catalysts

MDPI

Editorial

Special Issue Entitled "10th Anniversary of *Catalysts*: Recent Advances in the Use of Catalysts for Pharmaceuticals"

Andrés R. Alcántara

Department of Chemistry in Pharmaceutical Sciences, Pharmacy Faculty, Complutense University of Madrid (UCM), Ciudad Universitaria, Plaza de Ramon y Cajal, s/n, 28040 Madrid, Spain; andalcan@ucm.es

The worldwide market for active pharmaceutical ingredients (APIs) is currently in a favourable condition. This market was valued at USD 237.4 billion in 2023 and is expected to increase at a compound annual growth rate (CAGR) of 5.7% from 2024 to 2030 [1]. It has been reported that around 90% of all chemicals (including APIs) are derived from catalytic processes [2]. Beyond these raw data, the significant role of catalysis in the pharmaceutical sector goes beyond its mere involvement in synthetic pathways; it also plays a pivotal role in propelling the advancement of novel and more powerful drug candidates. In fact, the ability of catalysts to facilitate complex transformations with high selectivity enables the creation of molecular structures that might be challenging or even impossible to access through traditional methods [3]. This expanded chemical space allows researchers to explore new avenues for drug discovery, potentially leading to compounds with improved therapeutic properties, reduced side effects, or novel modes of action. Additionally, the adaptability of catalysis for pharmaceuticals spans its fundamental categories, namely homogeneous and heterogeneous, as well as the following specific types: metal-based catalysis [4–7], biocatalysis [8–11], organocatalysis [12–14] or photocatalysis [15,16]. Each type offers unique advantages, allowing academic researchers and industries to tailor the choice of catalyst to the specific requirements of a given synthetic transformation. This diversity enhances the toolbox available to chemists, fostering innovation in drug development and process optimization. Additionally, the application of catalysis in pharmaceutical manufacturing extends beyond the synthesis of APIs [17] to include the production of intermediates and key building blocks. By efficiently transforming starting materials into more complex intermediates, catalysis contributes to overall process efficiency.

The role of catalysis becomes even more pronounced in the context of sustainable chemistry. Green and sustainable practices are gaining traction in the pharmaceutical industry, driven by both regulatory pressure and a growing awareness of environmental impact [10,18]. Catalysis, with its ability to increase efficiency while minimizing the environmental footprint, aligns perfectly with these sustainability goals. As the industry strives to reduce its ecological impact, catalysis emerges as a key player in achieving greener and more sustainable pharmaceutical processes. In this sense, the increasing implementation of flow catalytic procedures [19–21] is undoubtedly fuelling the sustainable production of pharmaceuticals. This efficiency is crucial not only for reducing costs but also for enhancing the overall feasibility of bringing new drugs to market. The pharmaceutical industry's continuous quest for more economical and sustainable manufacturing processes further underscores the importance of catalysis in this field.

This Editorial is dedicated to the Special Issue entitled "10th Anniversary of Catalysts: Recent Advances in the Use of Catalysts for Pharmaceuticals". The primary objective of this Special Issue is to showcase recent examples that demonstrate the potential of various catalytic processes in the field of pharmaceuticals. In total, five papers were finally accepted for publication and inclusion in this Special Issue (four articles and one review). The contributions are listed below.

check for updates

Citation: Alcántara, A.R. Special Issue Entitled "10th Anniversary of *Catalysts*: Recent Advances in the Use of Catalysts for Pharmaceuticals". *Catalysts* **2024**, *14*, 161. https://doi.org/10.3390/catal14030161

