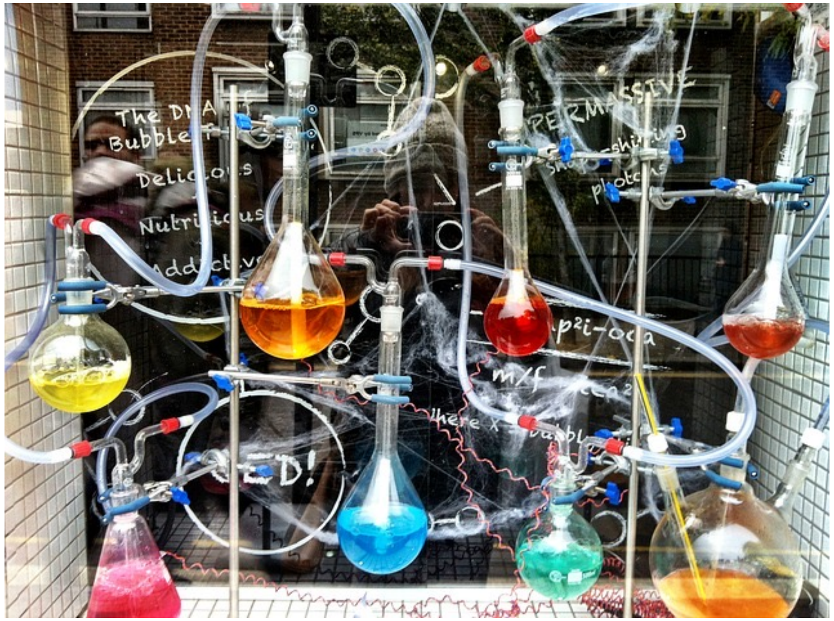


En synthèse
- Solvatation des réactifs
- Effets de solvant
- Transport de matière
- Transport de chaleur

Production mondiale de solvants:
25 millions de tonnes/an
Part recyclée: 20 %

IBMM Institut des Biomolécules Max Mousseron

Chimie en solution



IBMM
Institut des Biomolécules Max Mousseron

Les solvants

Les solvants organiques classiques sont souvent toxiques, volatiles, chers à produire et à éliminer

- Dichlorométhane 
- Acétone 
- Toluène 
- Methanol 
- Ether 
- Ethanol 
- Tetrahydrofuranne 
- DMF 

Cinabre

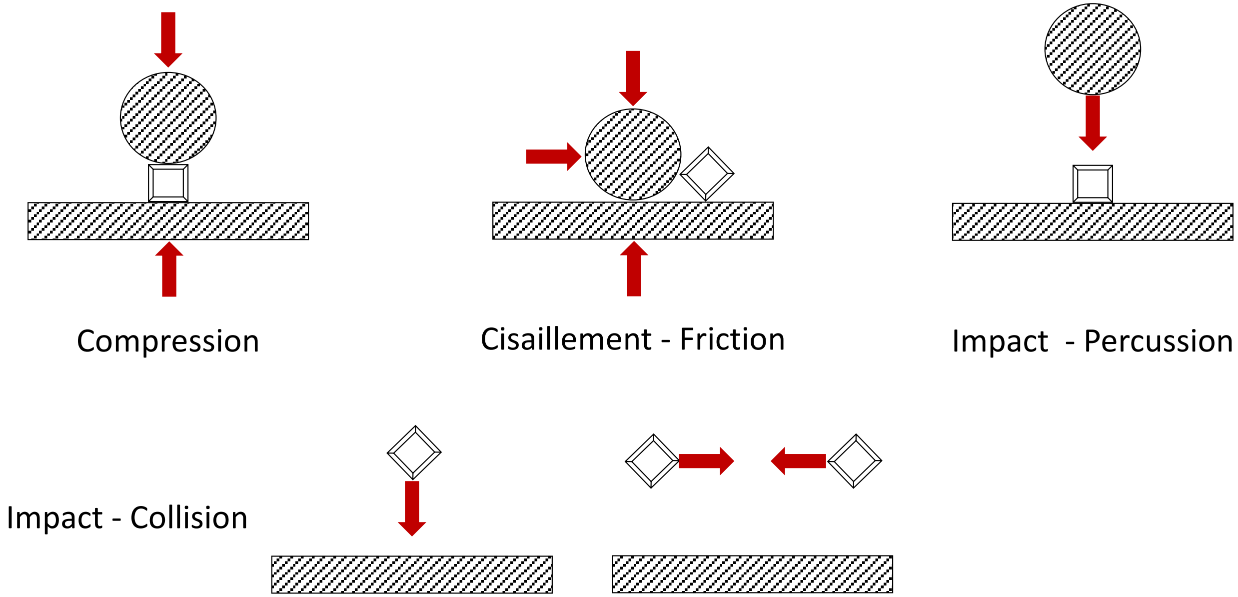
TRAITÉ DES PIERRES DE THÉOPHRASTE

$$HgS_{(s)} + Cu \xrightarrow{CH_3COOH} Hg_{(l)} + CuS_{(s)}$$

1050. Il eſt évident par tout ce que nous venons de dire, que l'Art imite la Nature, & quelquefois produit des choſes ſingulieres, dont les unes ſont pour l'uſage, & les autres pour l'amuſement ; comme celles que l'on emploie pour orner les édifices, & d'autres qui ſervent tant à l'amuſement qu'à l'utilité. Telle eſt la production du Mercure (p) qui a ſes propriétés ; on le tire du Cinabre naturel que l'on amalgame avec du vinaigre dans un mortier de Cuivre, avec un pilon du même métail ; & il y a bien d'autres choſes de cette eſpéce qu'on pourra peut-être encore imaginer.

315 av. J. C.

