International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Impact Factor 2024: 7.101

Synthetic Access to Morpholine and Oxazolidine Derivatives as Next-Generation Antifungal Scaffolds

Ravsaheb Kalyankar[1], Savita Desai (Dhongade)[2]

[1]Research Laboratory, Department of Chemistry, Devchand College, Arjun Nagar, Tal-Kagal, Dist-Kolhapur, Maharashtra, India
Corresponding Author Email: *rskalyankar[a]rediffmail.com*

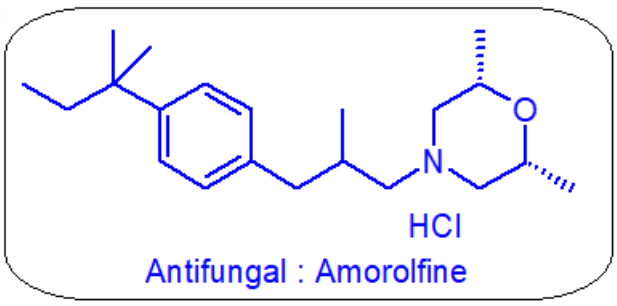
[2]Research Laboratory, Department of Chemistry, Devchand College, Arjun Nagar, Tal-Kagal, Dist-Kolhapur, Maharashtra, India
Email: *savitadhongade[at]yahoo.com*

Abstract: ***Antifungal agents are therapeutic compounds that selectively target fungal pathogens with minimal toxicity to the host, leveraging biochemical differences between mammalian and fungal cells. Allylamines such as naftifine and terbinafine, along with the morpholine-based drug amorolfine, inhibit ergosterol biosynthesis by acting on squalene epoxidase. Inspired by this mechanism, novel morpholine and oxazolidine scaffolds were explored for their synthetic potential and antifungal relevance. Scaffold-I was synthesized in 96 % yield via a self-catalyzing condensation of bromo benzoate with morpholine in DMF, circumventing the limitations of conventional Buchwald reactions that require palladium catalysts and pose challenges in catalyst removal. Morpholin-3-one and oxazolidin-2-one was prepared by condensing 2-aminoethanol with chloro acetyl chloride and by reacting epichlorohydrin with potassium isocyanate, respectively. These intermediates were further condensed with halo benzoates using K_2CO_3, NaI, and ethylenediamine in dry dioxane to yield Scaffolds II and III. Structural confirmation of the synthesized scaffolds was achieved through spectral analysis. These scaffolds are intended to be conjugated with selected linkers to develop antifungal agents with enhanced efficacy, broad administration routes, and minimal side effects. Their biological activity will be evaluated in comparison with amorolfine to assess their potential as next-generation antifungal therapeutics.***

Keywords: Morpholine, Oxazolidine, Antifungal agents, Ergosterol biosynthesis, Scaffold synthesis, Spectral analysis

1. Introduction

Fungal and bacterial infections are increasingly common in everyday life, underscoring the urgent need for novel therapeutic agents with antifungal and antibacterial properties. Despite extensive research, many available treatments—such as creams, lotions, ointments, and oral medications are associated with significant side effects and limited efficacy.



Among current antifungal agents, allylamines and morpholine derivatives have shown promising activity. Allylamines, including naftifine and terbinafine, inhibit ergosterol biosynthesis by targeting squalene epoxidase. The morpholine-based drug amorolfine also disrupts ergosterol synthesis, acting at a later stage in the same pathway. These mechanisms provide a valuable foundation for the development of new scaffolds with improved safety profiles and broader therapeutic potential.

