Molecular Catalysis 485 (2020) 110788

Contents lists available at ScienceDirect

Molecular Catalysis

journal homepage: www.elsevier.com/locate/mcat

Studies on the laccases catalyzed oxidation of norbelladine like acetamides

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ARTICLE INFO

Keywords:
Biocatalysis
Laccase Norbelladine
Phenol

ABSTRACT

Herein, we study for the first time, the Laccase catalyzed oxidation of Norbelladine like amides **1** and **2**. It was determined that the Laccases/ABTS and Laccases alone were able to catalyze the dimerization and trimerization reaction of the amides **1** and **2** in high conversions, respectively. The synthesis of the selectively deuterated substrates *D*-**1** and *D*-**2** and the analysis of their reaction products by HPLC-ESI-TOF MS allowed the determination of the bond (C—C— or C—O) formed between the monomers.

1. Introduction

Phenolic compounds are largely distributed in nature, especially in the plant kingdom where they are considered to play important roles in the defense of such organisms against infection. So, it does not come as a surprise that phenolic compounds are reported to display different biological activities [1] such as anti-inflammatory [2–7], anti-oxidant [6,8–12], antithrombotic [13–15], anti-atherogenic [16–19] and anti-microbial [20–24]. Additionally, these compounds have also found application in catalysis [25–28] and functional materials [29,30]. Such characteristics of phenolic compounds promoted a great amount of work in the synthesis of their derivatives in the search for bioactive and catalytic active ligands.

Laccasess (EC 1.10.3.2 p-diphenol: dioxygen oxidoreductase) are a multicopper oxidases (MCO) containing four copper atoms distributed in three different redox sites. In nature, these enzymes catalyze the synthesis and degradation of lignin with the concomitant four electron reduction of O_2 to H_2O while bypassing a stage of H_2O_2 production. These enzymes are common from fungal and vegetal origin. The enzyme contain four copper atoms that can be classified into three types based on their unique spectroscopic features. In the oxidized state, the Type 1 copper (T1) exhibits an intense absorption 600 nm, while the Type 2 (T2) Cu (II) shows no significant absorbance feature. The Binuclear Type 3 (T3) copper sites are EPR silent due to anti-ferromagnetic (AF) coupling resulting from a bridging hydroxo ligand between the coppers in the resting oxidized state. From the mechanistic point of view, the substrate is oxidized at T1, which transfers electrons through the Cys-His pathway to the trinuclear copper cluster (T2 and T3) which then accomplishes the four electron reduction of oxygen. This oxidation occurs through an outer-sphere mechanism on T1, where the first- and second-sphere residues surrounding the T1 control both the intermolecular ET to the T1 from the substrate, and the intramolecular ET from the T1 to the T2-T3 cluster [31].

Laccases are reported to perform the oxidation of structurally diverse compounds such as 2,2′-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) [32–34], 2,2,6,6-Tetramethyl-1-piperidinyloxy free radical (TEMPO) [35–39], N-hydroxyphtalimide [39–41], 1-Hydroxybenzotriazole [42–46] and hydroquinone [47]. It is proposed that many of these compounds once oxidized by the laccases (with concomitant reduction of molecular oxygen) reacts further oxidizing other compounds leading to the reaction product formation. In such cases these compounds are called mediators and this process is present in Figs. 1 and 2. These mediators present electrochemical potential that varies from 0.8 to 1.2 mV. The structure of mediators is show in Fig. 1.

The structural diversity of the mediators and the different mechanisms by which they oxidize the substrate, may allow the oxidation of structurally divergent compounds. Under these circumstances, the substrate non-specificity of Laccasess/mediator system is vastly explored in the literature [48–50], leading to its application in different fields such as pollutant and dye removal [33,39–41,51], clarification of beverages and paper bleaching [52–55].

Intramolecular phenolic coupling is a reaction present in the biosynthetic pathways of many important natural products. One

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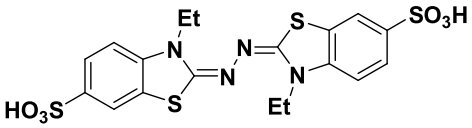
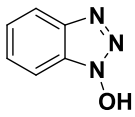
https://doi.org/10.1016/j.mcat.2020.110788
Received 14 November 2019; Received in revised form 23 January 2020; Accepted 24 January 2020



2,2?-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS)



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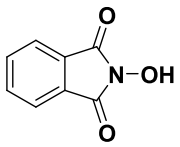
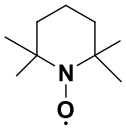
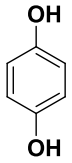


N-hydroxyphtalimide



2,2,6,6-Tetramethyl-1-piperidinyloxy radical



Hydroquinone

Fig. 1. Structure of mediators used in Laccases catalyzed reactions.