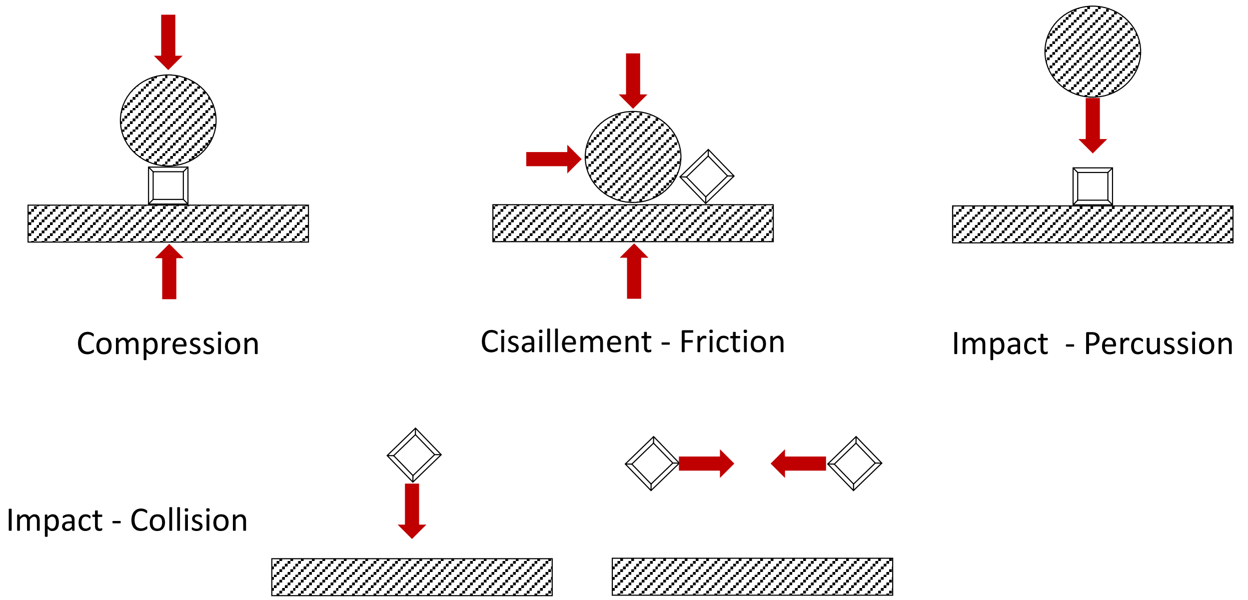
Forces mécaniques



Réduction de taille des particules : réactivité chimique ↗

- ↗ surface
- ↗ énergie de surface
- création de défauts, dislocations, déformations

Mécanochimie



IUPAC
International Union of Pure and Applied Chemistry

Réaction mécanochimique

Réaction chimique induite par absorption directe d'énergie mécanique





Mechanochemistry

Solvent-free/solventless conditions
➡ **Reduce costs and waste**
Overcome solubility issues

Excess reagents no longer required
➡ **Reduce costs and waste**
Better green chemistry metrics

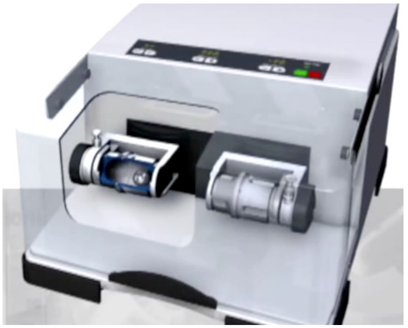
Increase the speed of the reactions
➡ **Time and energy saving**

Difference in reaction environment compared to conventional methods
➡ **Unlocks the door to different reactivities/selectivities**

IBMM
Institut des Biomolécules Max Mousseron

Broyeurs à billes

Vibratory ball-mill (vbm)



Planetary ball-mill (pbm)

Avantages:
- ✓ Réactions sans solvant
- ✓ Augmentation des vitesses de réaction
- ✓ Basse consommation énergétique

Attention
Ne pas utiliser de composés explosifs

Videos from www.retsch.com

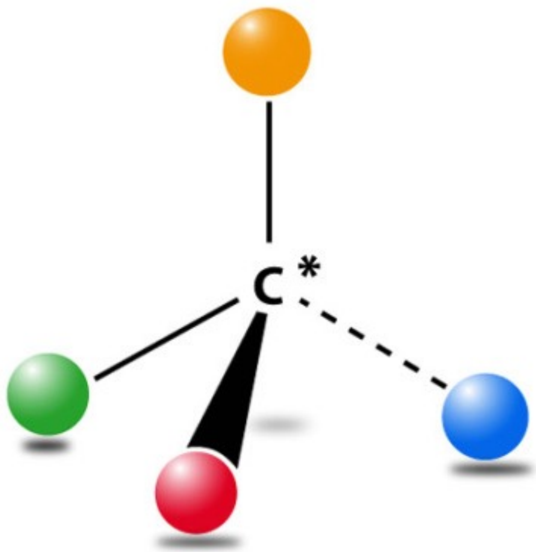
IBMM Institut des Biomolécules Max Mousseron

Broyeurs à billes

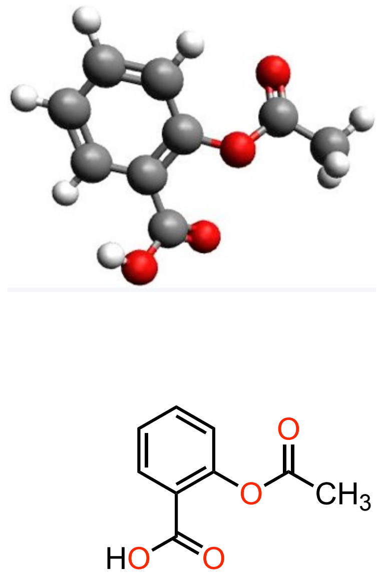
Crédits : Michael Brand (University of Cardiff) and Jean-Louis Do (McGill University)

Broyeur planétaire

Chimie organique



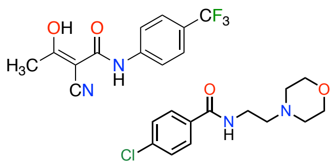
Chimie des éléments C, H, O, N



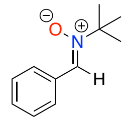
Acide acétylsalicylique

Made in IBMM

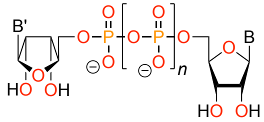
Amides



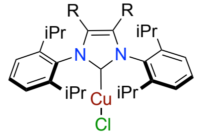
Nitrones/Hydrazones



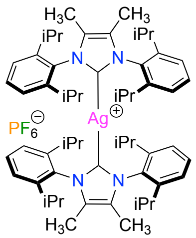
Nucleotides



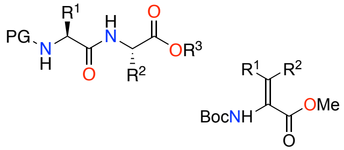
Reaction with gases (O_2 / CO_2)



Metal-NHC

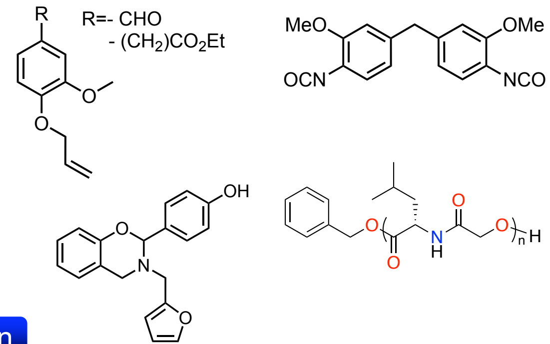


Peptides / Amino acids

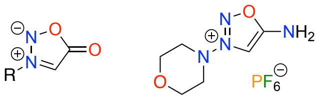


JUST MILL IT

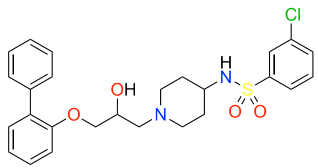
Monomers and polymers



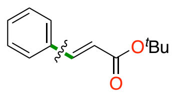
Sydnones / Iminosydnones

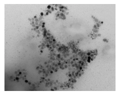


Serotoninergic receptor ligands



Mizoroki-Heck reaction

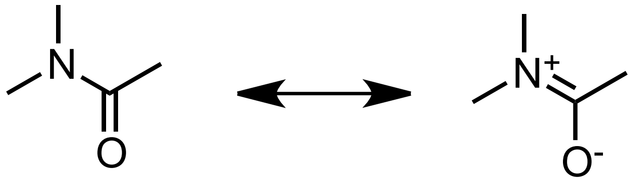




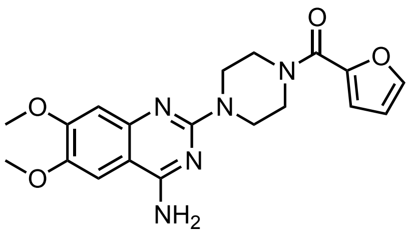
Sustainable mechanosynthesis of biologically active molecules
Bento, O.; Luttringer, F.; Mohy-El-Dine, T.; Pétry, N.; Bantreil X.; Lamaty, F. *Eur. J. Org. Chem.* **2022** e202101516