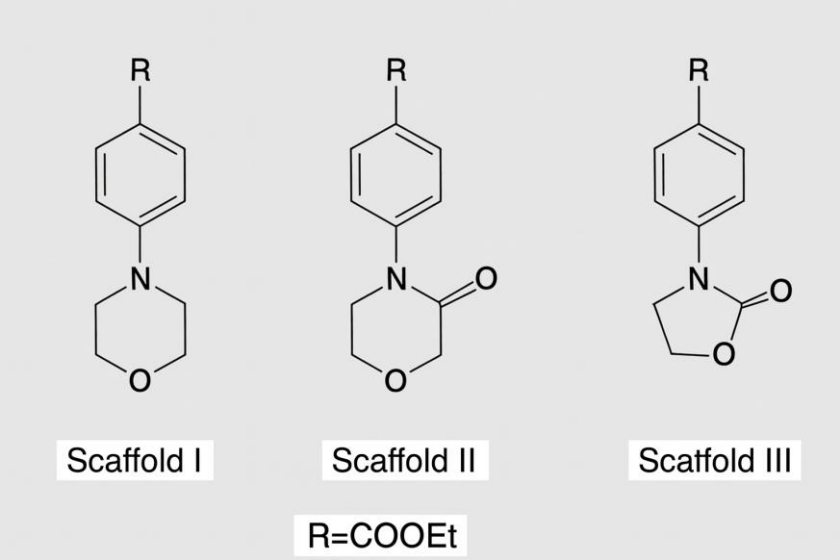
In the realm of drug discovery, the synthesis of a compound library using novel scaffolds and strategic linkers is a critical step. This library is screened against known standards to identify active compounds, referred to as "hits." Once a hit is identified, structural modifications are applied to optimize its pharmacological properties, ultimately leading to the development of a highly potent drug candidate.

With this approach in mind, our study focuses on designing and synthesizing innovative scaffolds under modified reaction conditions. Morpholine-based scaffolds were selected due to morpholine's high water solubility, which enhances bioavailability and facilitates formulation across various delivery systems.

In pursuit of novel antifungal agents, we synthesized a series of scaffolds bearing structural resemblance to amorolfine. These analogs incorporate diverse heterocyclic units to probe structure–activity relationships.

A series of novel scaffolds were planned to synthesize starting from substituted benzyl halides (R = F, Cl, Br), employing distinct nucleophilic partners and reaction conditions to generate structural diversity.

- **Scaffold-I** was planned by reacting substituted benzyl halides with a Morpholine derivative, resulting in the formation of a benzyl–Morpholine linkage.
- **Scaffold-II** was planned by reacting substituted benzyl halides with a Morpholine-3-one derivative, resulting in the formation of a benzyl–Morpholinone linkage.
- **Scaffold-III** was planned by reacting substituted benzyl halides with a 1,3-Oxazolidine-2-one derivative, resulting in the formation of a benzyl 1,3-Oxazolidine-2-one linkage, Bellow are the structures of planned scaffolds for synthesis:



Optimized reaction Conditions, Yield and Analysis for Scaffold-1:

Figure 1: Synthesis of Scaffold-1 via Morpholine condensation with substituted ethyl benzoate.

Condition A: The conventional approach to alkylation typically involves the use of a base and a polar solvent under ambient or elevated temperatures. In contrast, our method deliberately avoids the use of external base. Instead, we employed two equivalents of the alkylating agent (morpholine) in a minimal volume of DMF, maintaining the reaction at 90 °C for 8 hours. To evaluate the influence of the halide substituent (R) on reaction efficiency, we varied the halide group on the benzyl substrate.

The yields of Scaffold-1 were found to be highly dependent on the nature of R:

- **R = F**: Yield = 58.57 %; significant starting material remained, indicating incomplete conversion.
- **R = Cl**: Yield = 60.98 %; reaction proceeded partially, with residual starting material.
- **R = Br**: Yield = 94 %; reaction reached completion with excellent conversion.

Scaffold-1 was synthesized via a base-free alkylation approach using morpholine as both the nucleophile and internal base, with DMF as the solvent. The reaction was carried out at 90 °C for 8 hours. To evaluate the influence of the halide substituent on reactivity and yield, ethyl benzoate derivatives bearing fluorine, chlorine, and bromine were employed as starting materials. Among the tested substrates, **ethyl-4-bromobenzoate** demonstrated superior performance, yielding Scaffold-A at **94 %** without requiring further purification. Upon completion, the addition of water to the reaction mixture facilitated the precipitation of a white solid product.

These results highlight the superior reactivity of the bromo derivative under base-free conditions, making it the preferred substrate for efficient scaffold synthesis. The enhanced yield observed with the bromo derivative may be attributed to its **higher reactivity**, likely influenced by the **lower boiling point** and better leaving group ability of bromine compared to fluorine and chlorine. These findings underscore the importance of halide selection in optimizing reaction efficiency under mild, base-free conditions.