Received: 30 January 2024
Accepted: 20 February 2024
Published: 22 February 2024

The article by Sanchez et al. (contribution #1) details the synthesis of thymol octanoate through the lipase-catalysed esterification of thymol and octanoic acid. This involved the use of both soluble lipases and immobilised lipase biocatalysts in solvent-free systems. The interest in synthesizing and applying thymol esters has surged in recent years due to their diverse biological activities, including their antioxidant, anti-inflammatory, antibacterial, antifungal, antiparasitic, mosquito-repellent, and larvicidal properties, among others [22]. Among the six examined soluble lipases, lipase B from *Candida antarctica* demonstrated the highest activity in the reaction. In biocatalysis, immobilising enzymes is a conventional strategy facilitating the transition from homogeneous to heterogeneous catalysis, thereby enhancing the recovery and reutilisation of biocatalysts [23]. However, upon immobilisation, the lipase's activity diminished, possibly attributed to constraints in the conformational changes required for a bulky substrate like thymol to access the lipase's active site. Various strategies for feeding thymol and lipase were assessed to optimise thymol octanoate production, revealing lipase inhibition by the ester product of the reaction. Addressing this challenge, a thymol/acid molar ratio of 1:4 mol/mol emerged as the optimal condition, achieving a conversion rate approaching 94%. Under these conditions, the concentration of thymol octanoate remained below levels inducing notable inhibitory effects. Moreover, the immobilised lipase preserved over 90% of its initial activity post-reaction, underscoring the enzyme's potential for deployment in successive reaction cycles.

Khiari et al. (contribution #2) reported another biocatalysed process in the production of (*S*)-2-(4-isobutylphenyl)propanoic acid (ibuprofen eutomer, also known as dexibuprofen [24]). This was achieved through the enzymatic kinetic resolution of racemic ibuprofen. In this study, the authors explored the efficacy of immobilised lipase B from *Candida antarctica*, along with the combination of organic solvents and orthoformates with varying chain sizes (ranging from one to four carbon atoms). These orthoesters serve as "water trapper/alcohol releaser molecules", resulting in a significant improvement in the enantioselectivity and enantiomeric excess of the target compound. Simultaneously, this approach tackles a substantial challenge in biocatalysis in organic media by eliminating excess water in the medium, therefore impeding the undesired reversibility of the reaction. Through the optimization of reaction conditions, the utilization of these acyl donors in the presence of a cosolvent leads to an enhanced enantiomeric excess and enantioselectivity. Specifically, employing a reaction medium comprising *iso*octane/dichloromethane 80/20 (*v*/*v*), triethyl orthoformate (TEOF), and a small quantity of EtOH to facilitate the enzymatic esterification catalysed by immobilized CALB resulted in an outstanding kinetic resolution. This approach achieved higher enantioselectivity values (up to E = 31.8) compared to similar procedures reported in the literature.

Deep eutectic solvents (DESs) are becoming quite popular, as they are very useful and versatile [25], up to the point of being termed "Green and sustainable solvents of the future" [26]. In fact, DESs not only serve as solvents for many types of catalytic processes, but they can also promote reactions by themselves, acting as catalysts. In this sense, Procopio et al. (contribution #3) present an effective and sustainable approach for *N*-Boc deprotection using a choline chloride/p-toluenesulfonic acid DES, functioning as both a reaction medium and a catalyst. This Boc amine-protecting group is widely used in both synthetic organic chemistry and peptide synthesis within multistep reactions, which are very useful for the preparation of drugs or intermediates. Anyhow, the conventional approaches for Boc removal pose many drawbacks rendering them environmentally unsound. Consequently, there is a need for a gradual refinement of Boc removal techniques to ensure practicality, cleanliness, and the minimization of potential environmental impacts, according to green chemistry principles [18]. The applied conditions facilitate the deprotection of various *N*-Boc derivatives, showing a wide substrate scope, e.g., structurally diverse amines, amino acids, and dipeptides, yielding excellent results under very mild reaction conditions.