IBMM Institut des Biomolécules Max Mousseron

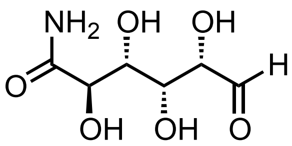
La fonction amide



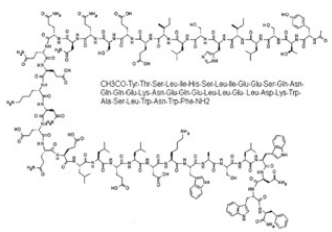
- Structure
- Polarité
- Solubilité
- Interactions



Prazosine : anti-hypertension



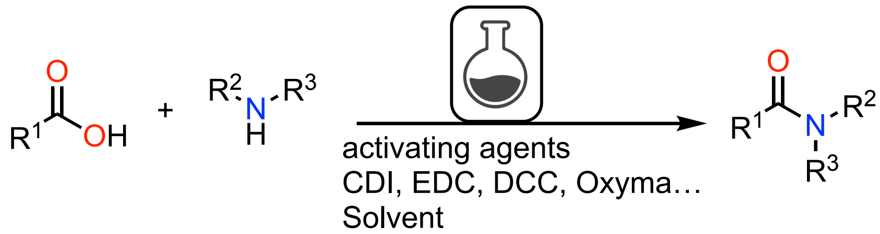
Guronsan : anti-asthenie



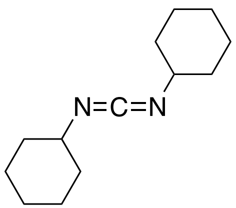
Enfuvirtide (Fuzeon, T20)

Inhibiteur de l'action du virus VIH

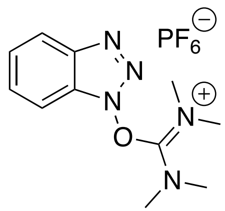
Réaction classique



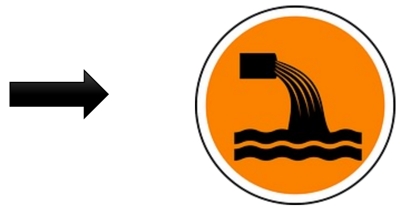
- Solvant toxiques: DMF, THF, CH_2Cl_2
- Agent de couplage:



DCC



HBTU

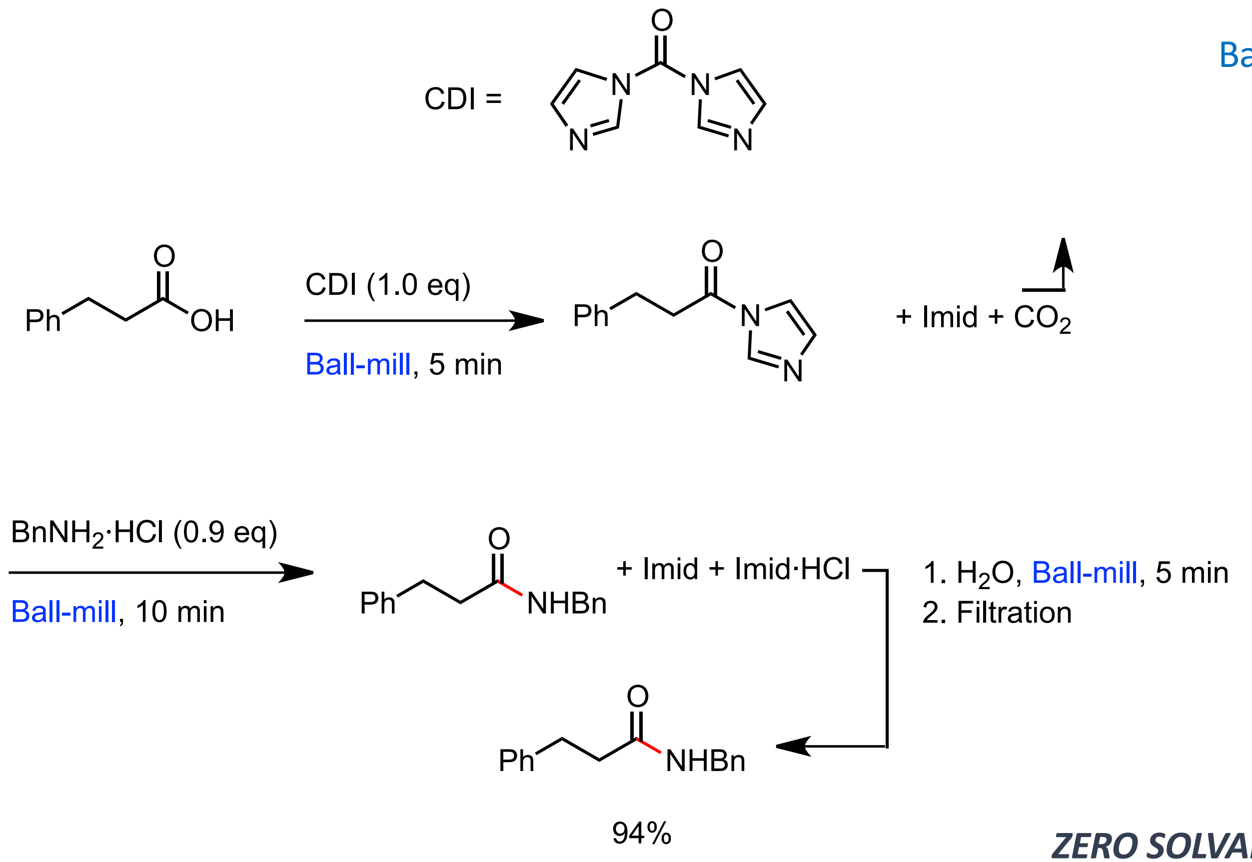


- Quantités stoechiométriques de réactifs/ sous-produits

Réaction dans un broyeur

Dr J. Bonnamour

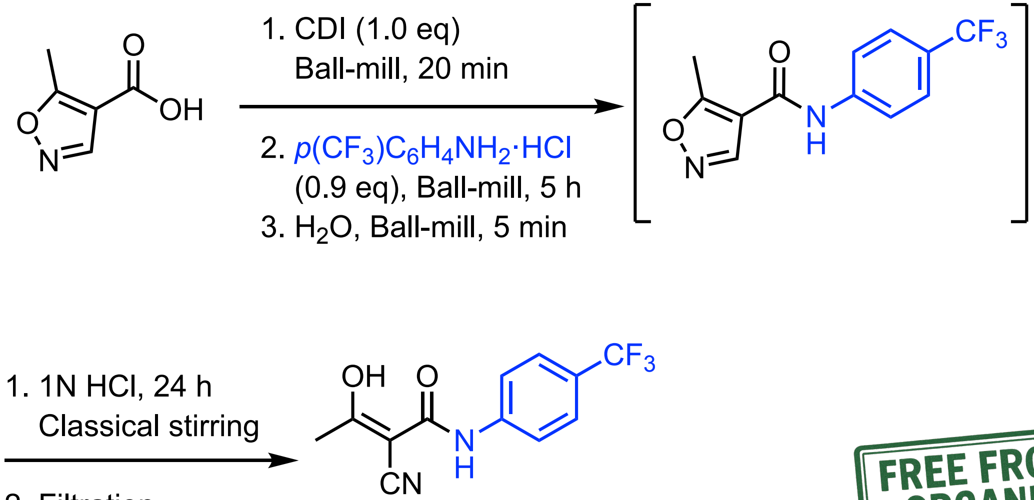
Ball-mill = Broyeur à billes



ZERO SOLVANT ORGANIQUE !

IBMM Institut des Biomolécules Max Mousseron

Synthesis of teriflunomide



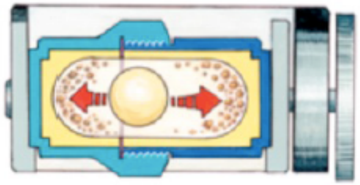
Teriflunomide (81% yield)

Teriflunomide: Actif pharmaceutique (Sclérose en plaques)

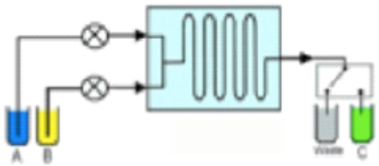
Métro, T. X.; Bonnamour, J.; Reidon, T.; Sarpoulet, J.; Martinez, J.; Lamaty, F. *Chem. Commun.* **2012**, *48*, 11781

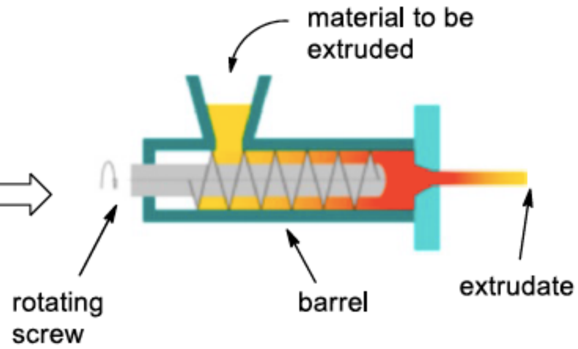
Métro, T.-X.; Bonnamour, J.; Reidon, T.; Duprez, A.; Sarpoulet, J.; Martinez, J.; Lamaty, F. *Chem. Eur. J.* **2015**, *21*, 12787

Mécanochimie en continu



+





Ball-milling

- ✅ Solid compatible
- ❌ Continuous flow
- ❌ Scalable

Solvent-based flow chemistry

- ❌ Solid compatible
- ✅ Continuous flow
- ✅ Scalable

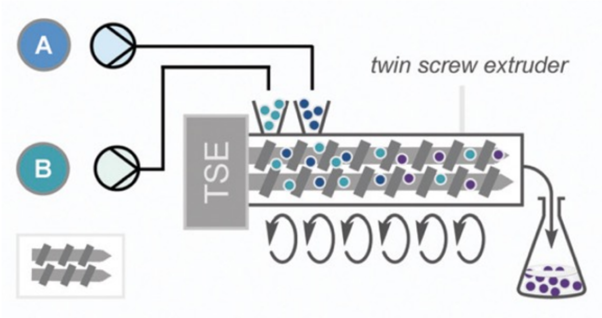
Reactive extrusion

- ✅ Solid compatible
- ✅ Continuous flow
- ✅ Easily scalable

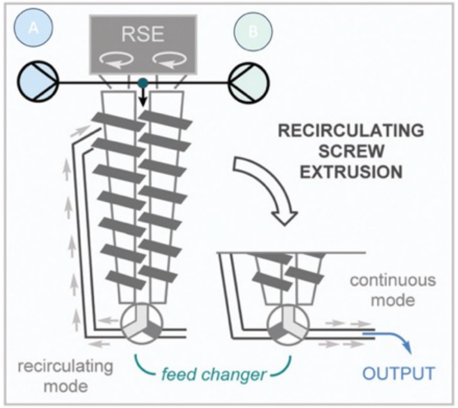
IBMM
Institut des Biomolécules Max Mousseron

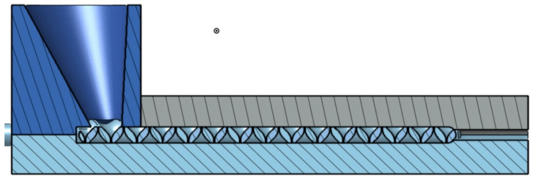
La main à la pâte

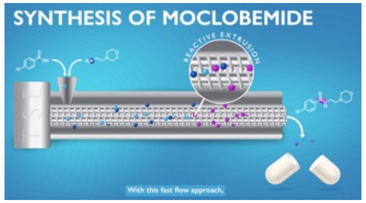
Extrudeuses double-vis



Bolt, R. R. A.; Leitch, J. A.; Jones, A. C.; Nicholson, W. I.; Browne, D. L. *Chem. Soc. Rev.* **2022**, *51*, 4243.