Development of a Pd-Free C–N Bond formation strategy for Scaffold-2:

Scaffold-2 involved two steps synthesis: initially, intermediate-3 was treated with intermediate-4 in presence of $NaHCO_3$ and DCM to get marpholine-2-one (5). This intermediate-5 was then treated with ethyl benzoate derivatives under optimized condition to get scaffold-2.

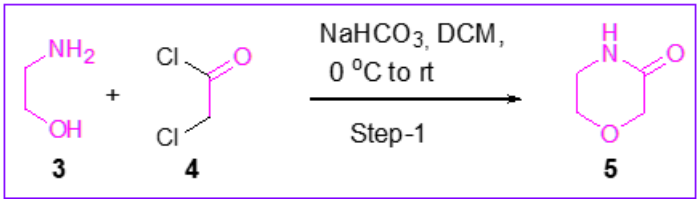


Figure 2: Synthesis of Morpholin-3-one via cyclization of 2-Aminoethanol with Chloroacetyl chloride

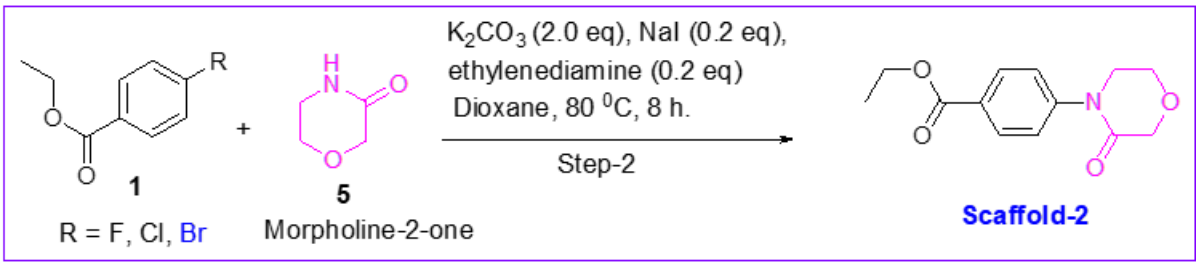


Figure 3: Synthesis of Scaffold-2 via condensation of substituted ethyl benzoate with morpholin-2-one

The synthesis was accomplished without employing any palladium-catalyzed conditions. Although numerous Pd-mediated protocols, such as the Buchwald reactions are well-documented in the literature, they often introduce trace metal impurities that are challenging to remove from the final product. To overcome this limitation, we developed a novel, metal-free approach for carbon–nitrogen bond formation. Our optimized reaction conditions involved the use of **K_2CO_3 (2.0 eq), NaI (0.2 eq), and ethylenediamine (0.2 eq)** in **dry dioxane** at **80 °C**,

Development of a Pd-Free C–N Bond formation strategy for Scaffold-3:

Scaffold-3 involved a two steps synthesis: initially, epichlorohydrin (7) intermediate was treated with potassium cyanate-6 (KCNO) under reflux in water to afford a urea-linked scaffold 1,3-Oxazolidine-2-one derivative to get intermediate-8. Further intermediate-8 was treated with para-substituted ethyl benzoate under the catalyst free optimized reaction condition to obtained enhanced functional complexity scaffold-3.

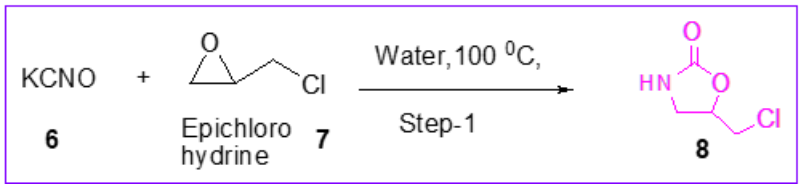


Figure 4: Synthesis of Oxazolidin-2-one via cyclization of epichlorohydrin with potassium cyanate