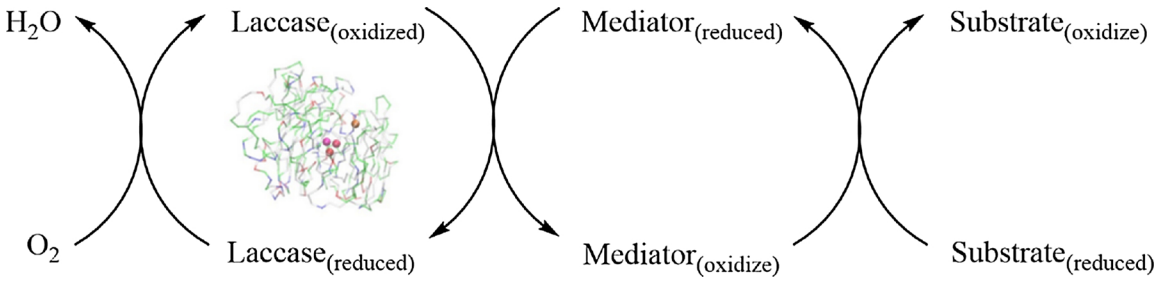
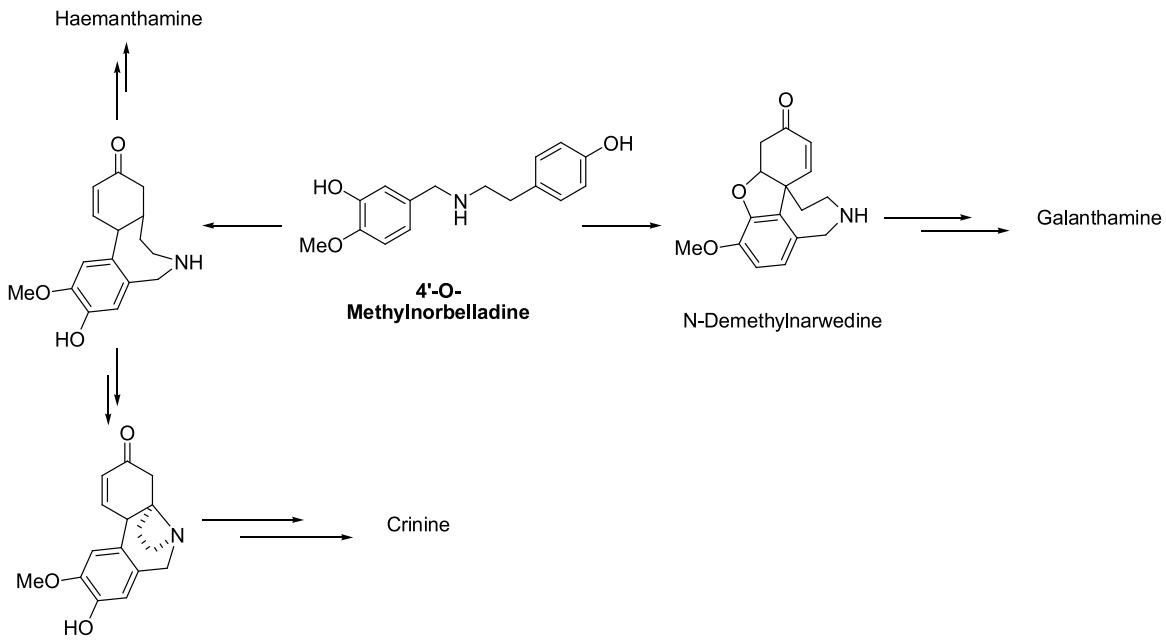


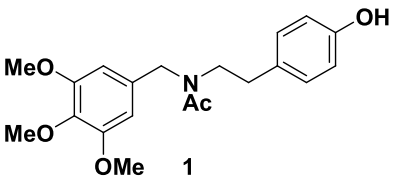
Fig. 2. The proposed coupling of the Laccase/mediator system with oxygen as the terminal oxidant.



Scheme 1. Norbelladine as intermediate in the biosynthesis of *Amaryllidaceae* alkaloids.

interesting group of substances where oxidative dearomative coupling of phenol plays a key role is the synthesis of *Amaryllidaceae* alkaloids [56] where Norbelladine is cyclized leading to the synthesis of Galantamine, Narwedine, Haemanthamine, Crinine and Lycorine, for example [57,58] as depicted in Scheme 1.

In cases where intra vs intermolecular phenol coupling reactions are concerned, studies report that its outcome is dependent on the oxidant and on the substitution pattern of the coupling phenols. According to Swartz and others [59–62], monophenolic compounds may not go intramolecular reaction trough the intermediacy of phenoxy radicals,



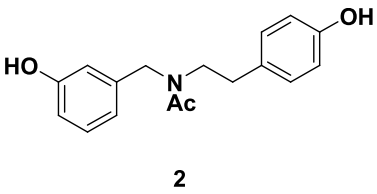


Fig. 3. Structure of the amides used in the present study.

where a more electrophilic intermediate such as the phenoxenium cation is necessary. The easy of formation of such phenoxenium cation is pH dependent where at neutral or weakly acidic conditions, a two electron oxidation process can be achieved with a 1200 mV potential [63,64]. On the other hand, at higher pH, the phenolate anion in oxidized to the same cation at much lower potential (800 mV). Such values are in the range of those compounds that are reported to be oxidized by Laccases or a Laccases/mediator system.