Video: www.greenchem.cnrs.fr

Lavayssiere, M.; Lamaty, F. *Chem. Commun.* **2023**, *59*, 3439

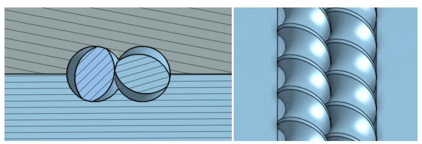
INSTITUT CARNOT Chimie Balard Cirimat

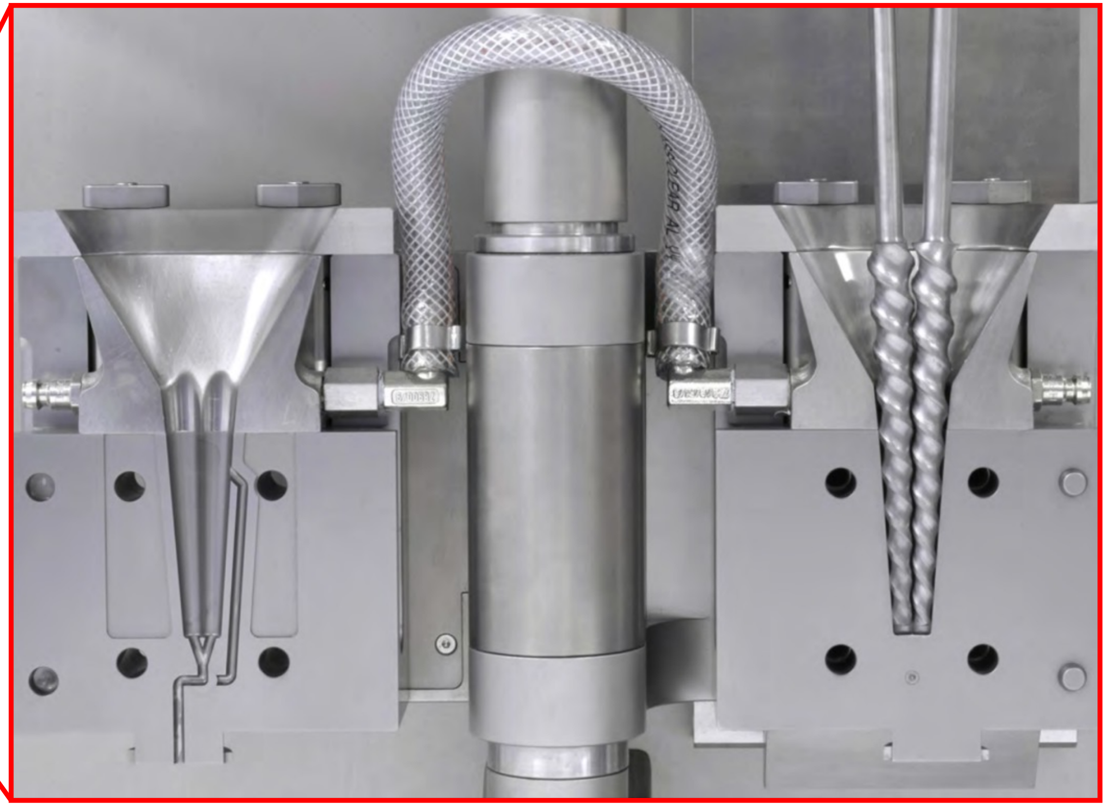
IBMM Institut des Biomolécules Max Mousseron

Extrudeuses double-vis

Pharma Melt Extruder

- Pharmaceutical compounder
- Internal volume 2 mL
- Temperature range : RT-450°C
- Speed range : 0-200 rpm
- Max torque/screw : 6 Nm



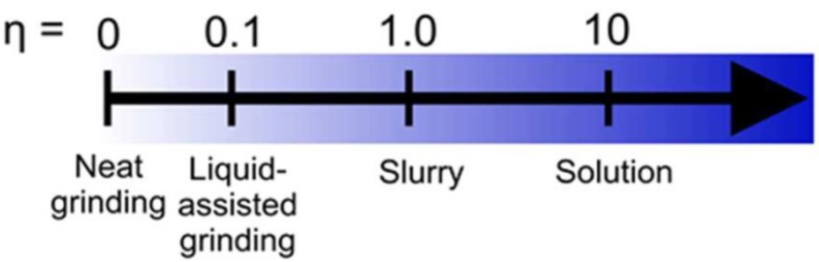


IBMM Institut des Biomolécules Max Mousseron

Additifs liquides

- De très faible quantité de liquide/solvent
- Quantification : paramètre η

$$\eta = \frac{Volume\ of\ liquid\ (\mu L)}{Total\ mass\ of\ solids\ (mg)}$$

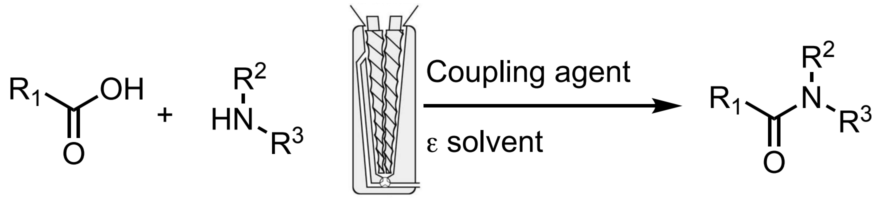


$$LAG \Leftrightarrow 0 < \eta \leq 1.0$$

Bowmaker, G.A. *Chem. Commun.* **2013**, 49, 334-348

IBMM Institut des Biomolécules Max Mousseron

Réaction dans une extrudeuse

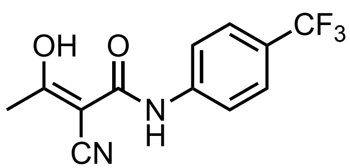


- Des solvents moins toxiques et en petite quantité: AcOEt , CH_3CN 
- Less toxic coupling agent:

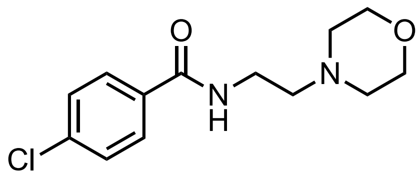
CDI

EDC.HCl (Oxyma)

