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Regioselective Oxidation of Tetrahydronaphthalenes to α-Tetralone Derivatives Using DDQ as Oxidizing Agent: Synthesis and Evaluation of Antibacterial and Antifungal Activities

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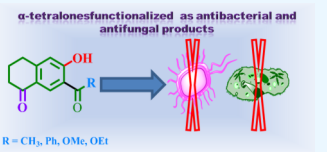
ABSTRACT: An easy and efficient approach for the synthesis of highly regioselective functionalized dihydronaphthalen-1(2*H*)-one family of α-tetralones from functionalized tetralone precursors which derived from Morita−Baylis−Hillman (MBH) adducts as starting substrates has been developed. The target dihydronaphthalen-1(2*H*)-ones are obtained through the oxidation of tetrahydronaphthalenes (THN) using DDQ as the oxidizing agent, conducted in aqueous acetic acid at reflux conditions. The yields obtained ranged from 90 to 98%. The resulting dihydronaphthalen-1(2*H*)-ones were evaluated for their *in vitro* antibacterial activity against nine Gram-positive and six Gram-negative strains. Additionally, their antifungal properties were assessed against three fungal pathogens by using the microdilution method and Biolog Phenotype Microarrays technology. Remarkably, the synthesized dihydronaphthalen-1(2*H*)-ones exhibited good antibacterial activity when compared to reference drugs such as vancomycin and ampicillin. Similarly, their antifungal activity is comparable to the effectiveness of the reference drugs cycloheximide and fluconazole.



1. INTRODUCTION

The α-tetralones, specifically the dihydronaphthalen-1(2*H*)-one family, represent a highly valuable class in organic synthesis. Various reactions have been successfully applied to this family, including the synthesis of zeolites,[1] electrophilic fluorination reactions,[2] α-alkylation reactions,[3−5] ortho-sulfonamidation,[6] and a spectrum of other organic synthesis methodologies.[7−10]

Beyond their significance as basic parts in organic synthesis intermediates, α-tetralones are important in the fields of biology and medicine. They are recognized as potent inhibitors of monoamine oxidase and serve as growth regulators in agricultural and horticultural applications. Medical applications have embraced α-tetralones not only for their antiproliferative properties but also for their therapeutic versatility in antibiotics, antidepressants and acetyl cholinesterase inhibitors, proving effective in Alzheimer's disease treatment.[11−16] Additionally, tetralones have been used as intermediates in the synthesis of several compounds, such as alkaloids, which have been shown to have antitumor and anticancer activity,[14−18] noteworthy antiviral activity, and play a role in the treatment of neurological disorders as adenosine receptor antagonists, demonstrating efficacy in addressing neurodegenerative disorders like Alzheimer's disease.[15,17,19] α-Tetralones have also shown promise as antimalarials and exhibit potent antifungal and antibacterial properties.[17,18] Impressively, they exhibit antioxidant, antidiabetic, and anti-inflammatory characteristics as well.[17−18]

Compounds containing structures with α-tetralones are inherently present in nature, signifying their status as natural products.[20] These compounds are in great demand due to their diverse applications, as previously noted. This opens up opportunities for researchers worldwide to expand their synthesis methods and discover more diverse applications. To investigate further, we thoroughly examined the literature to review the documented methods for synthesizing α-tetralones. One approach involves intramolecular Friedel−Crafts acylation reactions, resulting in the formation of α-tetralones.[19] Another method is the Robinson method,[21,22] although it requires a multistep synthesis. Additionally, radical cyclization reactions have been explored in the presence of peroxide.[23] The Diels−Alder (4 + 2) cycloaddition reaction is another pathway.[24−27] Other techniques include cyclization reactions catalyzed by transition metals, using rhodium as a catalyst,[28] or through the cyclization of cyclobutanols catalyzed by silver.[29] Furthermore, the coupling between 2-vinyl benzaldehyde and 3-alkenyl-2-bromoesters, catalyzed by copper(II) bromide, represents another viable synthesis route.[30]

Several additional methods have been devised for synthesizing α-tetralones, with notable approaches including the benzyl oxidation reaction using the LaLonde method or various

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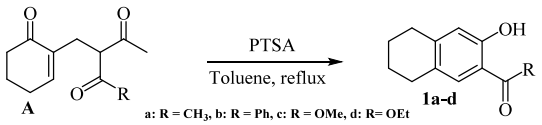
oxidizing agents, such as potassium permanganate ($KMnO_4$), chromium trioxide (CrO_3), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[31−33] The diversity of these methods emphasizes the range of possibilities for obtaining α-tetralones. Concluding our examples, we highlight the decarboxylative cyclization reaction of Dieckmann[34] and methods rooted in photocatalysis.[33] In our prior research endeavors, we successfully prepared functionalized tetrahydronaphthalenes (THN) from Morita−Baylis−Hillman adducts.[35,36] These adducts are renowned for their distinctive chemical and biological activities.[36−41] This work focuses on utilizing tetrahydronaphthalenes (THN) derived from Morita−Baylis−Hillman (MBH) adducts to establish an innovative pathway for the highly regioselective synthesis of a novel series of functionalized α-tetralones (dihydronaphthalen-1(2*H*)-one). This involves oxidizing THN using DDQ as the oxidant, with acetic acid serving as the solvent. Our focus extends to exploring the potential biological activities of these α-tetralones, specifically their efficacy against bacteria and fungi.

2. RESULTS AND DISCUSSION

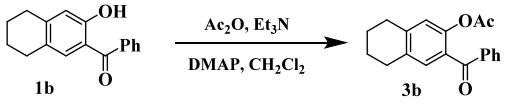
2.1. Chemistry. The synthesis of a series of tetrahydronaphthalenes (THN) (**1a−d**) were prepared from β-diketones (**A**) in the presence of a catalytic quantity of PTSA, at the reflux temperature of toluene with excellent yields (Scheme 1).[36]

Scheme 1. Synthesis of Tetrahydronaphthalenes 1a−d



In a first attempt, we adopted the approach of Gatak *et al.*, which involves the protection of the OH function within the aromatic core to prevent any potential oxidation of this hydroxyl group. Following this, and subsequent to the acquisition of THN in the acetate **3b** form using the standard method (as outlined in Scheme 2),we proceeded with the

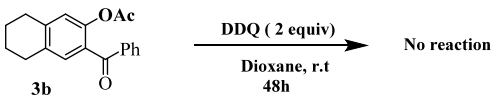
Scheme 2. Protection of Tetrahydronaphthol 1b



oxidation reaction of acetate **3b** in dioxane.[42] This reaction was conducted in the presence of 2 equiv of DDQ at room temperature, in alignment with the procedure detailed by Gatak *et al.* After 2 days, we recovered the intact starting substrate **3b** (Scheme 3).