On the other hand, when a phenol is present on both rings undergoing the intramolecular reaction, cyclization may occur through the intermediacy of a phenoxy diradical. Additionally, in cases where non phenolic electron rich arenes are anodically oxidized the cyclization products are the result of the intermediacy of the dication radical [65].

Finally, if the oxidation leads to a radical, instead of a phenoxycation or a diradical where intramolecular reaction is expected, the observed product may be the result of an intermolecular reaction that leads to a complex mixture of products from constitutional and regioisomeric dimers, trimers or even polymers [66] [67] [68]. Such approach is used in the synthesis of phenol derived polymers, antioxidants, metal ligands as well as (pseudo)symmetric alkaloids [69] [70] [71].

Herein, we study for the first time the Laccase catalyzed oxidation of Norbelladine like amides **1** and **2** (Fig. 3). According to the previous discussion, if the laccases or a laccases/mediator system is able to perform the oxidation of **1** to the phenoxenium cation, cyclization would occur through the attack of the electron rich ring B, with the formation of the four ring system present in alkaloids such as Galantamine. On the other hand, in the case of amide **2**, the presence of the two phenolic rings, cyclization would occur if the enzymatic system could lead to the formation of a phenoxy diradical. Finally, in both cases, If radical coupling is faster than the formation of the cation or the diradical, intermolecular dimerization and trimerization are to be expected as the reaction products.

2. Experimental section

2.1. General information

All chemicals and solvents were purchased from commercial sources and used without further purification. All solvents used in Liquid Chromatography-Mass Spectrometry (LC–MS) analysis were HPLC grade (HPLC/Spectro) and were purchased from Tedia (USA).

2.2. General procedure for the synthesis of the substrates 1 and 2

A solution of the respective aldehyde (7 mmol) and the tyramine (7 mmol) in 42 mL of methanol was stirred for 4 h at room temperature, under inert atmosphere. The reaction was then cooled with an Ice bath, and sodium triacetoxyborohydride (9.7 mmol) and 7 mL of glacial acetic acid were added and the mixture was stirred *overnight* at room temperature. After removal of the solvent, 12 mL of acetic anhydride was added on the residue and stirred in the presence of DMAP (0.38 mmol) at 45 °C for 4 h. Then, 12 mL of methanol was added and stirred for additional 30 min. After removal the solvent, the residue was taken up in ethyl acetate and washed with HCl 1 M. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was dissolved in 15 mL of methanol and stirred in the presence of K_2CO_3 (6.4 mmol) at 45 °C for 3 h. The mixture was filtered over celite and concentrated. After this, the residue was taken up in ethyl acetate and washed with HCl 3 M and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and the crude oil obtained after concentration was purified by column chromatography on silica gel (40 → 100 % AcOEt – Hex) to afford the respective products.

2.3. General procedure for the synthesis of the deuterated substrates (d-1 and d-2)

In a Schlenk flask under an inert atmosphere, the tyramine (5.6 mmol) and 5 mL of water were added, followed by 2.6 mmol of metallic sodium. The reaction mixture was stirred at 100 °C for 48 h. The reactions was then cooled to room temperature and the solution was acidified to pH = 6 when a slight precipitation occurred. Because of this, the supernatant was transfer and extracted with diethyl ether. GC–MS analysis indicated the product was in the aqueous phase. So, the aqueous phase was lyophilized getting a brown solid.

This solid was used without any additional purification in the synthesis of the abovementioned substrates (**1** and **2**) following the same protocol as the previous section, getting 19 % *d*-**1** and 17 % *d*-**2** after purification.

2.4. General procedure for the laccase catalyzed reactions

For both substrates, two reaction medium were studied:

I Phosphate buffer (0.1 M, pH = 6.4) : acetonitrile – 6:1
II Acetate buffer (0.02 M, pH = 5.4 : ethyl acetate – 1:1

When ABTS was used, this was added in 10 % mol of the substrate.

Laccase fromTrametes versicolor (30U) was dissolved in the corresponding buffer and then the substrate was added dissolved in the organic solvent and stirred at room temperature for 24h in an open vial. When acetonitrile was the solvent, the reaction medium was concentrated before its extraction with ethyl acetate. When ethyl acetate was the solvent, the phases were separated and aqueous phase was extracted with ethyl acetate. Lastly, the organic phases were combined, dried over anhydrous Na_2SO_4, filtered and evaporated.