COMU

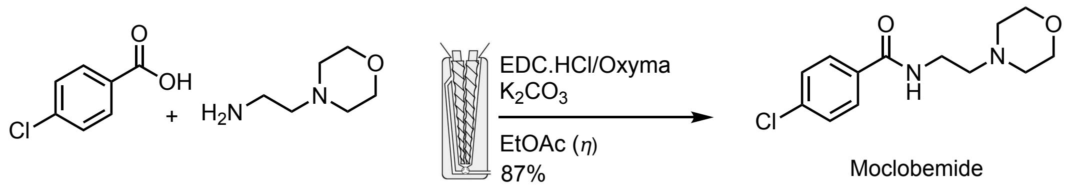


Teriflunomide

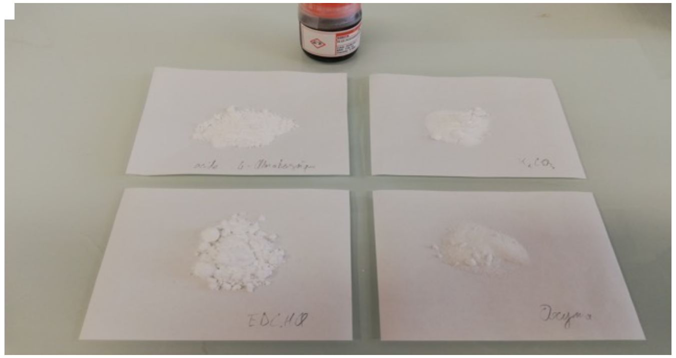


Moclobemide

Synthèse en continu du moclobemide



M. Lavayssiere

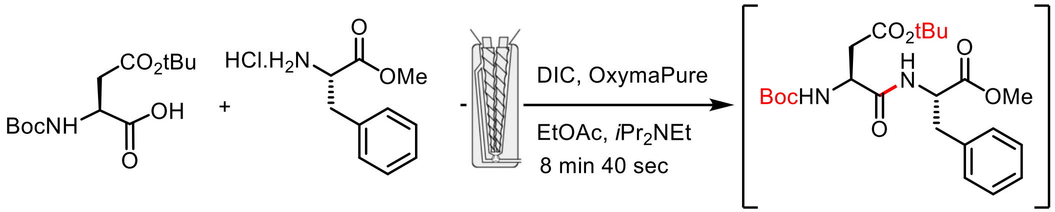


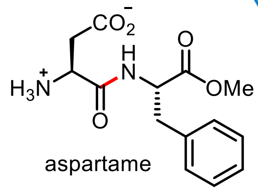
INSTITUT CARNOT
Chimie Balard Cirimat

Lavayssiere, M.; Lamaty, F.
Chem. Commun. **2023**, *59*, 3439

IBMM
Institut des Biomolécules Max Mousseron

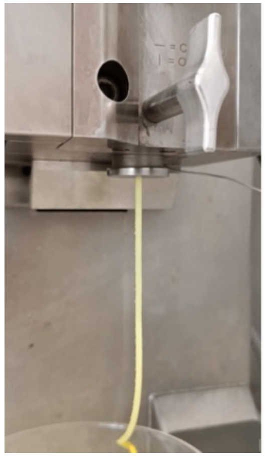
Synthèse en continu de l'aspartame

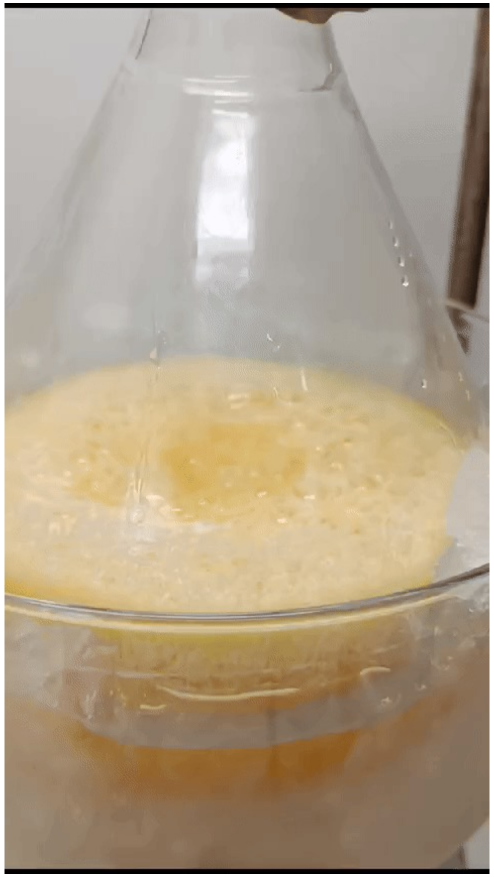


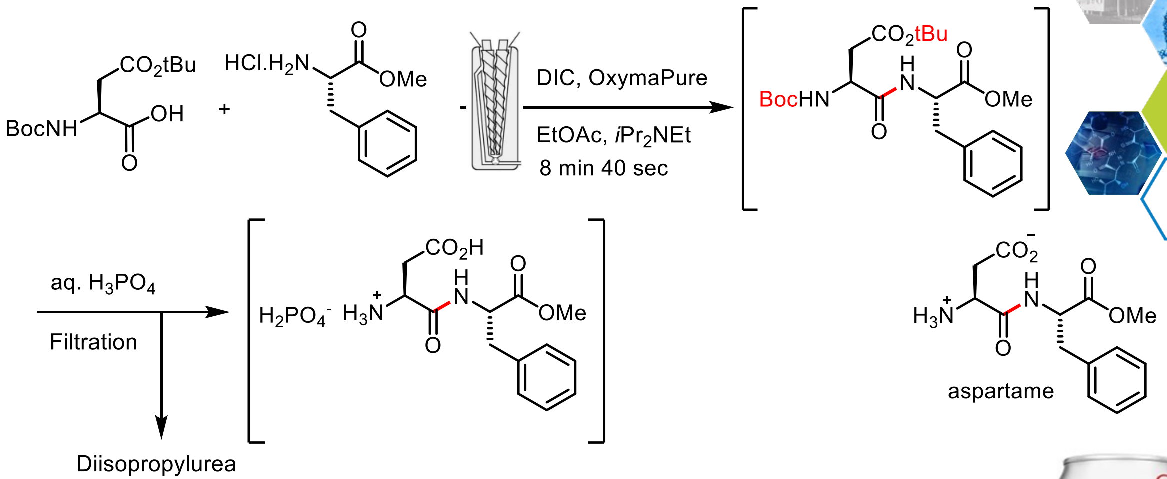


aspartame

Synthèse en continu de l'aspartame



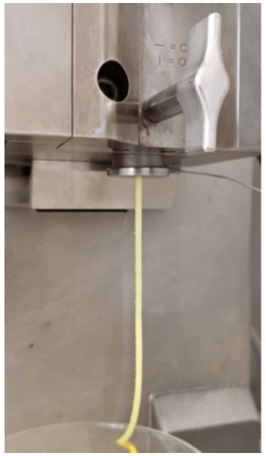


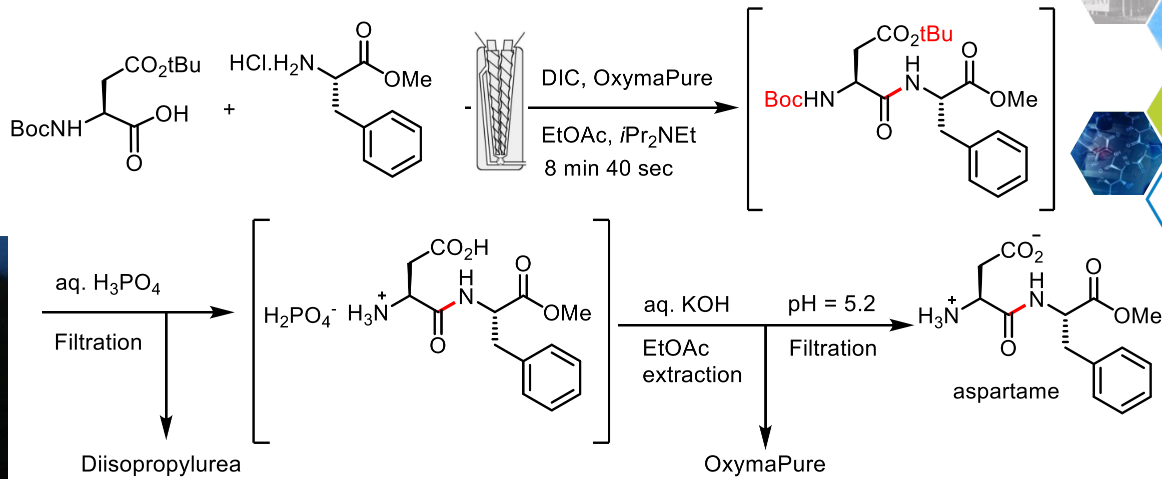


TFA = ~~CF_3COOH~~

IBMM Institut des Biomolécules Max Mousseron

Synthèse en continu de l'aspartame

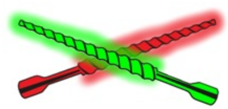




56.2 g en 8 min 40 sec (90% de rendement)