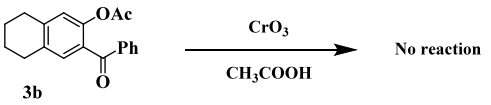
It is important to note that Gatak *et al.*,[42] employed the DDQ−dioxane method for a tetrahydronaphthalene (THN) featuring aromatic nuclei with two acetate groups. However,

Scheme 3. Attempt to Oxidize Acetate 3b Using DDQ



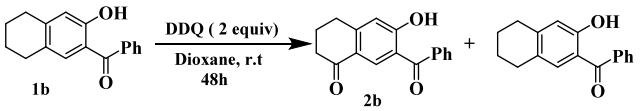
they encountered difficulties in achieving the oxidation product using this method, particularly for the THN carrying two acetate groups on the aromatic nucleus. To overcome this challenge, they turned to the chromium trioxide (CrO_3) method as an oxidant in glacial acetic acid, successfully obtaining their oxidation products. In our pursuit, we replicated this approach outlined by Gatak *et al.*, but unfortunately, the same method did not yield the desired results for our product **3b** (Scheme 4).[42]

Scheme 4. Attempt to Oxidize Acetate 3b Using CrO_3



In a recent study, Wang et al. employed the DDQ method in H_2O to oxidize a tetrahydronaphthalene (THN) featuring hydroxyl (OH) groups in its aromatic ring and, notably, without prior protection. They successfully achieved their intended final product.[42] Inspired by the successful work of Yazhou Wang *et al.* we similarly treated our THN **1b** without any protection of the hydroxyl group,[43] using 2 equiv of DDQ in dioxane at room temperature. After 2 days, we successfully recovered the expected α-tetralone **2b**, with a yield of 6.3% from the starting substrate **1b** (Scheme5).

Scheme 5. Oxidation of 1b in the Presence of DDQ



In an effort to enhance the yield of the oxidation reaction for THN **2b**, we replicated the procedure under identical conditions, but this time employing 4 equiv of DDQ instead of the previous 2 equiv. After 36 h of stirring at room temperature, we obtained tetralone **2b**, displaying a faint coloration due to residual traces of THN **1b**. There was an improvement in yield (40%) compared to the initial conditions (Scheme 5) (Table 1, entry 2, condition A).

To validate this outcome, we extended the application of DDQ as an oxidant in dioxane at room temperature to substrates **1a−d**. This resulted in the synthesis of a new series of α -tetralones, denoted as **2a−d**, with yields ranging from 18% to 40% (Table 1, condition A).

To refine the reaction conditions and enhance the overall quality of α-tetralones **2a−d**, we drew inspiration from the studies conducted by Lee *et al.* and Dufour *et al.*, which focused on the regioselective oxidation of various tetrahydronaphthalenes.[44,45] This oxidation, occurring in the benzylic position, was carried out in the presence of DDQ in refluxing aqueous acetic acid.

Subsequently, we applied this method to THN **1a**, and within 2 h, achieved the synthesis of tetralone **2a** with very high regioselectivity and a good yield of 98% (Table 1, Condition B, Scheme 6).

To extend the applicability of this protocol, we subjected different tetrahydronaphthalenes, namely, **1b−d**, to the same conditions. Remarkably, under these specified conditions, the desired tetralones **2b−d** were obtained with excellent yields, reaching up to 95% (Table 1, Condition B, Scheme 6).[43]

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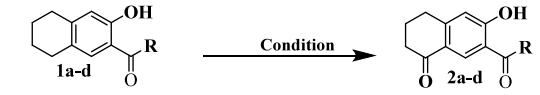
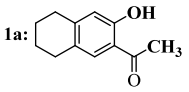
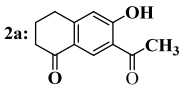
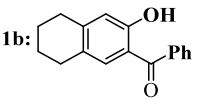
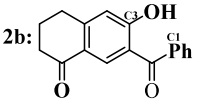
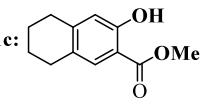
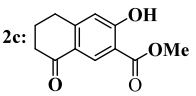
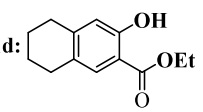
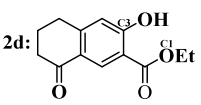
Table 1. Oxidation of Tetrahydronaphthalenes 1 to α-Tetralones 2 in the Presence of DDQ



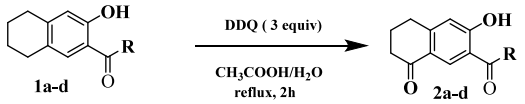
R = CH_3, Ph, OMe, OEt

Condition A: DDQ 4 equiv, Dioxane, r.t 36h

Condition B: DDQ 3 equiv, CH_3COOH/H_2O, reflux, 2h (Yield: 90-98%)

Entry	Tetrahydronaphthalene (1)	Tetralone (2)	Condition A	Condition B
			Yield (2) (%)	Yield (2) (%)
1	1a: 	2a: 	40	98
2	1b: 	2b: 	40	93
3	1c: 	2c: 	18	90
4	1d: 	2d: 	27	95

Scheme 6. Oxidation of Tetrahydronaphthalenes 1 to α-Tetralones 2 in the Presence of DDQ in CH_3COOH



R = CH_3, Ph, OMe, OEt

In proposing the structures for tetralones **2a−d**, our investigation builds upon prior research on the oxidation of functionalized tetrahydronaphthalenes into their corresponding α-tetralones. Notably, it has been demonstrated that the oxidation of tetrahydronaphthalenes **1** proceeds independently of the nature and relative positions of other groups carried by THN **1**.[43]

2.2. Discussion of the C═O position of the cycle by the 2D HMBC NMR technique. According to the 2D HMBC NMR spectrum of compound **2a** (Figure 1), if carbon 9 was of type SP3, we would expect to find at least one correlation between an SP3 carbon in the low-frequency zone and the H5 proton of the aromatic ring. However, such a correlation is absent in our spectrum. Instead, we observe a correlation between an SP2 type carbon (C9) and the H5 proton of the aromatic ring (phenol). The C12 is SP3 hybridized and shows correlation with the H2 proton of the aromatic ring (phenol). Carbon 2, which carries the H2 proton, couples to the H13 proton of the hydroxyl group. Additionally, the H5 proton couples with carbon 7, which is a carbonyl, and carbon 7 also couples with the H8 protons of the CH_3 group adjacent (in alpha) to the carbonyl attached to the phenol.

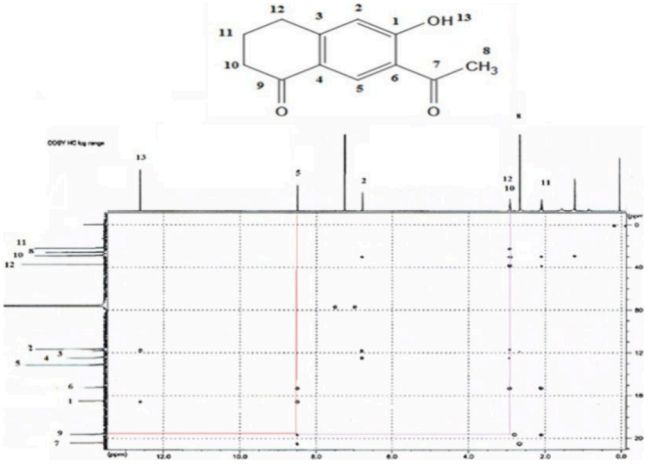


Figure 1. 2D HMBC NMR spectrum of compound **2a**.