Applications of catalytic methodologies in the pharma industry are not exclusively limited to their use in the reaction itself, but also in the downstream processes. For these

purposes, photocatalysis is as powerful tool. In this sense, the article from Quian et al. (contribution #4) reports the application of a visible-light-driven (VLD) hybrid photocatalyst (created by covalently doping Fe phthalocyanine (FePc) into a graphitic carbon nitride (gCN) skeleton) for the elimination of highly toxic nitroaromatic compounds (NACs) from wastewater [27]. Thus, the photocatalytic reduction is capable of converting NACs into their corresponding aromatic amines, easily degraded and less toxic than NACs. Utilizing p-nitrophenol (p-NP) as the model pollutant, the best of the designed hybrid catalysts (gCN-FePc-1) proved to be very effective and feasible to be reused; additionally, it showed excellent photocatalytic universality for other NACs. The authors also proposed a plausible mechanism to illustrate the photocatalytic reduction process of p-NP, highlighting how the covalent modification of FePc into the gCN skeleton is an effective strategy to modulate the electronic structure, confirming the potential of this VLD photocatalysts for eliminating NAC contamination in wastewater.

Asymmetric oxidation has emerged as a valuable tool in the synthesis of active pharmaceutical ingredients (APIs), particularly for generating optically active sulfoxides possessing different biological activities. It is well known that traditional oxidative protocols often involve non-sustainable conditions requiring the use of hazardous reagents and solvents, so that greener solvents, reagents, and catalysts are demanded. The article from García-Fernández et al. (Contribution #5) is an updated review focusing on the latest advancements in the development of environmentally friendly approaches for the synthesis of APIs and their intermediates using oxidative procedures. Many of these approaches involve biocatalytic methods, employing mild reaction conditions and reagents [28]; in this field, biocatalysed oxidative processes leading to several APIs, islatravir, captopril and modafinil are noted. Additionally, recent years have witnessed the exploration of alternative greener synthetic approaches for oxidative API synthesis, including light or light-mediated reactions and electrochemical synthesis, which are also discussed in this review. Hence, the collective use of these techniques, coupled with sustainable solvents and reagents, empowers chemists to execute green procedures in the preparation of APIs.

In conclusion, catalysis stands as a cornerstone in the synthesis of pharmaceuticals, offering unprecedented benefits in terms of efficiency, selectivity, and sustainability. As evidenced by the articles included in this Special Issue, the integration of catalytic processes has propelled drug synthesis into a new era of innovation and environmental responsibility. Continued research and collaboration across disciplines will undoubtedly shape the future landscape of catalysis in pharmaceutical development.

Acknowledgments: As the Guest Editor for the Special Issue "10th Anniversary of Catalysts: Recent Advances in the Use of Catalysts for Pharmaceuticals", I wish to convey my sincere gratitude to all the authors whose valuable contributions were featured in this issue, thereby enhancing the success of this edition. Additionally, I extend my thanks to those scientists who served as reviewers for the original manuscripts: their contributions undoubtedly played a vital role in enhancing the overall quality of the final articles. Last but not least, I would also like to thank the MDPI staff members for their help and support.

Conflicts of Interest: The author declares no conflicts of interest.

List of Contributions

1. Sánchez, D.A.; Tonetto, G.M.; Ferreira, M.L. Enzymatic Synthesis of Thymol Octanoate, a Promising Hybrid Molecule. *Catalysts* **2023**, *13*, 473. https://doi.org/10.3390/catal13030473.
2. Khiari, O.; Bouzemi, N.; Sánchez-Montero, J.M.; Alcántara, A.R. On the Use of Orthoformates as an Efficient Approach to Enhance the Enzymatic Enantioselective Synthesis of (S)-Ibuprofen. *Catalysts* **2023**, *13*, 251. https://doi.org/10.3390/catal13020251.
3. Procopio, D.; Siciliano, C.; De Rose, R.; Trombino, S.; Cassano, R.; Di Gioia, M.L. A Brønsted Acidic Deep Eutectic Solvent for N-Boc Deprotection. *Catalysts* **2022**, *12*, 1480. https://doi.org/10.3390/catal12111480.
4. Qian, J.; Liu, Y.; Zheng, W.; Zhou, B.; Dong, X. Covalent Modification of Iron Phthalocyanine into Skeleton of Graphitic Carbon Nitride and Its Visible-Light-Driven Photocatalytic Reduction of Nitroaromatic Compounds. *Catalysts* **2022**, *12*, 752. https://doi.org/10.3390/catal12070752.