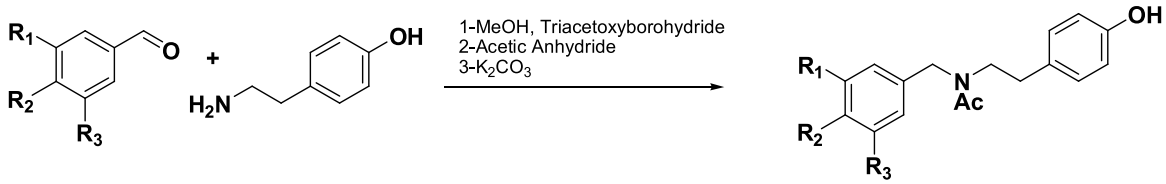
The same protocol was used with *d*-**1** and *d*-**2**

3. Results and discussion

Compounds **1** and **2** were obtained through the reductive amination between Tyramine and the corresponding aldehyde, 2,3,4-trimethoxybenzaldehyde **3** for the synthesis of **1** and 3-hydroxybenzaldehylde **4** for the synthesis of **2**, respectively. The secondary amines were then acylated lending to the desired amides. Compounds **1** and **2** were obtained in 56 % and 44 % overall yield respectively, and observed as a pair of rotamers (scheme 2) in the NMR analysis.

The laccases catalyzed reactions of **1** and **2** were conducted with the Laccase from *T. versicolor (30 U)* in a phosphate (pH = 6.4) : acetonitrile or acetate (pH = 5.4) : Ethyl Acetate buffer solvent mixture and in the presence or absence of ABTS as mediator as depicted in Table 1.

As can be seen in Table 1, the conversion was highly sensitive to the reaction conditions. For both compounds, the higher conversions were observed at higher pH. In the case of the reaction of **1**, the presence of



Scheme 2. Synthesis of substrates **1** and **2**.

Table 1
The laccases catalyzed reaction of 1 and 2 under different conditions.

Entry	Substrate	Buffer pH	Mediator	Conversion (%)	Selectivity Dimer/ Trimer	(C-C): (C-O)
1	1	6,4[a]	–	5	ND	ND
2			ABTS[c]	98	3.23	10:90
3		5,4[b]	–	33	3.80	64:36
4			ABTS[c]	38	4.52	62:38
5	2	6,4 [a]	–	93	1.24	55:45[d]
6			ABTS[c]	91	1.43	3:97[d]
7		5,4 [b]	–	61	3.85	67:33[d]
8			ABTS[c]	68	4.41	62:38[d]

Conditions: [substrate] 20 mM, 30U of laccase T. versicolor. [a] Solvent mixture Phosphate buffer 100 mM (pH = 6.4) : acetonitrile (6:1) [b] Solvent mixture Acetate 50 mM (pH = 5.4) : Ethyl Acetate (1:1) [c] 10 % mol ABTS [d]-these selectivities are relative to the C-C linked dimer detected., see discussion.
ND: Not Determined.

ABTS had profound influence in the reaction outcome where only at pH = 6.4 complete conversion was observed. The same reaction conditions yielded 91 % of conversion for substrate **2**. However, in the case of substrate **2** the presence of the mediator did not impacted the conversion as compared to substrate **1,** once 93 % conversion was observed in the absence of the mediator.

As can be seen in Figures S5-S-8, all the reactions presented the same product profile through HPLC-UV analysis of the crude isolated reaction. Unfortunately, in order to get structural information concerning the reaction products, all the attempts to obtain a fraction with adequate purity for spectroscopic characterization after chromatography were deemed with failure. To get insight into the type of products formed, the reactions were then analyzed by hyphenated HPLC-UV-ESI-TOF-MS.

For the reaction of **1** and **2**, products with the mass correspondent to the proton adduct of dimers and trimers could be detected. In the case of substrate **1** the dimers were the major products as can be seen in table Table 1. In the case of substrate **2** the amount of dimers and trimer were almost the same at higher pH, where the phenolic compounds are more reactive due to higher concentration of the phenolate species. This issue associated with the presence of two phenols in the structure can be responsible for this selectivity.

These dimers and trimers can be built up through the formation of a carbon-carbon or a carbon-oxygen bond. The above presented analysis do not shed any light into the nature of the bond formed, and consequentially, into the structure of these products. Once no pure compound could be obtained, and in order to elucidate this issue, the synthesis of selectively deuterium labeled derivatives *D*-**1** and *D*-**2** was pursued, as depicted in Scheme 3. Tyramine was deuterated through its reflux in a solution of NaOD in D_2O (formed by diluting Na(0) in D_2O, see SI). The subsequent reductive amination and acylation afforded the desired deuterium labeled compounds in 19 % and 17 % yields for *D*-**1** and *D*-**2**, respectively.

