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Electronic Supporting Information for Inhibition in Multicopper Oxidases: A Critical Review

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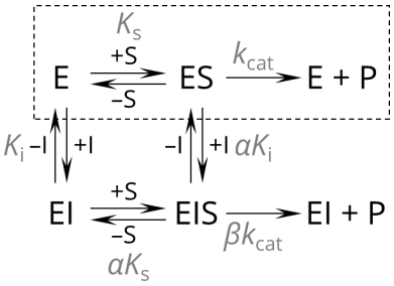
S1. Introduction to steady-state enzyme inhibition kinetics

In the most common case for enzymes, the reaction rate (v) asymptotically approaches a limiting maximum rate (v_{max}) at high substrate concentration. The Michaelis–Menten kinetic scheme is shown in the dashed box in **Scheme S1**. This scheme captures this change in reaction order by assuming the reversible association of enzyme (E) and substrate (S) to form an enzyme–substrate complex (ES) that irreversibly produces product and regenerates the original enzyme.



Scheme S1. The general modifier mechanism scheme for the inhibition of enzymes that follow Michaelis–Menten kinetics, assuming no interaction between substrate, products and inhibitors, as proposed by Botts and Morales[1] and using the symbol convention of Baici.[2] Dashed box indicates Michaelis–Menten kinetics in the absence of inhibition. Key: E = enzyme, S = substrate (reactant), I = inhibitor, P = product, ES = enzyme–substrate complex, EI = enzyme–inhibitor complex, EIS = enzyme–inhibitor–substrate complex, K = dissociation equilibrium constant, k_{cat} = catalytic rate constant, α = reciprocal of the allosteric coupling constant, β = modifier for k_{cat} for inhibited enzyme

At steady state, the Michaelis–Menten scheme predicts a relation between substrate concentration ([S]), total enzyme concentration ($[E]_0$) and reaction rate:

$$v = \frac{v_{max}[S]}{K_M + [S]} \qquad \textbf{Equation S1}$$

where the Michaelis–Menten constant K_M is the substrate concentration at which an enzyme's catalytic rate is half its maximum (i.e., $v/v_{max} = 0.5$). Enzyme catalysis for a set of conditions (substrate, temperature, pH, etc.) is quantified by K_M and k_{cat}.

Inhibitors reduce the rate of product formation for a given amount of enzyme and substrate. In a general reaction scheme based around Michaelis–Menten kinetics, an inhibitor (I) can bind to either E or ES to form an enzyme–inhibitor complex (EI) or an enzyme–inhibitor–substrate complex (EIS), and both the substrate-bound complexes (ES and EIS) can form product. The strength of the affinity between an enzyme and substrate is given by its substrate dissociation constant (K_s):

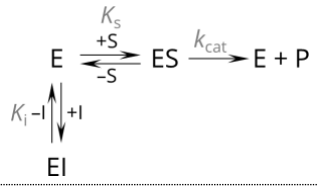
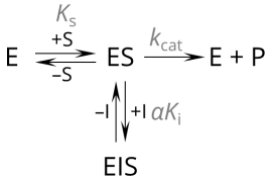
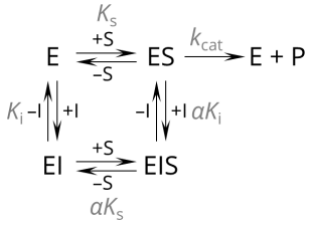
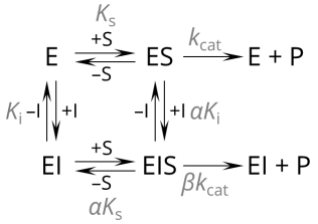
$$K_s = \frac{k_{-s}}{k_{+s}} = \frac{[E][S]}{[ES]} \qquad \textbf{Equation S2}$$

Higher values for the dissociation constant indicate greater stability of the two free components than the bound complex, that is, a weaker affinity for the enzyme for a substrate. A similar dissociation constant exists for inhibitor binding (K_i = ([E][I])/[EI]); weaker inhibitors have higher K_i values. Equilibria

involving the EIS complex have a modifier α, the reciprocal of the allosteric coupling constant;[2] the product conversion step involving EIS has a modifier β to reflect the change in catalytic rate for a partially inhibited enzyme.