5. García-Fernández, P.D.; Coto-Cid, J.M.; de Gonzalo, G. Green Oxidative Catalytic Processes for the Preparation of APIs and Precursors. *Catalysts* **2023**, *13*, 638. https://doi.org/10.3390/catal13030638.

References

1. *Active Pharmaceutical Ingredients Market Size, Share & Trends Analysis Report by Type of Synthesis (Biotech, Synthetic), by Type of Manufacturer (Captive, Merchant), by Type, by Application, by Type of Drug, by Region, and Segment Forecast to 2024–2030)*; Report ID: GVR-1-68038-348-5; Grand View Research: San Francisco, CA, USA, 2023. Available online: https://www.grandviewresearch.com/industry-analysis/active-pharmaceutical-ingredients-market (accessed on 14 February 2024).
2. Burke, A.J.; Marques, C.S.; Turner, N.J.; Hermann, G.J. *Active Pharmaceutical Ingredients in Synthesis: Catalytic Processes in Research and Development*; Wiley: Hoboken, NJ, USA, 2018; pp. 1–426.
3. Beaver, M.G.; Caille, S.; Farrell, R.P.; Rötheli, A.R.; Smith, A.G.; Tedrow, J.S.; Thiel, O.R. Building Complexity and Achieving Selectivity through Catalysis—Case Studies from the Pharmaceutical Pipeline. *Synlett* **2021**, *32*, 457–471. [CrossRef]
4. Hayler, J.D.; Leahy, D.K.; Simmons, E.M. A Pharmaceutical Industry Perspective on Sustainable Metal Catalysis. *Organometallics* **2019**, *38*, 36–46. [CrossRef]
5. Economidou, M.; Mistry, N.; Wheelhouse, K.M.P.; Lindsay, D.M. Palladium Extraction Following Metal-Catalyzed Reactions: Recent Advances and Applications in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2023**, *27*, 1585–1615. [CrossRef]
6. Borths, C.J.; Walker, S.D. Accelerating Pharmaceutical Development via Metal-Mediated Bond Formation. *Isr. J. Chem.* **2020**, *60*, 340–350. [CrossRef]
7. Chiarini, T.; Ciabatti, I.; Rossi, G.; Tavanti, C.; Zambardi, C. The role and the recovery of Platinum-Group metal catalysts in the pharmaceutical industry. *Chim. Oggi* **2020**, *38*, 10–13.
8. Schwarz, J.; Rosenthal, K.; Snajdrova, R.; Kittelmann, M.; Lütz, S. The Development of biocatalysis as a tool for drug discovery. *Chimia* **2020**, *74*, 368–377. [CrossRef]
9. Mann, G.; Stang, F.V. A Bio-logical approach to catalysis in the pharmaceutical industry. *Chimia* **2020**, *74*, 407–417. [CrossRef]
10. Alcántara, A.R.; Domínguez de María, P.; Littlechild, J.A.; Schürmann, M.; Sheldon, R.A.; Wohlgemuth, R. Biocatalysis as Key to Sustainable Industrial Chemistry. *ChemSusChem* **2022**, *15*, e202102709. [CrossRef]
11. Alcántara, A.R. Biocatalysis and Pharmaceuticals: A Smart Tool for Sustainable Development. *Catalysts* **2019**, *9*, 792. [CrossRef]
12. Farina, V. How to Develop Organometallic Catalytic Reactions in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2023**, *27*, 831–846. [CrossRef]
13. Burke, A.J. Asymmetric organocatalysis in drug discovery and development for active pharmaceutical ingredients. *Expert Opin. Drug Discov.* **2023**, *18*, 37–46. [CrossRef]