To confirm that the deuterium atoms were introduced at the desired position, ^{2}D NMR of the substrates were obtained, confirming the incorporation only at the *ortho* positions relative to the phenol (see figure S15). The *D*-**1** and *D*-**2** were also analyzed through ESI-TOF MS. For compound *D*-**1** the deuterated compound presented the exact mass of 362.1944 Da for its proton adduct (Theoretical $[M+H]^+$ =362.1937 Da) and for *D*-**2** a mass of 288.1556 also for its proton adduct (Theoretical $[M+H]^+$ =288.1569 Da), two units higher then the non-deuterated compounds

The deuterated amides D-**1** and D-**2** were submitted to the reaction condition presented in Table 1 entries 2 and 6, respectively, where higher conversion was obtained. Important to note that the reaction with the deuterated compounds afforded the same profile as for the non-deuterated (Figures S46 and S51). This identical reaction outcome, allowed the determination of the structure of the dimers and trimers formed.

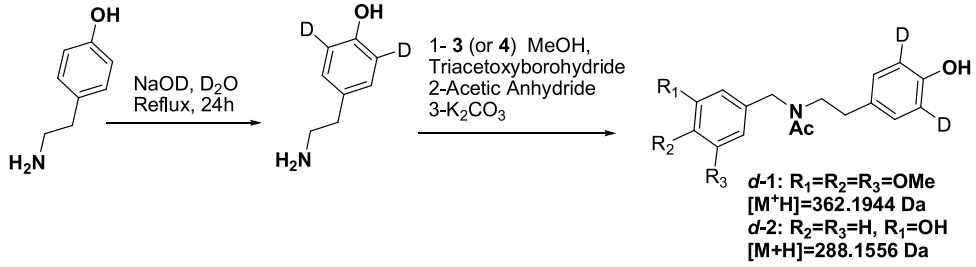
For the substrate D-**1**, dimeric compounds with molecular mass two ($[M+H]^+$ = 719.3496) and three units ($[M+H]^+$ = 720.3558) heavier than that of the dimer of the non-deuterated ($[M+H]^+$ = 717.3373) compound could be observed. These results are consistent with the presence of two and three deuterium atoms, respectively. In the present case, that dimer that contain two deuterium atoms may have the monomers linked through a carbon-carbon bond, and that with three deuterium atoms may be linked through a carbon-oxygen bond, as depicted in, Fig. 4.

Concerning the region corresponding to the molecular mass of the trimers, compounds containing the presence of two, three and four deuterium atoms were detected corresponding to the presence of trimers linked by two carbon-carbon bonds one carbon-carbon and one carbon-oxygen bond one carbon-carbon and two carbon-oxygen bonds, respectively. The respective structures of these products are depicted in Fig. 4.

In the case of compound **2**, three peaks with the molecular mass corresponding to the dimers were detected; one with molecular mass two units higher than the non deuterated counterpart and two with three units higher. While the dimer containing two units higher can be attributed to the C—C bonded dimer. The elucidation of the structures of the dimers with molecular mass three units higher is more complicated since the coupling between the phenolic ring from the aldehyde derived portion of **2** with the tyramine portion through a carbon-carbon (or oxygen-carbon bond) bond would also present three deuterium atoms in its structure, being isobaric with the product obtained from the formation of a carbon-oxygen bond between the two tyramine portion of the molecule, Fig. 5.

In an attempt to obtain information on the structure of the other two dimers detected, *i. e.* to differentiate between these isobaric dimers **11**-**13,** these two peaks observed on the HPLC-UV-ESI-TOF-MS were fragmented and their Ms/Ms fragmentogram were recorded. In these fragmentograms, the ion with m/z = 392.1827 Da was used as a diagnostic. This ion presents the molecular formula of $C_{24}H_{22}D_2NO_4^+$ theoretical = 3,921,825 Da and is compatible only with structure **11**, as depicted in Fig. 5. For a discussion and structure of the other ions present in these fragmentograms see supporting information Figure S58-S60. Concerning the structure of the third dimer, the data did not allow the distinction between structures **12** an **13** in Fig. 6.

In relation to the trimers, three different were detected, where two contains molecular mass two units higher and one three units higher



Scheme 3. Synthesis of *D*-**1** and *D*-**2**.

then their non deuterated counterparts. These results demonstrate that there is at least two carbon-carbon bond linked through the tyramine moiety.

Concerning the selectivity of the bond formed, in the case of substrate **1** it is interesting that, with the exception of the reaction with ABTS at pH 6.4, entry 2 and Table 1, all reaction conditions presented a small selectivity favoring the C—C linked dimer. The case of entry 2 is interesting once it presented high selectivity for the C—O linked dimer. The same selectivity is also observed for the reaction with the deuterated substrate.