The HMBC spectrum confirms our proposed structure, as the carbonyl function resulting from oxidation appears at position 9, not position 12.

3. BIOLOGICAL ACTIVITY

All of the newly synthesized functionalized tetralones (**2a−d**) in this study represent novel compounds not previously documented in the existing literature. Their *in vitro* antibacterial activity was assessed against nine Gram-positive bacteria (*Enterococcus faecalis* ATCC 29212, *Enterococcus faecium* ATCC 19436, *Staphylococcus aureus* ATCC 25923, *S. aureus* ATCC 6538, Methicillin-Resistant *S. aureus* MRSA 39, MRSA 59, Methicillin-Sensitive *S. aureus* MSSA 60, MSSA 69,

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Table 2. MIC and MFC of Tetralones against Fungi (μg/mL)

		Aspergillus niger		*Aspergillus flavus*		*Penicillium expansum*	
Entry	Compound	MIC	MFC	MIC	MFC	MIC	MFC
1	**2a**	125	250	250	500	250	500
2	**2b**	62.5	125	250	500	31.25	125
3	**2c**	125	125	250	250	62.5	125
4	**2d**	62.5	62.5	62.5	62.5	31.25	125
5	fluconazole	62.5	62.5	62.5	62.5	7.81	7.81
6	cycloheximide	62.5	250	62.5	≥500	-	-

Table 3. MIC and MBC of Tetralones against Gram Negative Bacteria (μg/mL)

		E.c[a]		*E.c*[b]		*E.c*[c]		*E.c*[d]		*P.a*[e]		*S.* spp[f]	
Entry	Compound	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	**2a**	31.25	250	125	500	125	>500	62.5	125	250	500	31.25	125
2	**2b**	250	>500	500	>500	62.5	500	125	500	500	>500	250	>500
3	**2c**	500	>500	500	>500	500	>500	500	>500	250	>500	250	>500
4	**2d**	62.5	250	125	>500	125	500	62.5	62.5	-	-	-	-
5	amp	≤3.9	≤3.9	250	250	250	250	≤3.9	≤3.9	500	≥500	62.5	62.5
6	van	250	≥500	62.5	-	250	250	62.5	62.5	250	250	250	250

[a]*E.c*: *Escherichia coli* ATCC 8739. [b]*E.c*: *Escherichia coli* Aq3 (ESBL). [c]*E.c*: *Echerichia coli* Aq10 (ESBL). [d]*E.c*: *Echerichia coli* DH5α. [e]*P.a*: *Pseudomonas aeruginosa* (MDR). [f]*S* spp: *Salmonella* spp. IPT13.

and *Bacillus cereus* ATCC 11778), and six Gram-negative strains (*Escherichia coli* DH5α, *E. coli* ATCC 8739, *E. coli* (Extended Spectrum Beta Lactamases) ESBL Aq3, *E. coli* ESBL Aq10, *Pseudomonas aeruginosa* (Muli Drug Resistant) **MDR**, and *Salmonella* spp. IPT13).

Additionally, their antifungal activity against important fungal pathogens *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium expansum* was evaluated using the Broth microdilution method with a Biolog Phenotype Microarrays system. Reference medicines, including vancomycin and ampicillin for bacteria, and fluconazole and cycloheximide for fungi, were employed. The results are presented in terms of minimum inhibitory concentration (MIC) and minimum bactericidal or fungicidal concentration (MBC or MFC).

3.1. *In vitro* Antifungal Activity. Certain tetralones, as documented in the literature, have been established to possess biological activities. Notably, research studies have elucidated the activities of tetralone derivatives and compounds incorporating the tetralone moieties in their structures.[46−49] These findings align well with outcomes observed by Jalilian *et al.*, who evaluated the antifungal potential of dihydronaphthalene derivatives. Their study revealed that compounds with electron donor groups exhibited no antifungal effect, while those with nitro or sulfamoyl groups demonstrated a moderate to significant effect.

In another study, Nakibet *et al.*,[47] synthesized a series of variously substituted 3-benzylidenechroman-4-ones, 3-benzylidene-thiochroman-4-ones, and 2-benzylidene-1-tetralones, testing them *in vitro* as fungicides. Sun *et al.*,[48] identified hydroxyanthraquinones and new derivatives featuring a tetralone fragment, specifically the coniothyrinones, which exhibited antifungal activity. Additional tetralone derivatives have shown effectiveness against the *A. niger* and *C. albicans* pathogens.[49]

Building on these insights, we chose to investigate the antifungal activity of tetralones **2a−d**, comparing them to reference antifungals, to assess the efficacy of each synthesized product against tested fungi (*A. niger*, *A. flavus*, and *P. expansum*). The results, detailed in Table 2, demonstrate varying activities against different fungi with MIC values comparable to those of cycloheximide.

For *A. niger*, tetralones **2a** and **2c** exhibit intermediate antifungal activity with an MIC of 125 μg/mL. However, their activity is comparatively modest when compared with cycloheximide. On the other hand, compound **2d** showcase significant activity against *A. niger*, displaying a fungicidal effect with an MIC of 62.5 μg/mL, (Table 2, entry 4).

Turning to *A. flavus*, tetralones **2a**, **2b**, and **2c** show limited antifungal activity, with MIC values of 250 μg/mL, (Table 2, entries 1, 2, 3). Compound **2d** presents an MIC of 62.5 μg/mL similar to that of cycloheximide (Table 2, entry 4).

For *Penicillium expansum*, tetralones **2b**, **2c**, and **2d** exhibit activity with MIC values ranging from 31.25 to 62.5 μg/mL. The MFC values indicate fungistatic activity, albeit weaker than that of fluconazole (Table 2, entries 2, 3, and 4).

In exploration of the structure−activity relationship, it is evident that the antifungal activity of tetralones (**2b−d**) is influenced by the nature of the R group on the carbonyl moiety. Specifically, the MIC values for tetralones **2b−d** with R = Ph, R = OMe, and R = O−CH_2−CH_3 range from 31.25 to 250 μg/mL, demonstrating superior potency compared to tetralone **2a** with R = CH_3, expressing MIC values between 125 and 250 μg/mL against fungal pathogens (Table 2, entry 1).

The most potent antifungal activity was evident in compound **2d**, substituted by an O−CH_2−CH_3 group while substitution with O−CH_3 (**2c**) or CH_3 (**2a**) decreases the antifungal efficacy. Thus, this result showed that replacement by an O-Et group is more important for the optimal antifungal activity of tetralones.[50,51] The MFC test results indicate a fungicidal effect for derivatives with replacement of R = O−CH_3 (**2c**) and R = O−CH_2−CH_3 (**2d**) against *A. niger* at a concentration range from 62.5 to 125 μg/mL.