14. Han, B.; He, X.H.; Liu, Y.Q.; He, G.; Peng, C.; Li, J.L. Asymmetric organocatalysis: An enabling technology for medicinal chemistry. *Chem. Soc. Rev.* **2021**, *50*, 1522–1586. [CrossRef]
15. Callard-Langdon, E.E.; Steven, A.; Kahan, R.J. Shining a Light on the Advances, Challenges and Realisation of Utilising Photoredox Catalysis in Pharmaceutical Development. *ChemCatChem* **2023**, *15*, e202300537. [CrossRef]
16. Yang, X.; Wang, D. Photocatalysis: From Fundamental Principles to Materials and Applications. *ACS Appl. Energy Mater.* **2018**, *1*, 6657–6693. [CrossRef]
17. Chodankar, N. Use of Catalysis for API Manufacturing. In *Industrial Catalytic Processes for Fine and Specialty Chemicals*; Elsevier Inc.: Amsterdam, The Netherlands, 2016; pp. 509–595.
18. Bryan, M.C.; Dunn, P.J.; Entwistle, D.; Gallou, F.; Koenig, S.G.; Hayler, J.D.; Hickey, M.R.; Hughes, S.; Kopach, M.E.; Moine, G.; et al. Key Green Chemistry research areas from a pharmaceutical manufacturers' perspective revisited. *Green Chem.* **2018**, *20*, 5082–5103. [CrossRef]
19. Meyer, L.-E.; Hobisch, M.; Kara, S. Process intensification in continuous flow biocatalysis by up and downstream processing strategies. *Curr. Opin. Biotechnol.* **2022**, *78*, 102835. [CrossRef] [PubMed]
20. Benítez-Mateos, A.I.; Contente, M.L.; Roura Padrosa, D.; Paradisi, F. Flow biocatalysis 101: Design, development and applications. *React. Chem. Eng.* **2021**, *6*, 599–611. [CrossRef]
21. Amenós, L.; Alza, E.; Pericàs, M.A. Organocatalysis in Continuous Flow for Drug Discovery. In *Flow Chemistry in Drug Discovery*; Alcazar, J., de la Hoz, A., Díaz-Ortiz, A., Eds.; Topics in Medicinal Chemistry; Springer Nature: Cham, Switzerland, 2021; Volume 38, pp. 241–274.
22. Kowalczyk, A.; Przychodna, M.; Sopata, S.; Bodalska, A.; Fecka, I. Thymol and thyme essential oil—New insights into selected therapeutic applications. *Molecules* **2020**, *25*, 4125. [CrossRef] [PubMed]
23. Guisan, J.M.; Fernandez-Lorente, G.; Rocha-Martin, J.; Moreno-Gamero, D. Enzyme immobilization strategies for the design of robust and efficient biocatalysts. *Curr. Opin. Green Sustain. Chem.* **2022**, *35*, 100593. [CrossRef]
24. Gliszczyńska, A.; Sánchez-López, E. Dexibuprofen therapeutic advances: Prodrugs and nanotechnological formulations. *Pharmaceutics* **2021**, *13*, 414. [CrossRef]
25. Abranches, D.O.; Coutinho, J.A.P. Everything You Wanted to Know about Deep Eutectic Solvents but Were Afraid to Be Told. *Annu. Rev. Chem. Biomol. Eng.* **2023**, *14*, 141–163. [CrossRef] [PubMed]
26. Prabhune, A.; Dey, R. Green and sustainable solvents of the future: Deep eutectic solvents. *J. Mol. Liq.* **2023**, *379*, 121676. [CrossRef]

27. Xiong, Z.; Zhang, H.; Zhang, W.; Lai, B.; Yao, G. Removal of nitrophenols and their derivatives by chemical redox: A review. *Chem. Eng. J.* **2019**, *359*, 13–31. [CrossRef]
28. Hollmann, F.; Woodley, J. Biocatalytic oxidation reactions to create sustainable chemistry for the future. *Curr. Opin. Green Sustain. Chem.* **2023**, *41*, 100804. [CrossRef]