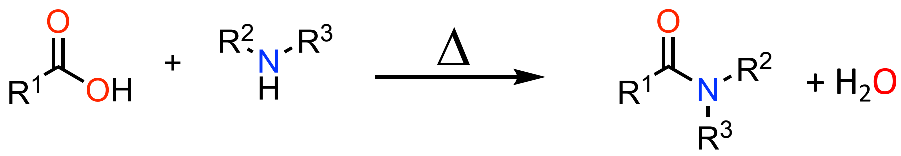
Productivité : 8 kg par jour

Déchets: 12 kg (au lieu de 200 kg)



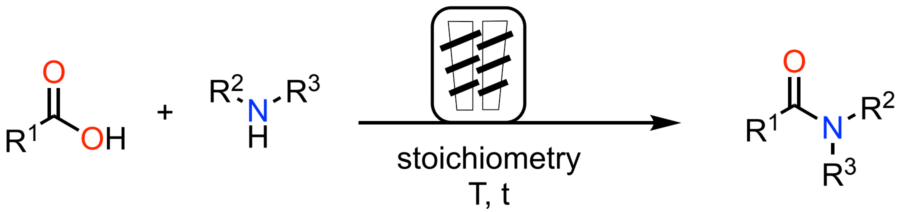
IBMM
Institut des Biomolécules Max Mousseron

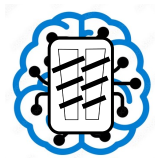
Amidation thermique et intelligence artificielle



- Sans solvant en ballon
- Sans solvant en continu
- Solvant avec un pont d'ébullition élevé
- Micro-ondes
- Tamis moléculaire

Chauffe jusqu'à 400°C



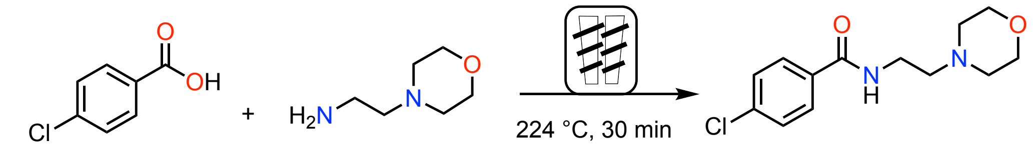


Intelligence artificielle

M. Lavayssiere

IBMM Institut des Biomolécules Max Mousseron

Optimisation Bayésienne: moclobémide



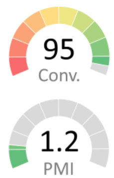
4-Chlorobenzoic acid
1 equiv.

4-(2 Aminoethyl)morpholine
1.22 equiv.

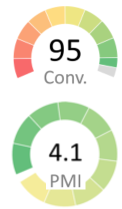
conv.: 95.2%, yield: 89%

moclobemide

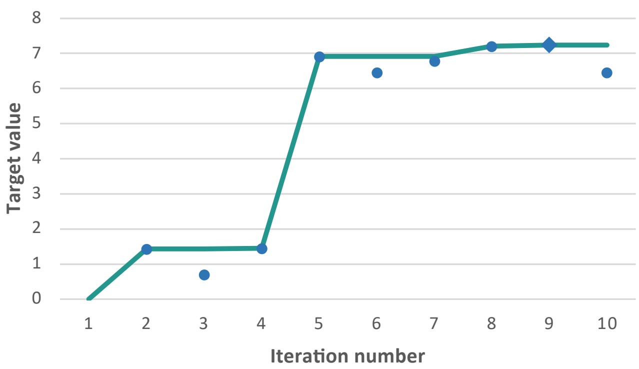
no. 09

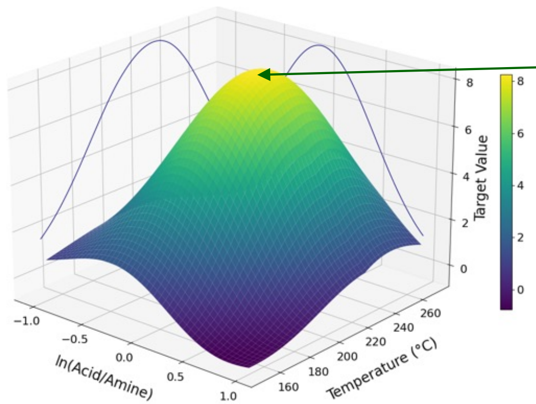


Précédemment
EDC.HCl (1)
K_2CO_3 (0.3)
oxyma (1)



Cumulative best result





- ✓ Synthèse de 16 g de moclobémide
- ✓ Absence totale de solvant, de la synthèse à la purification du produit

Lavayssiere, M.; Bantreil, X.; Lamaty, F. **2025**, ChemRxiv: 10.26434/chemrxiv-2025-zgpnz

IBMM Institut des Biomolécules Max Mousseron

What else ?

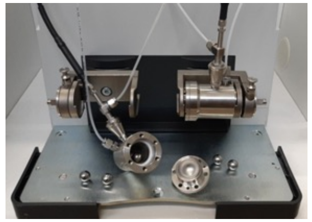
Procédé Haber-Bosch: synthèse d'ammoniac pour les engrais

$$N_{2(g)} + 3H_{2(g)} \underset{\substack{400\text{-}600\ °C \\ 20\text{-}40\ MPa}}{\overset{\text{Fe catalyst}}{\rightleftharpoons}} 2NH_{3(g)}$$

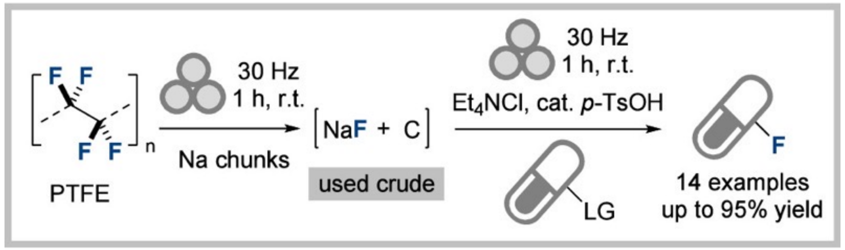
$\sim$1% des émissions mondiales de CO_2

$\sim$2% de l'énergie consommée mondiale

Mécanochimie des gaz



Recyclage des PFAS



+ cheap metal chunks + direct F^- upcycling to valuable fluorochemicals

J. Am. Chem. Soc. 2025, 147, 44, 40895

Ten Chemical Innovations That Will Change Our World

100 IUPAC

IUPAC identifies emerging technologies in Chemistry with potential to make our planet more sustainable

by Fernando Gomollón-Bel

Chemistry International April-June 2019

4 Flow chemistry

Flow synthesis has already proven to often be cheaper, higher yielding, less wasteful and sometimes safer than batch production, both in the laboratory and on an industrial scale. It also lends itself to automation, allowing chemists to run thousands of reactions a day. Combining continuous flow chemistry and polymer synthesis can produce compounds that would be hard to make in a flask.