Products **2a** and **2b** each carry a carbonyl functionality while products **2c** and **2d** carry ester functions and are better than **2a** and **2b**, this is already mentioned in the literature which shows that compounds carrying ester functions present antifungal activity.[52] Indeed, we find that the activity of **2d** is more

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Table 4. MIC and MBC of Tetralones against Gram-Positive Bacteria (μg/mL)

		S.a[a]		S.a[b]		S.a[c]		S.a[d]		S.a[e]		S.a[f]	
Entry	Compound	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
1	**2a**	250	500	250	>500	125	>500	250	>500	125	250	125	>500
2	**2b**	500	>500	≥500	>500	500	>500	≥500	>500	250	>500	250	>500
3	**2c**	31.25	>500	≥500	>500	250	>500	≥500	>500	125	500	250	>500
4	**2d**	500	>500	≥500	>500	500	>500	≥500	>500	250	>500	250	>500
5	amp	≥500	>500	≥500	-	≤3.9	≤3.9	≤3.9	≤3.9	15.62	15.62	≤3.9	≤3.9
6	van	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9	≤3.9

[a]*S.a*: *Staphylococcus aureus* 39 (MRSA). [b]*S.a*: *Staphylococcus aureus* 59 (MRSA). [c]*S.a*: *Staphylococcus aureus* 69 (MSSA). [d]*S.a*: *Staphylococcus aureus* 60 (MSSA). [e]*S.a*: *Staphylococcus aureus* ATCC 6538. [f]*S.a*: *Staphylococcus aureus* ATCC 25923, (SAMR): *Staphylococcus aureus* methicillin resistant, (SAMS): *Staphylococcus aureus* methicillin sensitive.

Table 5. MIC and MBC of Tetralones against Gram-Positive Bacteria (μg/mL)

		E.f[a]		E.f[b]		B.c[c]	
Entry	Compound	MIC	MBC	MIC	MBC	MIC	MBC
1	**2a**	250	250	250	500	62.5	>500
2	**2b**	500	>500	≥500	>500	250	>500
3	**2c**	500	500	250	>500	125	>500
4	**2d**	250	250	500	>500	250	>500
5	amp	≥500	>500	-	-	250	250
6	van	≥500	>500	-	-	≤3.9	≤3.9

[a]*E.f*: *Enterococcus faecium* ATCC 19436. [b]*E.f*: *Enterococcus faecalis* ATCC 29212. [c]*B.c*: *Bacillus cereus* ATCC 11778.

pronounced than the activity of **2b**, which is due to the lengthening of the alkyl group linked to the carbonyl of the aromatic group, which increases the lipophilic character in this molecule.

3.2. *In vitro* Antibacterial Activity. The findings indicate the effectiveness of most tested tetralones against strains of *E. coli*, *Salmonella* spp. IPT13, MRSA, and *B. cereus*, with MIC values ranging from 31.25 to 62.5 μg/mL for the most potent compounds. Antibacterial activity is notably affected by the nature of the R group, as in compounds **2a** and **2d**, with R = CH_3 and R = O−CH_2−CH_3, respectively.

As evident in Table 3, compound **2a** is the most active product displaying greater potency than ampicillin against *P. aeruginosa* and *Salmonella* spp. with an MIC range between 31.25 and 250 μg/mL. Compound **2b** is active against *E. coli* ESBL with MIC values ranging between 62.5 μg/mL and 250 μg/mL. Moreover, compound **2c** inhibited the growth of *E. coli* ESBL strains at an MIC value of 500 μg/mL.

For Gram-positive bacteria, all recently synthesized compounds exhibited good to modest activity in comparison with standard drugs. Notably, compound **2c**, with an MIC of 31.25 μg/mL, was active against *S. aureus* 39 (MRSA). Additionally, compound **2a**, with an MIC of 62.5 μg/mL, outperformed ampicillin against the reference strain of *B. cereus,* (Table 4 and 5).

The exploration of the structure−activity relationship revealed that the most potent compound (**2a**), featuring an OH group at C3 and an acetyl group at C1 (Table 1, Entry 2), outperformed other derivatives. Interestingly, replacing an alkyl with a benzene ring, as in compound **2b** (Table 1, Entry 2), led to a reduction in antibacterial activity. Furthermore, compound **2c**, with an OH group at C3 and carbomethoxy group at C1 (Table 1, Entry 4), demonstrated efficacy in inhibiting the growth of *S. aureus* MRSA at a concentration of 31.25 μg/mL. In contrast, replacing carbomethoxy group with a carboethoxy group (**2d**) (Table 1, Entry 4) appeared to enhance the antibacterial activity of these derivatives, particularly against Gram-negative bacteria.[50,51]

Thus, the methyl group emerged as the most potent substitution among the evaluated tetralone derivatives.

A study by Ceylan *et al.*, highlighted the antibacterial potency of 1,4-benzothiazepine tetralone derivatives containing methoxy and hydroxy groups against strains of *S. aureus*, *S. epidermidis*, *K. pneumoniae*, *P. aeruginosa*, and *E. coli*.[53] Comparable structural derivatives, as evaluated in this study, were also noted by Liu *et al.*[54] to exhibit significant antibacterial activity, with hydroxytetralone derivatives proving most effective against *S. aureus* and MRSA.

3.3. Cytotoxicity Assay. The findings from the cytotoxicity assay revealed low toxicity against VERO cells for most tested compounds, except for compound **2c**, as evidenced by the CC50 values outlined below (Table 6).

Table 6. Cytotoxicity of Tetralones 2a−2d

Entry	Compound	CC50 (μg/mL)
1	**2a**	107.8
2	**2b**	103
3	**2c**	27.94
4	**2d**	256.25

The compound bearing R = O−CH_2−CH_3 (**2d**), exhibited the least toxicity followed by compounds **2a** (R = CH_3) and **2b** (R = Ph). The results imply that the tested molecules show promise as antimicrobial agents, with the exception of compound **2c**, which displayed toxicity at lower concentrations.

4. MATERIALS AND METHODS

4.1. Organic Synthesis. *4.1.1. Synthesis of α-Tetralones (2a−d).* In a three-neck flask equipped with a condenser, tetrahydronaphthalene **1** (1 mmol) was introduced at 80 °C in 10 mL of acetic acid. Then, 20 mL of water was added using a

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dropping funnel. Finally, we added the DDQ (3 mmol). The reaction mixture was left stirring for 3 h at reflux. The progress and end of the reaction were controlled by TLC.

At the end of the reaction, the mixture was filtered through a Büchner funnel. The organic phase was washed several times with water. The residue was purified on a silica column (eluent: ether−petroleum ether 5:95).