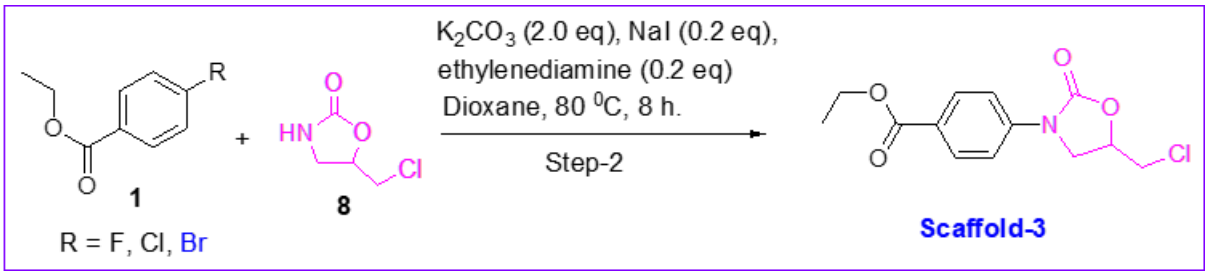


Figure 5: Synthesis of Scaffold-3 via condensation of substituted benzyl esters with oxazolidin-2-one

2. Results and Discussion

Optimized reaction conditions for Scaffold-1:

A base-free alkylation strategy was employed for the synthesis of Scaffold-1, using morpholine as both nucleophile and internal base. The reaction was conducted in DMF at 90 °C for 8 hours. To assess the impact of halide substituents on reactivity, ethyl benzoate derivatives bearing fluorine, chlorine, and bromine were tested:

Halide Substituent (R)	Yield (%)	Observation
F	58.57	Incomplete conversion; residual starting material
Cl	60.98	Partial reaction; residual starting material
Br	94	Complete conversion; excellent yield

The bromo derivative exhibited superior reactivity, attributed to its better leaving group ability and lower boiling point. The reaction yielded a white solid upon aqueous workup, requiring no further purification.

Pd-Free C–N Bond Formation Strategy for Scaffold-2:

To circumvent the limitations of palladium-catalysed protocols, a metal-free approach was developed. The reaction utilized K_2CO_3 (2.0 eq.), NaI (0.2 eq.), and ethylenediamine (0.2 eq.) in dry dioxane at 80 °C. This method yielded Scaffold-2 in 78 % isolated yield. Alternative solvents such as DMF and THF were evaluated, but dioxane consistently provided cleaner reactions and higher yields.

Optimized Synthesis of Scaffold-3:

Scaffold-3 was synthesized under similar conditions using K_2CO_3, NaI, and ethylenediamine in dry dioxane at 80 °C. The reaction afforded the desired product scaffold-3 in 72 % yield. This strategy offers a sustainable and efficient alternative to metal-catalysed methods.

Strategic Scaffold Development:

The synthesized scaffolds serve as modular platforms for further diversifications and coupling with nucleophilic partners such as amines and Grignard reagents, and incorporation of heterocyclic frameworks, enables systematic exploration of structure–activity relationships.

Each scaffold introduces unique heterocyclic or functional motifs, contributing to a diverse compound library for antifungal screening. The modular approach allows for systematic variation of substituents and ring systems, facilitating structure activity relationship (SAR) studies.

3. Experimental Section

Scaffold-1: Synthesis of 4-Morpholine Ethyl Benzoate:
Ethyl-4-bromobenzoate (10.0 g, 43.65 mmol) was dissolved in DMF (20 mL) and treated with morpholine (15.19 g, 174.6 mmol). The mixture was heated at 90 °C for 8 hours. TLC (10 % ethyl acetate in hexane) confirmed completion. Then added Water (100 mL), and the precipitate was filtered to yield a white solid (9.75 g, 94 %).

Analytical Data:

- Molecular Formula: $C_{13}H_{17}NO_3$; Mass (ESI-MS): $[M+H]^+$ = 236.28
- ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22 (t, J = 7.2 Hz, 3H), 3.21-3.34 (m, 4H), 3.80-3.92 (m, 4H), 4.38 (q, J = 6.7 Hz, 2H), 6.87 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H).

Using the same reaction conditions, **ethyl-4-fluorobenzoate** afforded a **white solid** (8.2 g) in **58.57 % yield**, while **ethyl-4-chlorobenzoate** produced a **white solid** (7.80 g) in **60.98 % yield**. In both cases, incomplete conversion was observed, with residual starting material remaining. These results suggest that the nature of the halogen substituent significantly influences the reactivity and overall yield, with bromine proving to be the most effective leaving group under the applied conditions.