5 Mechanochemistry and reactive extrusion

Mechanochemistry – inducing reactions though mechanical forces – sometimes makes processes possible that are hard to do by traditional solution synthesis. But scientists are still struggling to understand how the process works on a molecular scale.

IBMM Institut des Biomolécules Max Mousseron

ENS C M Chimie Montpellier

GREEN CHEMISTRY AND ENABLING TECHNOLOGIES

Prof. Xavier Bantreil
Dr Nicolas Pétry

Prof. Jean Martinez
Dr Thomas-Xavier Métro

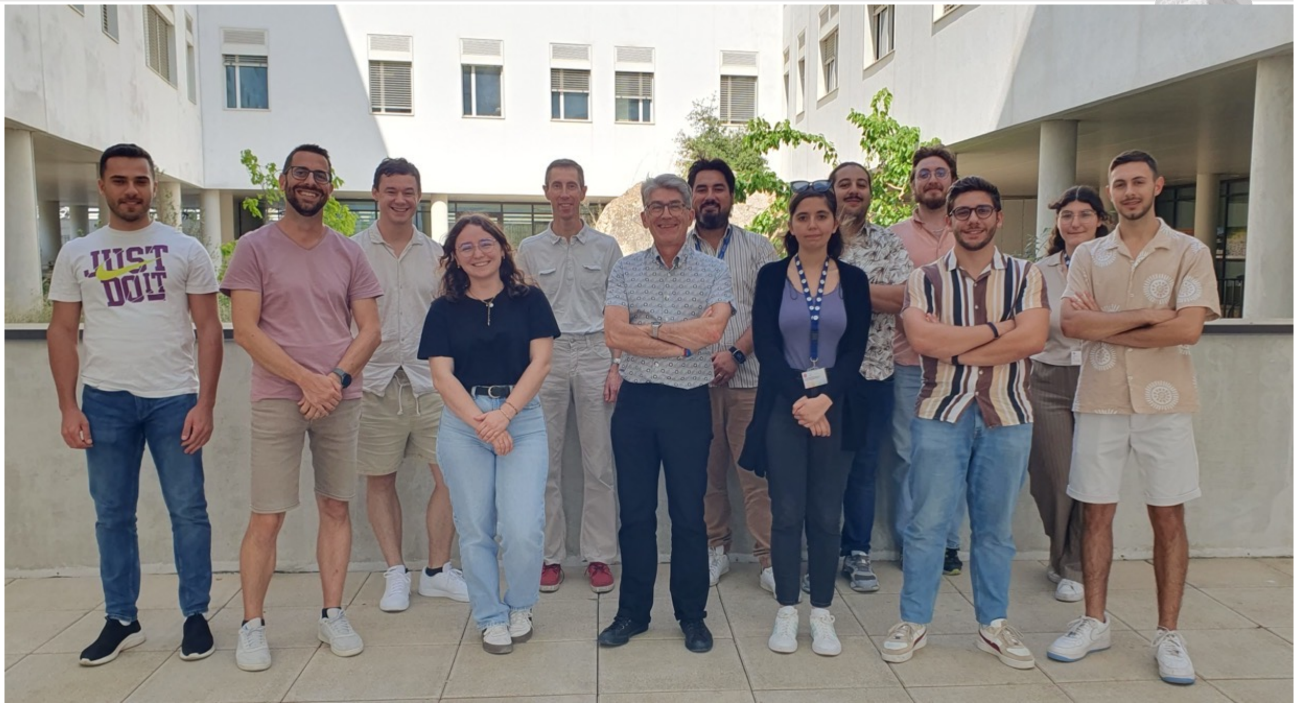
Dr Julien Bonnamour
Yves Yeboue
Dr Tharwat Mohy El-dine
Matthieu Lavayssiere

IBMM Peptides Prof. Gilles Subra
IBMM Nucleosides Prof. Béatrice Roy,
Dr Suzanne Peyrottes

JUMC Kraków (Poland)
Vittorio Canale, Prof. Paweł Zajdel

PolyPeptide GROUP

Dr Hélène Adihou
Dr Olivier Ludemann-Hombourger



Liberté • Égalité • Fraternité
République Française
Ambassade de France en Pologne

anr

LabEx CheMISyst

INSTITUT CARNOT Chimie Balard Cirimat

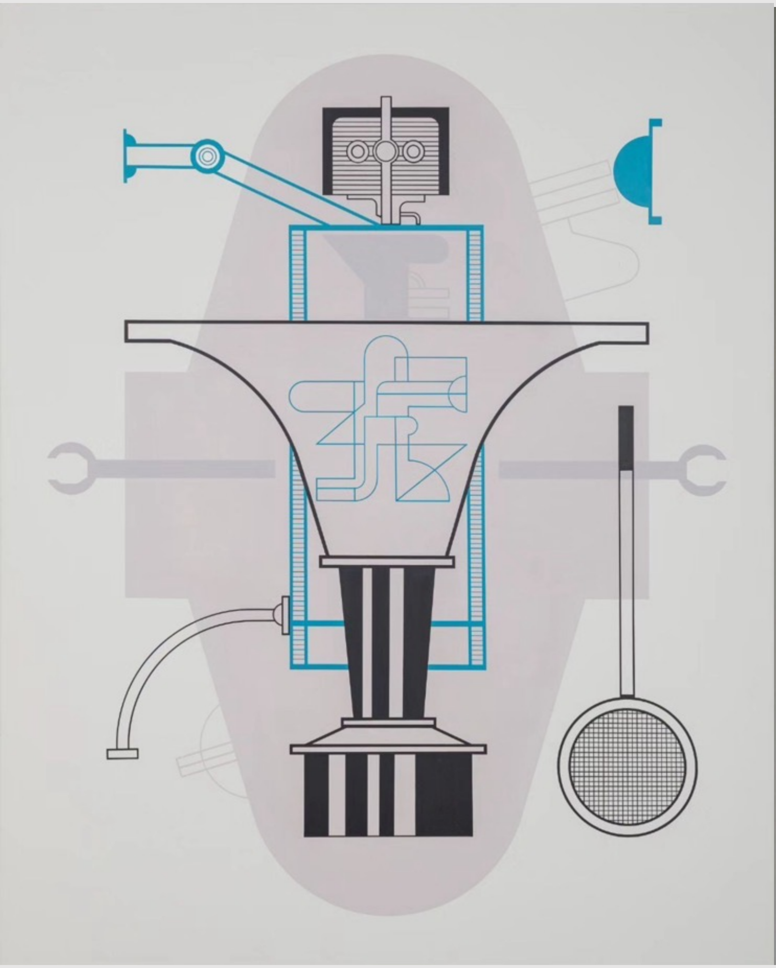
MUSE MONTPELLIER UNIVERSITY OF EXCELLENCE

IUF

PolyPeptide GROUP

IBMM Institut des Biomolécules Max Mousseron

Merci !



Ján Vasilko