4.1.2. Materials. The progress and end of the chemical reactions are monitored by thin layer chromatography on Merck Kieselgel 60 F254 silica (eluent: ether−petroleum ether). The α-tetralones **2a−d** are purified by chromatography on a silica column (70−230 mesh ASTM). Their structures are identified by ^{1}H and ^{13}C NMR on a Bruker AC300 apparatus and by GC-MS. The chemical shifts δ are expressed in ppm relative to tetramethylsilane and the coupling constants J are given in Hz. The following notations are used: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet).

4.2. Antibacterial Activity. The *in vitro* antibacterial activity of a series of chemically synthesized α-tetralones was evaluated against a diverse range of Gram positive strains (*E. faecium* ATCC 19436, *E. faecalis* ATCC 29212, *S. aureus* ATCC 25923, *S. aureus* ATCC 6538, MRSA 39 and 59, MSSA 60 and 69, and *B. cereus* ATCC 11778) and Gram negative strains (*E. coli* ATCC 8739, *E. coli* DH5α, *E. coli* ESBL Aq3 and Aq10, *P. aeruginosa*, and *Salmonella spp* IPT13) using Biolog's Omnilog (BiologOmnilog Phenotype MicroArray, Hayward, CA, USA) tool.[55]

The assays were conducted in 96-well microplates capable of monitoring the chemical sensitivities. Cell response in each assay well was determined by the extent of color development resulting from the reduction of a tetrazolium compound during cell respiration.

Colonies from Brain Heart Infusion Agar (BHIA) plates were suspended in Brain Heart Infusion broth (BHIB), and the suspension was adjusted to 80−85% transmittance (T). Mueller Hinton Broth (MHB, Biolife Italiana S.r. I. viale Monza, 272-20128 Milano, Italy) with Biolog Redox Dye Mix (0.1%) was prepared as a control. Tetralones stock solutions were 2-fold serially diluted in dimethyl sulfoxide (DMSO) in sterile 96-well microtiter plates containing the mixed MHB-Biolog Redox Dye. The prepared cell suspension was then added to each well.

Wells containing the inoculum alone and inoculum with DMSO served as negative controls, while standard ATB Amp and Van were used as positive controls. The plates were incubated at the optimal temperature in the OmniLog plate incubator and reader with color changes monitored. Readings were recorded automatically every 15 min for 18 to 24 h. The generated curves were compared to those of negative and positive controls, and Minimum Inhibitory Concentrations (MICs) were determined as the lowest concentrations at which no bacterial growth was observed.

4.3. Antifungal Activity. *A. niger, A. flavus*, and *P. expansum* were cultured on Potato Dextrose Agar (PDA) plates at 28 °C. Colonies were harvested from the agar plates and suspended in a 0.85% NaCl solution, with the fungal suspension adjusted to 62% transmittance (T).

Malt Extract (ME) (2%) with Biolog Redox Dye Mix was prepared, and α-tetralone stock solutions were subjected to 2-fold serial dilution in DMSO within sterile 96-well microtiter plates containing the ME-Biolog Redox Dye Mix. Subsequently, a fungal suspension was introduced. Wells containing only the inoculum and inoculum with DMSO were designated as negative controls, while cycloheximide and fluconazole served as positive controls.

The microplates underwent incubation at 28 °C for a duration ranging from 72 to 120 h within the OmniLog plate reader. The resulting curves were compared to those of the control wells, and Minimum Inhibitory Concentrations (MICs) were determined as the lowest concentrations at which no fungal growth was observed.

4.4. Determination of Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC). The Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) of tetralones were assessed following the procedures outlined by Mbah *et al.*[56]

Briefly, 10 μL aliquots from wells corresponding to 1, 2, 3, and 4 times the Minimum Inhibitory Concentration (MIC) were inoculated onto Nutrient Agar (for bacteria) and PDA (for fungi). The plates were then incubated at appropriate temperatures for 24 and 72 h, respectively. MBC and MFC were defined as the lowest concentrations at which no bacterial or fungal growth was observed, providing a clear determination of the potent bactericidal and fungicidal effects of α-tetralones.

4.5. Cytotoxicity Assay. Cytotoxicity evaluation of α-tetralones was conducted on VERO (African green monkey kidney) cell lines obtained from the Pasteur Institute of Tunis, Tunisia, utilizing the MTT assay developed by Mosman.[57] A suspension of 0.5×10^4 cells in 100 μL was seeded into 96-well tissue culture plates (Orange Scientific, Belgium) and incubated in RPMI 5% FBS at 37 °C under a humidified 5% CO_2 atmosphere. After 24 h, a 100 μL solution containing 2-fold serial dilutions of each tetralone compound, ranging from 3333 to 6.87 μg/mL, was added to the semiconfluent cell cultures. Following a 72-h incubation period, the culture medium was removed and 50 μL of MTT solution (5 mg/mL in PBS) was introduced to each well. After a 4-h incubation at 37 °C, DMSO (100 μL) was used to solubilize the formazan formed in each well. Absorbance readings were obtained at 540 nm using a plate reader (ELx800, BioTeck, USA). The percentage of cytotoxic effect was calculated using the following formula:

$$\text{percentage cytotoxicity} = \frac{\text{absorbance of control} - \text{absorbance of sample}}{\text{absorbance of control}} \times 100$$

The 50% cytotoxic concentration (CC50), representing the compound concentration capable of reducing cell viability by 50% compared with the untreated control, was determined through linear regression analysis applied to the dose−response curve.

5. CONCLUSION

This work presents the synthesis of novel functionalized α-tetralones employing a straightforward and efficient method, distinct from those documented in the literature. The process, completed within a reasonable time frame, underwent optimization to ensure the highly regioselective production of these α-tetralones. Our exploration extended to a preliminary biological study, evaluating their impact on both Gram-positive and Gram-negative bacteria as well as fungi. Compounds **2b** and **2d** exhibit significant fungicidal activity against *A. niger*, compound **2d** as well proving effective against *A. flavus*, comparable to cycloheximide. The antifungal efficacy of α-tetralones (**2b−d**) is influenced by the R group on the

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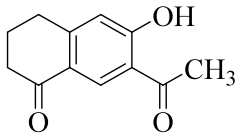
phenyl unit, with compound **2d**, having the highest activity. The study reveals the effectiveness of most tested α-tetralones against *E. coli*, *Salmonella spp*, MRSA, and *B. cereus*. Antibacterial activity is notably affected by the nature of the R group, as in compounds **2a** and **2d**, with R = CH_3 and R = $O-CH_2-CH_3$, respectively; importantly, most of the tested compounds show low toxicity. The results of the biological activity were promising, suggesting a potential avenue for these compounds to evolve into future drug candidates within this chemical family.

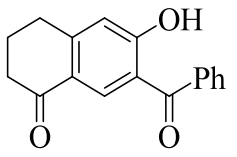
6. ^{1}H AND ^{13}C NMR DATA OF COMPOUNDS (2A−D)

6-Acetyl-7-hydroxy-3,4-dihydronaphthalen-1(2H)-one (2a).