In the case of substrate **2**, the determination of such selectivity is difficult due the ambiguity in stablishing the reaction products, once

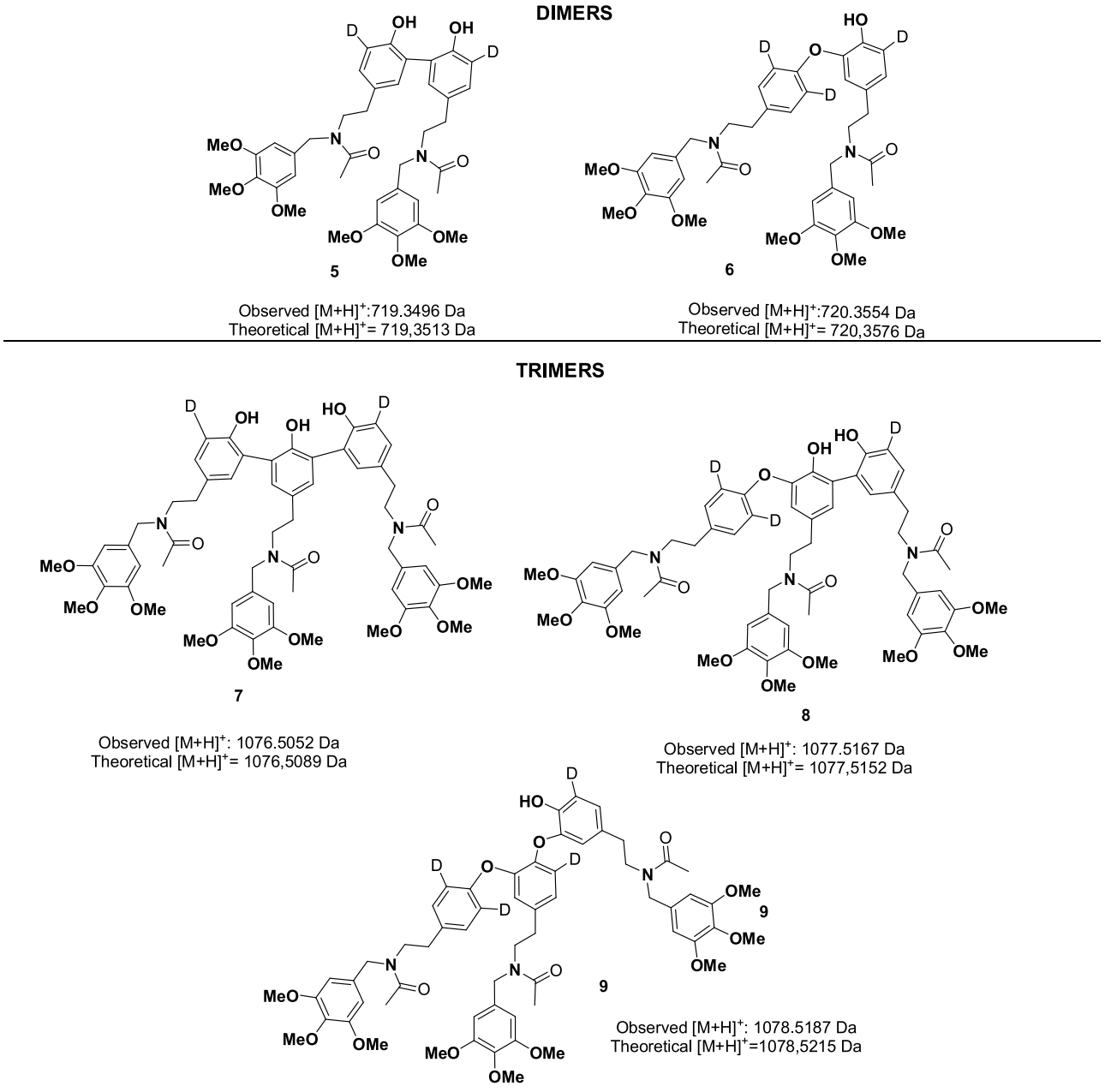


Fig. 4. The attributed structure for the dimers and trimers for the reaction of D-**1** with the laccases of *T.versicolor*.