Synthesis of Morpholin-3-one:
To a solution of 2-Aminoethanol (10.0 g, 163.45 mmol) in DCM (100 mL) was cooled to 0 °C and treated with sodium bicarbonate and then Chloro acetyl chloride (27.69 g, 245.17 mmol) was added dropwise. The mixture was stirred at room temperature for 8 hours. TLC (5 % methanol in DCM) confirmed completion of 2-Aminoethanol and new non-polar spot-on TLC stain (KMnO4). Then reaction mixture quenched with water (100 mL) and extracted product in DCM (100*2) and dried over sodium sulphate and concentrated to obtained **Morpholin-3-one** (12.0 g, 75.66 %) as white solid.

Analytical Data:

- Molecular Formula: $C_4H_7NO_2$; Mass (ESI-MS): $[M+H]^+$ = 102.28
- ^1H NMR ($CDCl_3$, 400 MHz): δ 3.60-3.72 (m, 2H), 4.13-4.21 (m, 2H), 4.38 (s, 2H).

Scaffold-2: (4-Morpholin-3-one Ethyl Benzoate):
Ethyl-4-bromobenzoate (10.0 g, 43.65 mmol) in dry dioxane (60 mL) was treated with NaI (1.64 g, 8.67 mmol), K_2CO_3 (11.98 g, 86.72 mmol), ethylenediamine (0.5 g, 8.67 mmol), and morpholin-3-one (5.29 g, 52.38 mmol). The mixture was stirred at 80 °C for 4 hours. TLC (50 % ethyl acetate in hexane) confirmed complete conversion of starting material and new polar spot was observed. Then reaction was quenched by water (100 mL) and product was extracted in ethyl acetate (500 mL) dried over sodium sulphate and organic layer evaporated under reduced pressure to obtained Morpholin-3-one Ethyl Benzoate (8.4 g, 78.46 %) as solid compound.

Analytical Data:

- Molecular Formula: $C_{13}H_{15}NO_4$; Mass (ESI-MS): $[M+H]^+$ = 250.38
- ^1H NMR ($CDCl_3$, 400 MHz): δ 1.23 (t, J = 7.2 Hz, 3H), 3.67-3.74 (m, 2H), 4.05-4.12 (m, 2H), 4.30 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 7.17 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 8.0 Hz, 2H).

Synthesis of 5-(Chloromethyl)-1,3-Oxazolidine-2-one:
Potassium isocyanate (13.12 g, 162.15 mmol) in water (100 mL) was treated with epichlorohydrin (10.0 g, 108.07 mmol) and stirred at 80 °C for 8 hours. TLC (5 % methanol in DCM) confirmed the starting material consumed then reaction quenched with water (150 mL) and extracted in DCM (200*2) dried over sodium sulphate and organic layer evaporated under reduced pressure to obtained 5-(Chloromethyl)-1,3-Oxazolidine-2-one (12.3 g, 87.86 %) solid compound.

Analytical Data:

- Molecular Formula:$C_4H_6ClNO_2$; Mass (ESI-MS): $[M+H]^+$ = 135.98
- ^1H NMR ($CDCl_3$, 400 MHz): δ 3.52 (d, J = 10.5 Hz, 2H), 3.86 (d, 2H), 4.86 (m, 1H), 5.88 (bs, 1H)

Scaffold-3: (Oxazolidine Ethyl Benzoate): Synthesis of 4-5-(chloromethyl)-1,3 oxazolidine -2-one ethyl benzoate: In the solution of ethyl-4-bromo benzoate (10.0 g,43.65 mmol) in 1:4 dioxine (60 mL) under dried nitrogen atmosphere added NaI (1.64 g, 8.67 mmol), K_2CO_3 (11.98 g, 86.72 mmol), ethylenediamine (0.5 g, 8.67 mmol) and 5-(chloromethyl)-1,3 oxazolidine -2-one (7.10 g, 52.38 mmol) stirred at 80 ^{0}C for 4 h. The reaction monitored with TLC solvent 50 % ethyl acetate in hexane new polar spot was observed. The reaction was quenched by water (100 mL) and extracted in ethyl acetate (500 mL) dried over sodium sulphate and organic layer evaporated under reduced pressure to obtained 4-5-(chloromethyl)-1,3 oxazolidine -2-one ethyl benzoate (8.60 g, 72.76 %) solid compound.