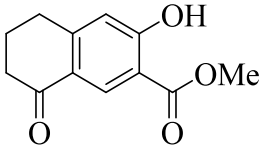
Yield: 210.44 mg (98%), 1.052 mmol reaction scale. White solid, mp = 99−101 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (m, 2H), 2.50 (s, 3H), 2.78 (m, 4H), 6.78 (s, 1H), 7.46 (s, 1H), 12.53 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$,) δ 23.3, 27.1, 30.3, 38.7, 114.4,118.7, 128.1, 128.5, 146.2, 161.1,198.7, 203.3. HRMS (TOF-MS-ES): calcd for $C_{12}H_{12}O_3$: 204.07864, found 204.07973.

6-Benzoyl-7-hydroxy-3,4-dihydronaphthalen-1(2H)-one (2b).



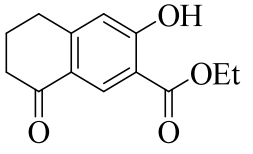
Yield: 196.33 mg (93%), 0.793 mmol reaction scale. White solid, mp = 143−145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83 (m, 2H), 2.91 (m, 4H), 7.24 (s, 1H), 7.51−7.98 (m, 5H), 8.63 (s, 1H), 12.43 (s, 1H).^{13}C NMR (75 MHz,$CDCl_3$) δ 23.3, 30.4, 38.6, 112.2, 120.1, 127.7, 128.6, 128.9, 132.5, 137.7, 146.2, 161.6, 196.9, 198.5. HRMS (TOF-MS-ES): calcd for $C_{17}H_{14}O_3$: 266.09429, found 266.09650.

Methyl 3-Hydroxy-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (2c).



Yield: 180 mg (90%), 0.97 mmol reaction scale. White solid, mp = 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (m, 2H), 2.73 (m, 4H), 3.57 (s, 3H), 6.70 (s, 1H), 7.60 (s, 1H), 11.16 (s, 1H).^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.3, 27.1, 30.3, 38.7, 114.4,118.7, 128.1 128.5, 146.2,161.4,198.7, 203.3. HRMS (TOF-MS-ES): calcd for $C_{12}H_{12}O_4$: 220.07356, found 220.07373.

Ethyl 3-Hydroxy-5-oxo-5,6,7,8-tetrahydronaphthalene-2-carboxylate (2d).



Yield: 202 mg (95%), 0.90 mmol reaction scale. White solid, mp = 85−87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 6 Hz, 3H), 1.77 (m, 2H), 2.73 (m, 4H), 3.50 (q, J = 6 Hz, 2H), 6.70 (s, 1H), 7.60 (s, 1H), 11.29 (s, 1H). ^{13}C NMR (75 MHz,$CDCl_3$) δ 14.2, 23.3, 30.5, 38.6, 61.1, 113.9, 114.3, 127.7, 128.3, 146.3, 163.0, 167.6, 198.3. HRMS (TOF-MS-ES): calcd for $C_{13}H_{14}O_4$: 234.08921, found 234.09043.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c02130.

Detailed information on the ^{1}H and ^{13}C NMR spectra of compounds **2a−d** can be found in Figures S1−S12 and Tables S1−S4 (PDF)

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Author Contributions

We certify that all authors Ahmed Meddeb, Amal Thebti, Haitham Elleuch, Sami Ayari, Lamjed Bouslama, Hadda-Imene Ouzari, mutually agreed to submit this original work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Prasomsri, T.; Galiasso Tailleur, R. E.; Alvarez, W. E.; Sooknoi, T.; Resasco, D. E. Conversion of 1- and 2-Tetralone Over HY Zeolite. *Catal. Lett.* **2010**, *135*, 226−232.