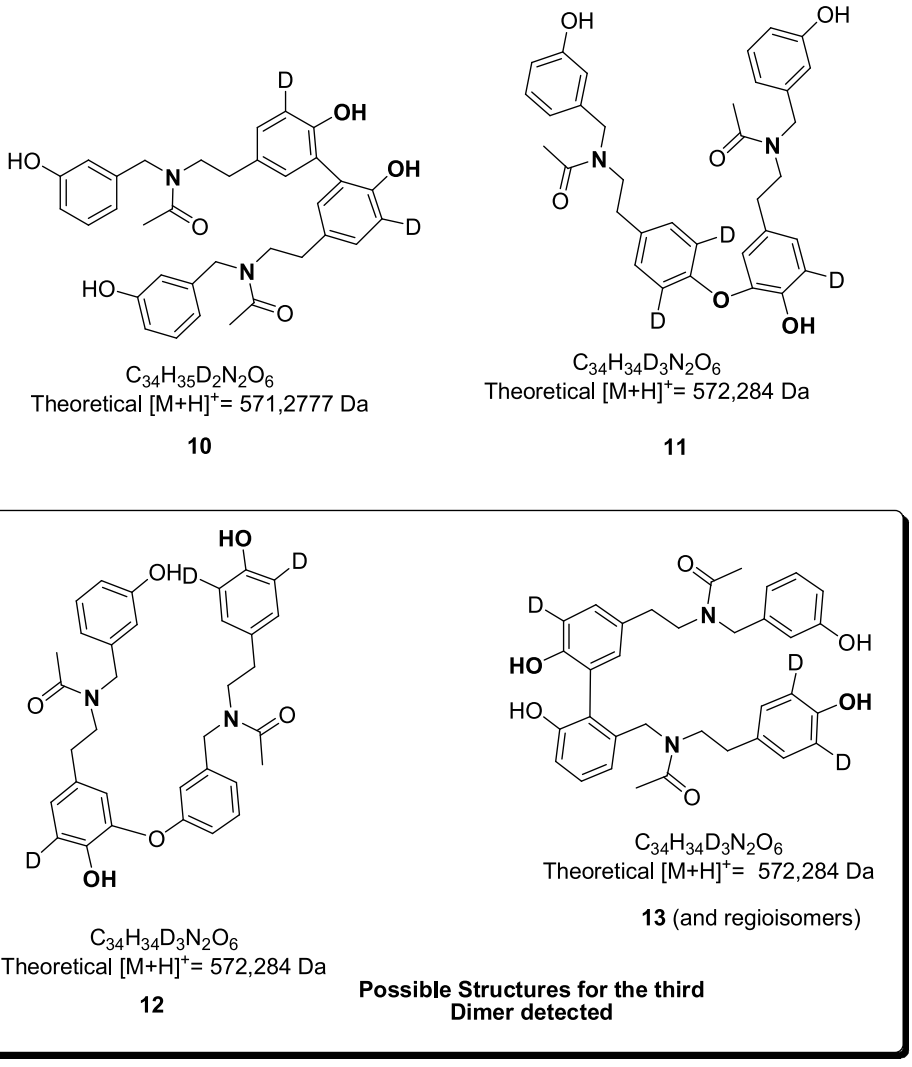


Fig. 5. Structure **10, 11** and **12** (or **13**) of the dimers detected with two or three deuterium atoms.

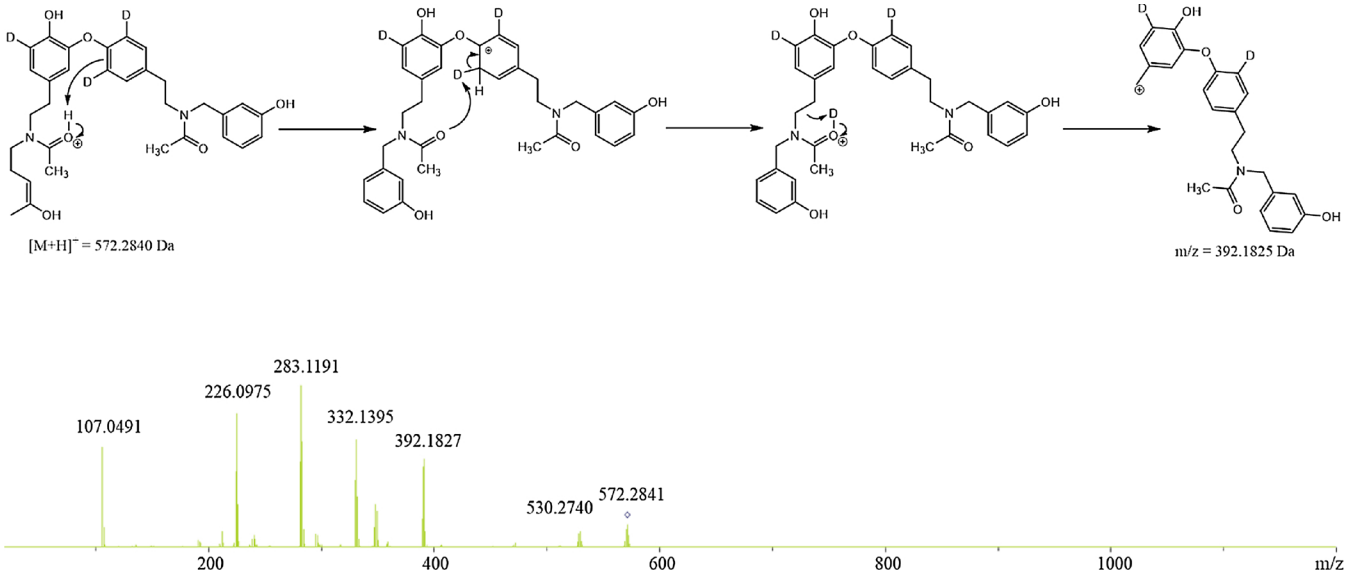
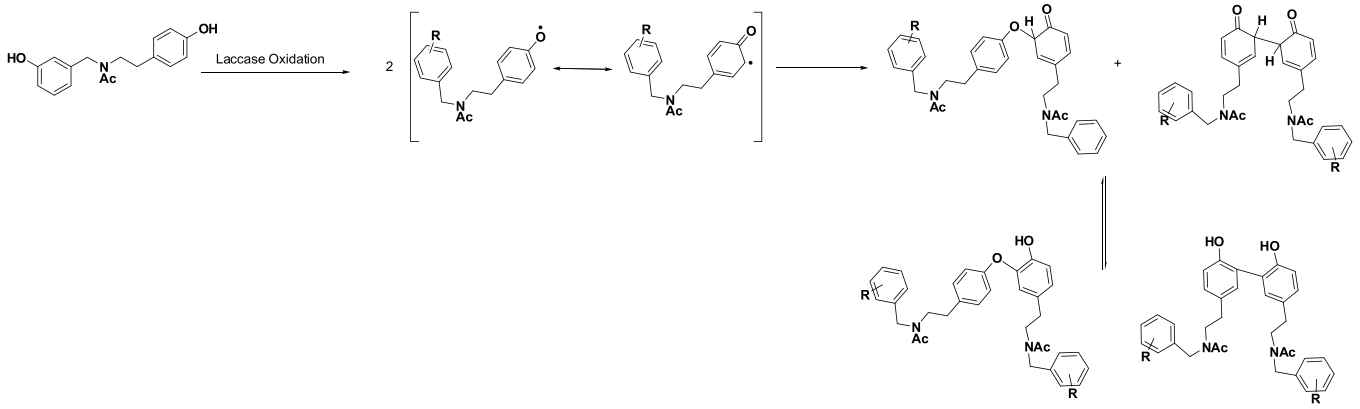