Analytical Data:

- Molecular Formula: $C_{13}H_{14}ClNO_4$; Mass (ESI-MS): $[M+H]^+$ = 270.78
- ^1H NMR ($CDCl_3$, 400 MHz): δ 1.22 (t, J = 7.2 Hz, 3H), 3.76 (t, J = 6.2 Hz, 2H), 3.85 (t, J = 6.5 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.15-4.24 (m, 1H), 4.83-4.90 (m, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H).

4. Conclusion

The successful synthesis of morpholine- and oxazolidine-based scaffolds through efficient, catalyst-free and high-yielding routes highlights their strong potential as novel antifungal frameworks. Structural validation confirms the integrity of these intermediates, which are designed for further conjugation with linkers to optimize pharmacological properties. By circumventing conventional palladium-catalyzed limitations and enabling versatile scaffold construction, this work establishes a foundation for developing next-generation antifungal agents. The

comparative biological evaluation against amorolfine will determine their efficacy, paving the way toward safer, more effective therapeutics with broad applicability.

Acknowledgment

The author, *Ravsaheb Kalyankar*, wishes to express his heartfelt gratitude to the Principal of Devchand College, Arjun Nagar, Tal-Kagal, Dist-Kolhapur, Maharashtra, India, for providing the invaluable opportunity to carry out research work in the chemistry laboratory. The author is deeply thankful for the principal's kind support in facilitating the preparation of this publication and for enabling access to analytical data from the University Department, which greatly strengthened the quality of this research. The author extends sincere thanks to *Dr. Savita Desai* for her valuable guidance and unwavering support throughout the course of this work.

References

[1] Phan, H.M.; Mai, T.T.; Don, T.N.Q.; Do, D.T.; Minh, K. *Curr. Top. Med. Chem.* 2025, *21*(1), 61–68. DOI: 10.2174/0115734064316022240801093905.
[2] Urgaonkar, S.; Xu, J.; Verkade, J.G. *J. Org. Chem.* 2003, *68*, 8416–8423.
[3] Jachak, G.R.; Ramesh, R.; San, D.G. *ACS Med. Chem. Lett.* 2015, *6*(11), September 22.
[4] Dolengovski, E.L.; Gryaznova, T.V.; Sinyashin, O.G.; Gavrilova, E.L.; Kholin, K.V.; Budnikova, Y.H. *Catalysts* 2023, *13*, 1279.
[5] Kőnig, B.; Sztanó, G.; Holczbauer, T.; Soós, T. *J. Org. Chem.* 2023, *88*, 6182–6191.
[6] Yadav, R.N.; Srivastava, A.K.; Banik, B.K. In *Green Approaches in Medicinal Chemistry for Sustainable Drug Design*; Elsevier: 2020; pp. 353–425.
[7] Han, C.; Cai, L.; Zhang, D.; Pan, R.; Li, Q.; Lin, A.; Yao, H. *CCS Chem.* 2022, *4*, 616–624.
[8] Chen, Z.; Hu, S.; Wu, X.-F. *Org. Chem. Front.* 2020, *7*, 223–254.
[9] Kumari, A.; Singh, R.K. *Bioorg. Chem.* 2020, *96*, 103578.
[10] Skoulikas, M. *Novel Morpholine-Based MTORC Inhibitors as Anti-Tumour Agents*; University of Huddersfield: 2020.
[11] Wang, H.; Meng, Y.; Yang, J.; Huang, H.; Zhao, Y.; Zhu, C.; Wang, C.; Liu, F.-W. *Eur. J. Med. Chem.* 2022, *238*, 114420.
[12] Tzara, A.; Xanthopoulos, D.; Kourounakis, A.P. *ChemMedChem* 2020, *15*, 392–403.
[13] Sıcak, Y.; Aktar, B.S.K.; Yılmaz, G.T.; Öztürk, F.A.; Öztürk, M.; Tok, T.B.T.K.; Emre, E.E.O. *ACS Omega* 2023, *8*, 38641–38657.