(2) Souza, L. G.; de O. Domingos, J. L.; de A. Fernandes, T.; Renno, M. N.; Sansano, J. M.; Najera, C.; Costa, P. R.R. Enantio selective electrophilic fluorination of α-aryl-tetralonesusing a preparation of *N*-fluoroammoniumsalts of cinchonine. *J. Org. Chem.* **2019**, *217*, 72−79.
(3) Labadie, G. R.; Cravero, R. M.; Gonzalez-Sierra, M. Studies of Birch Reductive Alkylation of Substituted α-Tetralones. *Synth. Commun.* **2000**, *30*, 4065−4079.
(4) Urruzuno, I.; Mugica, O.; Oiarbide, M.; Palomo, C. Bifunctional Brønsted Base Catalyst Enables Regio-, Diastereo-, and Enantioselective Cα-Alkylation of β-Tetralones and Related Aromatic-Ring-Fused Cycloalkanones. *Angew. Chem., Int. Ed.* **2017**, *56*, 2059−2063.
(5) Labadie, G. R.; Estiu, G. L.; Cravero, R. M.; Sierra, M. G. Decompositionmechanism of Birch alkylation products of α-tetralones. *J. Mol. Struct.* **2003**, *635*, 173−182.
(6) Krishna Rao, M. V.; Reddy, K. N.; Sridhar, B.; Subba Reddy, B. V. RuII-Catalyzed ortho-Sulfonamidation of α-Tetralones with SulfonylAzides and Synthesis of Sivelestat by Aromatic C−H Activation. *Asian J. Org. Chem.* **2017**, *6*, 1851−1856.
(7) Ferraz, H. M. C.; Silva, L. F.; Aguilar, A. M.; Vieira, T. O. The reaction of α-tetralones with thallium trinitratesupported on clay: ring contraction vs alpha-oxidation. *J. Braz. Chem. Soc.* **2001**, *12*, 680−684.
(8) Karmakar, R.; Mal, D. N-Methylaniliniumtrifluoroacetate-promoted Prins reaction of α-methylene-α-tetralone dimers: generation of new molecular scaffolds. *Tetrahedron Lett.* **2011**, *52*, 6098−6102.
(9) Jha, A.; Dimmock, J. R. Convenient, tandem and one-reactionvesselsynthesis of mixed dialkylated 2-naphthols from 2-tetralone. *Can. J. Chem.* **2003**, *81*, 293−296.
(10) Kantin, G.; Krasavin, M. P. Reaction of α-tetralone, 1H-tetrazol-5-amine, and aromatic aldehydes upon microwave irradiation − a convenient method for the synthesis of 5,6,7,12-tetrahydrobenzo-[h]tetrazolo[5,1-b]quinazolines. *Chem. Heterocycl. Compd.* **2016**, *52*, 918−922.
(11) Cloete, S. J.; N'Da, C. I.; Legoabe, L. J.; Petzer, A.; Petzer, J. P. The evaluation of 1-tetralone and 4-chromanone derivatives as inhibitors of monoamine oxidase. *Mol. Divers* **2021**, *25*, 491−507.
(12) Legoabe, L. J.; Petzer, A.; Petzer, J. P. α-Tetralone derivatives as inhibitors of monoamine oxidase. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2758−2763.
(13) Nyangulu, J. M.; Nelson, K. M.; Rose, P. A.; Gai, Y.; Loewen, M.; Lougheed, B.; Quail, J. W.; Cutler, A. J.; Abrams, S. R. Synthesis and biologicalactivity of tetraloneabscisicacid analogues. *Org. Biomol. Chem.* **2006**, *4*, 1400−1412.
(14) de Souza, L. G.; Salustiano, E. J.; da Costa, K. M.; Costa, A. T.; Rumjanek, V. M.; Domingos, J. L.O.; Renno, M. N.; Costa, P. R.R. Synthesis of new α-Aryl-α-tetralones and α-Fluoro-α-aryl-α-tetralones, preliminaryantiproliferativeevaluation on drugresistantcelllines and in silico prediction of ADMEToxproperties. *Bioorg. Chem.* **2021**, *110*, 104790.
(15) Gibson, M. Z.; Nguyen, M. A.; Zingales, S. K. Design, Synthesis, and Evaluation of (2-(Pyridinyl)methylene)-1-tetralone Chalcones for Anticancer and AntimicrobialActivity. *Med. Chem.* **2018**, *14*, 333−343.
(16) Gauni, B.; Mehariya, K.; Shah, A.; Duggirala, S. M. Tetralone Scaffolds and Their Potential Therapeutic Applications. *Lett. Drug Des. Discovery* **2021**, *18*, 222−238.
(17) Akkus, G. U. Synthesis of α-Naphthol and 2,4,7-Trimethyl-Quinolin-5-ol by Using Manganese (III) Acetate and Analysis of Its Antimicrobial Properties. *Int. J. Org. Chem.* **2016**, *6*, 12−19.
(18) N., A.; Reuben Jonathan, D.; Ramesh, S.; Manivannan, S.; Ahamed, J. I. Synthesis of Biologically Active α-Tetralone Condensate: Growth of Single Crystal, Characterization by Experimental and Simulation Methods. *Polycyclic Aromatic Compounds* **2024**, *44*, 2394−2418.
(19) Thorat, S. S.; Sibi, M. P. Total Synthesis of Natural Products Containing the Tetralone Subunit. *Arkivoc* **2023**, *2*, 202312053.
(20) Poon, P. S.; Banerjee, A. K.; Vera, W. J.; Mora, H. D.; Laya, M. S.; Bedoya, L.; Cabrera, E. V.; Melean, C. E. Use of 5-methoxy, 6-methoxy and 7-methoxy-α-tetralones in the Synthesis of Diterpenes, Sesquiterpenes and Other Natural Products. *J. Chem. Res.* **2008**, 181−187.
(21) Gopinath, K. W.; Govindachari, T. R.; Parthasarathy, P. C.; Viswanathan, N. Synthesis of dihydronitidine. *J. Chem. Soc.* **1959**, 4012.
(22) Kametani, T.; Kigasawa, K.; Hüragi, M.; Wagatsuma, N.; Saitoh, S.; Sugi, H. Snytheses of analgesics. Part XXXVII. An alternative synthesis of 1,2,3,4, 5, 6-hexahydro-8-hydroxy-2,6-methano-6, h-dimethyl-3-phenethyl-3-benzazoeine [studies on the syntheses of heterocyclic compounds. Part DXXI. *J. Heterocycl. Chem.* **1973**, *10*, 313−315.
(23) Ishida, N.; Sawano, S.; Murakami, M. Synthesis of 3,3-disubstituted α-tetralones by rhodium-catalysed reaction of 1-(2-haloaryl)cyclobutanols. *Chem. Commun.* **2012**, *48*, 1973−1975.
(24) Hornback, J. M.; Poundstone, M. L.; Vadlamani, B.; Graham, S. M.; Gabay, J.; Patton, S. T. Photochemical cyclization of o-methylphenyl 1,3-diketones. *J. Org. Chem.* **1988**, *53*, 5597−5601.
(25) Liao, Y.; Ran, Y.; Liu, G.; Liu, P.; Liu, X. Transition-metal-free radical relay cyclization of vinyl azides with 1,4-dihydropyridines involving a 1,5-hydrogen-atom transfer: access to α-tetralone scaffolds. *Org. Chem. Front* **2020**, *7*, 3638−3647.
(26) Roy, P.; Shrestha, D.; Akhtar, M. S.; Lee, Y. R. Rh-Catalyzed Annulation of Enaminones with Maleimides for Functionalized Aza-spiro α-Tetralones and Benzo[e]isoindoles via C−H Activation/C-C Bond Cleavage. *Org. Lett.* **2024**, *26*, 142.
(27) Tanaka, K.; Hojo, D.; Shoji, T.; Hagiwara, Y.; Hirano. M.Rh-Catalyzed [4 + 2] Carbocyclization of Vinylarylaldehydes with Alkenes and Alkynes Leading to Substituted Tetralones and 1-Naphthols. *Org. Lett.* **2007**, *9*, 2059.
(28) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. A new synthesis of α-tetralones. *Tetrahedron Lett.* **1997**, *38*, 1759−1762.
(29) Yu, J.; Zhao, H.; Liang, S.; Bao, X.; Zhu, C. A facile and regioselective synthesis of 1-tetralones via silver-catalyzed ring expansion. *Org. Biomol. Chem.* **2015**, *13*, 7924.
(30) Zhu, H.; Nie, X.; Huang, Q.; Zhu, G. Copper-catalyzed coupling of 2-vinyl benzaldehydes with 3-alkenyl 2-bromocarbonyls for the rapid construction of 3,4-cyclopenta-1-tetralones. *Tetrahedron Lett.* **2016**, *57*, 2331.
(31) Ramdayal, F. D.; Kiemle, D. J.; LaLonde, R. T. Directed, DDQ-Promoted Benzylic Oxygenations of Tetrahydronaphthalenes. *J. Org. Chem.* **1999**, *64*, 4607.
(32) Ghatak, A.; Dorsey, J. M.; Garner, C. M.; Pinney, K. G. Synthesis of methoxy and hydroxy containing tetralones: versatile intermediates for the preparation of biologically relevant molecules. *Tetrahedron Lett.* **2003**, *44*, 4145.
(33) Sherwood, T. C.; Xiao, H.-Y.; Bhaskar, R. G.; Simmons, E. M.; Zaretsky, S.; Rauch, M. P.; Knowles, R. R.; Dhar, T. G. M. Decarboxylative Intramolecular Arene Alkylation Using N-(Acyloxy)-phthalimides, an Organic Photocatalyst, and Visible Light. *J. Org. Chem.* **2019**, *84*, 8360−8379.
(34) Chen, Z.; Hong, A. Y.; Linghu, X. Construction of Polycyclic β-Ketoesters Using a Homoconjugate Addition/DecarboxylativeDieckmann Annulation Strategy. *J. Org. Chem.* **2018**, *83*, 6225−6234.
(35) Rezgui, F.; El Gaied, M. M. DMAP-catalyzedhydroxymethylation of 2-cyclohexenones in aqueous medium throughBaylis-Hillman-reaction. *Tetrahedron Lett.* **1998**, *39*, 5965.
(36) J'mour, A.; Rezgui, F. Annelation of Baylis−HillmanDerivatives: Synthesis of Highly Functionalised Tetrahydronaphthalenes. *J. Chem. Res.* **2009**, 642.
(37) Elleuch, H.; Msalbi, D.; Mhasni, O.; Yaccoubi, F.; Aifa, S.; Legros, J.; Rezgui, F. New Morita-Baylis-Hillman (MBH) phosphoniumsaltsfromalcohols to the synthesis of 2-alkenyl- and 2-alkylidenecyclohexenones. *J. Mol. Struct.* **2023**, *1286*, 135532.
(38) Elleuch, H.; Mihoubi, W.; Mihoubi, M.; Ketata, E.; Gargouri, A.; Rezgui, F. Potential antioxidant activity of Morita-Baylis-Hillman adducts. *Bioorg.Chim.* **2018**, *78*, 24.
(39) Ketata, E.; Elleuch, H.; Neifar, A.; Mihoubi, W.; Ayadi, W.; Marrakchi, N.; Rezgui, F.; Gargouri, A. Anti-melanogenesis potential