Fig. 6. Fragmentogram of the ion m/z 572.2829 Da, and the proposed structure of the fragment ion with m/z 392.1827 Da, for the peak eluting at 19.5 min in Figure S40.



Scheme 4. The proposed events for the dimerization of **1** and **2**.

only the C—C and one C-O— bonded products could be elucidated. Then a selectivity toward this C—C linked product was calculated (Table 1), and interestingly the selectivity for this C—C linked dimer is smaller at pH 6.4 in the presence of ABTS, Table 1 entry 6, as analogous to substrate **1**. The different outcome of the Laccase catalyzed oxidation of phenols concerning the bond formed is reported in the literature, however rarely discussed [72–75]. Lahtinen and co-workers have reported [72] an increase formation of C—O bond in the case of the dimerization of vannilyl alcohol with increasing pH (7.0). However the influence of the mediator in such selectivity remains to be elucidated.

The abovementioned results demonstrate that the laccases catalyzed reaction of substrates **1** and **2** lead mainly to the dimers and trimers once no other type of product could be detected. From the mechanistic point of view, the data make it clear that the laccases catalyzed reaction of phenols occurs through a one electron oxidation reaction even in the presence of the mediator ABTS. The dimerization of the herein studied phenolic compounds is believed to occur through a phenoxy radical-radical coupling. as depicted in Scheme 4 [73] [74].

4. Conclusion

In conclusion, it was determined that the Laccases/ABTS and Laccases alone were able to catalyze the dimerization and trimerization reaction of Norbelladine like amides **1** and **2** in high conversions, respectively. The synthesis of the selectively deuterated substrates *D*-**1** and *D*-**2** and the analysis of their reaction products by HPLC-ESI-TOF MS allowed the determination of the all C—C and CO— linked dimers and trimers and mixed C—C and CO— linked trimers in the case of **1**, and the all C—C bonded dimers and trimers for the case of **2.** Additionally, the development of the Laccase catalyzed reaction of deuterated compounds may afford a valuable tool for its application in the study of the Laccase catalyzed synthesis of (pseudosymmetric) ligands or natural products.

Credit author statement

Leandro Soter de Mariz e Miranda and Rodrigo Octávio Mendonça Alves de Souza contributed to the conceptualization of the Project, project administration and also to the writing of the manuscript.

Viviane Marques de Aguiaa, Rodrigo Esquinelato Silva contributed elaborating the methodology, running the experiments, quantification of the products, 13C, 1H and 2D NMR.

Raquel A. C. Leão and Raoni Schroeder B. Gonçalves contributed with the HPLC-UV-ESI-TOF-MS data analysis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors acknowledge financial support and fellowships from FAPERJ, CAPES, and CNPq.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.mcat.2020.110788.

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