https://doi.org/10.1021/acsomega.4c02130
ACS Omega 2024, 9, 39344−39352

of a new series of Morita-Baylis-Hillman adducts in B16F10 melanoma cell line. *Bioorg. Chim.* **2019**, *84*, 17.
(40) Mihoubi, W.; Elleuch, H.; Boudabbous, M.; Ketata, E.; Borgi, I.; Rezgui, F.; Gargouri, A. Selection of electron-deficient substances as antifungal candidates. *Mycol. Prog.* **2023**, *22*, 58.
(41) Elleuch, H.; Baioui, N.; Bouajila, J.; Rezgui, F. Chemoselective-reaction of ethane-1,2-dithiol, hydrazines, and hydroxylamine onto γ-ketoallylphosphonates and phosphine oxides. *Arkivocpartiv* **2017**, *2017*, 265−272.
(42) Ghatak, A.; Dorsey, J. M.; Garner, C. M.; Pinney, K. G. Synthesis of methoxy and hydroxy containing tetralones: Versatile intermediates for the preparation of biologically relevant molecules. *Tetrahedron Lett.* **2003**, *44*, 4145.
(43) Wang, Y.; Liu, W.; Ren, W.; Shi, Y. Synthesis and Evaluation of 5,5′-Bitetralone-Based Chiral Phosphoric Acids. *Org. Lett.* **2015**, *17*, 4976.
(44) Lee, H.; Harvey, R. G. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in acetic acid, a convenient new reagent for the synthesis of aryl ketones and aldehydes via benzylic oxidation. *J. Org. Chem.* **1988**, *53*, 4587.
(45) Dufour, F.; Kirsch, G. Efficient Synthesis of 1,2,3,4-Tetrahydro-11H-benzo[a]carbazole and its Regioselective Oxidation. *Synlett.* **2006**, 1021−1022.
(46) Jalilian, A. R.; Sattari, S.; Bineshmarvasti, M.; Daneshtalab, M.; Shafiee, A. Synthesis and in vitro antifungal and cytotoxicityevaluation of substituted 4,5-dihydronaphtho[1,2-d][1,2,3]thia(or Selena)-diazoles. *Il Farmaco* **2003**, *58*, 63−68.
(47) Al Nakib, T; Bezjak, V; Meegan, M.; Chandy, R Synthesis and antifungal activity of some 3-benzylidenechroman-4-ones, 3-benzylidenethiochroman-4-ones and 2-benzylidene-1-tetralones. *Eur. J. Med. Chem.* **1990**, *25*, 455−462.
(48) Sun, P.; Huo, J.; Kurtan, T.; Mandi, A.; Antus, S.; Tang, H.; Drager, S.; Schulz, B.; Hussain, H.; Krohn, K.; Pan, W.; Yi, Y.; Zhang, W. Structural and Stereochemical Studies of Hydroxyanthraquinone Derivatives from the Endophytic Fungus Coniothyrium sp. *Chirality* **2013**, *25*, 141−8.
(49) Hucchegowda, K. M.; Basavaiah, B. Y.; Basavaiah, U.; Basavaiah, S. S. Synthesis and study of antimicrobialactivity of new tetralone esters. *Eur. J. Chem.* **2014**, *5*, 584−587.
(50) Wang, X.; Sun, S.; Hou, X. Synthesis of Lipophilic Caffeoyl Alkyl Ester Using a Novel Natural Deep Eutectic Solvent. *ACS Omega* **2020**, *5* (19), 11131−11137.
(51) Toth, S.; Hughes, R. A.; Ward, P.; McColm, A. M.; Cox, D. M.; Anderson, G. J.; Gibbons, W. A. Fatty peptides VI. Penicillin and cephalosporin esters with increased lipophilic character. *Int. J. Pharm.* **1991**, *77*, 13−20.
(52) Miklasińska-Majdanik, M.; Kępa, M.; Wojtyczka, R. D.; Idzik, D.; Wąsik, T. J. Phenolic Compounds Diminish Antibiotic Resistance of Staphylococcus Aureus Clinical Strains. *Int. J. Environ. Res. Public. Health.* **2018**, *15*, 2321.
(53) Ceylan, M.; Kocyigit, U.; Usta, M. N.C.; Gürbüzlü, B.; Temel, Y.; Alwasel, S. H.; Gülçin, I. Synthesis, carbonic anhydrase I and II isoenzymes inhibition properties, and antibacterial activities of novel tetralone-based 1,4-benzothiazepine derivatives. *J. Biochem. Mol. Toxicol.* **2017**, *31*, e21872.
(54) Liu, Q.; Zhao, P.; Li, X.-C.; Jacob, M. R.; Yang, C. R.; Zhang, Y.-J. New α-Tetralone Galloylglucosides from the Fresh Pericarps of Juglanssigillata. *Helv. Chim. Acta* **2010**, *93*, 265−271.
(55) *Biolog*. https://www.biolog.com/products-portfolio-overview/phenotype-microarrays-for-microbial-cells/ (accessed on 16 December 2022).
(56) Mbah, J.; Ngemenya, M. N.; Abawah, A.; Babiaka, S. B.; Nubed, L. N.; Nyongbela, K. D.; Lemuh, N.; Efange, S. M. Bioassay-guided discovery of antibacterial agents: *In vitro* screening of *Peperomia-vulcanica, Peperomiafernandopoioana* and *Scleriastriatinux*. *Ann. Microbiol. Antimicrob.* **2012**, *11*, 102−113.
(57) Mosmann, T. Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J. Immunol. Meth.* **1983**, *65*, 55−63.

https://doi.org/10.1021/acsomega.4c02130
ACS Omega 2024, 9, 39344−39352