Common linear and hyperbolic schemes are shown in **Table S1**. According to the guidelines from the International Union of Biochemistry, "linear" means that the terms in the denominator of the rate equation are linear with respect to inhibitor concentration.[3] Inhibition mechanisms where $\beta = 0$ are linear and those where $\beta \neq 0$ are hyperbolic. The table uses both the older terminology[3, 4] and the more descriptive terms from Baici:[2] the descriptor "mixed" is preferred to "non-competitive" and "hyperbolic" is used instead of "partial".

Table S1. Four common inhibition schemes. Each type is based on simplifications of Scheme S1.

Type	Scheme
Competitive • I binds only to E • $\alpha = \infty$, $\beta = 0$ • Linear specific inhibition	
Uncompetitive inhibition • I binds only to ES • $\alpha K_i > 0$, $K_i \neq \infty$, $\beta = 0$ • Linear catalytic inhibition	
Linear mixed inhibition • Predominantly specific • $\alpha > 1$, $\beta = 0$ • "Non-competitive" when $\alpha = 1$	
Hyperbolic inhibition • ES and EIS form product at different rates • $\alpha > 0$, $\beta \neq 0$ • "Partial" inhibition	

Competitive (specific) inhibition is modelled on I and S competing for the same binding, meaning that S cannot bind to EI and I cannot bind to ES. In uncompetitive (catalytic) inhibition, I can only bind to ES. In linear mixed inhibition, I can bind to either E or ES and S can bind to either E or EI. The case of linear mixed inhibition in which the strength of inhibition is unaffected by substrate binding (i.e., $\alpha = 1$) was formerly called non-competitive inhibition, but the International Union of Biochemistry now discourages using this term.[2, 3] Cases where the EIS state can break down to form product lead to hyperbolic inhibition profiles.[5]

Baici's treatment of enzyme inhibition also includes two schemes that include multiple inhibitor binding, termed "parabolic inhibition". Such schemes are potentially relevant because MCOs have two substrate binding sites (for the electron-donor and O_2) and several solvent channels, that is, multiple sites for inhibitor–enzyme interaction. However, there has been only one report in which parabolic inhibition has been attributed to MCO inhibition, but the authors did not factor in their measurement uncertainty into their analyses and did not run statistical tests discriminate between competing models.[6]

Table S2. Formulas relating IC_{50} values and K_i for linear and hyperbolic inhibition schemes, where $\sigma = [S]/K_M$. A "true" IC_{50} value is the inhibitor concentration required to halve the *maximum* reaction rate (i.e., at infinite [S]). The "apparent" IC_{50} value is the concentration of inhibitor required to halve the reaction rate *at a fixed substrate concentration*.

Inhibition parameter	**General**	**Competitive (linear specific)** $\alpha = \infty$, $\beta = 0$	**Linear mixed** $0 < \alpha < \infty$, $\beta = 0$	**Uncompetitive (linear catalytic)** $\alpha K_i > 0$, $K_i = \infty$, $\beta = 0$
$IC_{50,true}$	$= \frac{\alpha\,(\sigma - 1)}{\alpha + \sigma\,(1 - 2\beta)}\,K_i$	$= (\sigma - 1)\,K_i$	$= \frac{\alpha(\sigma - 1)}{\alpha + \sigma}\,K_i$	$= \frac{\sigma - 1}{\sigma}\,K_i$
$IC_{50,app}$	$= \frac{\alpha\,(\sigma + 1)}{\alpha + \sigma - 2\beta\,(\sigma + 1)}\,K_i$	$= (\sigma + 1)\,K_i$	$= \frac{\alpha(\sigma + 1)}{\alpha + \sigma}\,K_i$	$= \frac{\sigma + 1}{\sigma}\,K_i$
$\frac{\text{true } IC_{50}}{\text{app. } IC_{50}}$	$= \left\lvert \frac{\sigma - 1}{\sigma + 1} \right\rvert \left\lvert \frac{\alpha + \sigma - 2\beta\,(\sigma + 1)}{\alpha + \sigma\,(1 - 2\beta)} \right\rvert$	$= \frac{\sigma - 1}{\sigma + 1}$	$= \frac{\sigma - 1}{\sigma + 1}$	$= \frac{\sigma - 1}{\sigma + 1}$

S2. Mechanism of O_2 reduction in MCOs

The O_2 reduction reaction (ORR) in MCOs has been studied extensively by Solomon *et al.* who have proposed mechanisms (**Figure S1**) based on the spectroscopic and computational studies of MCOs.[7-13]

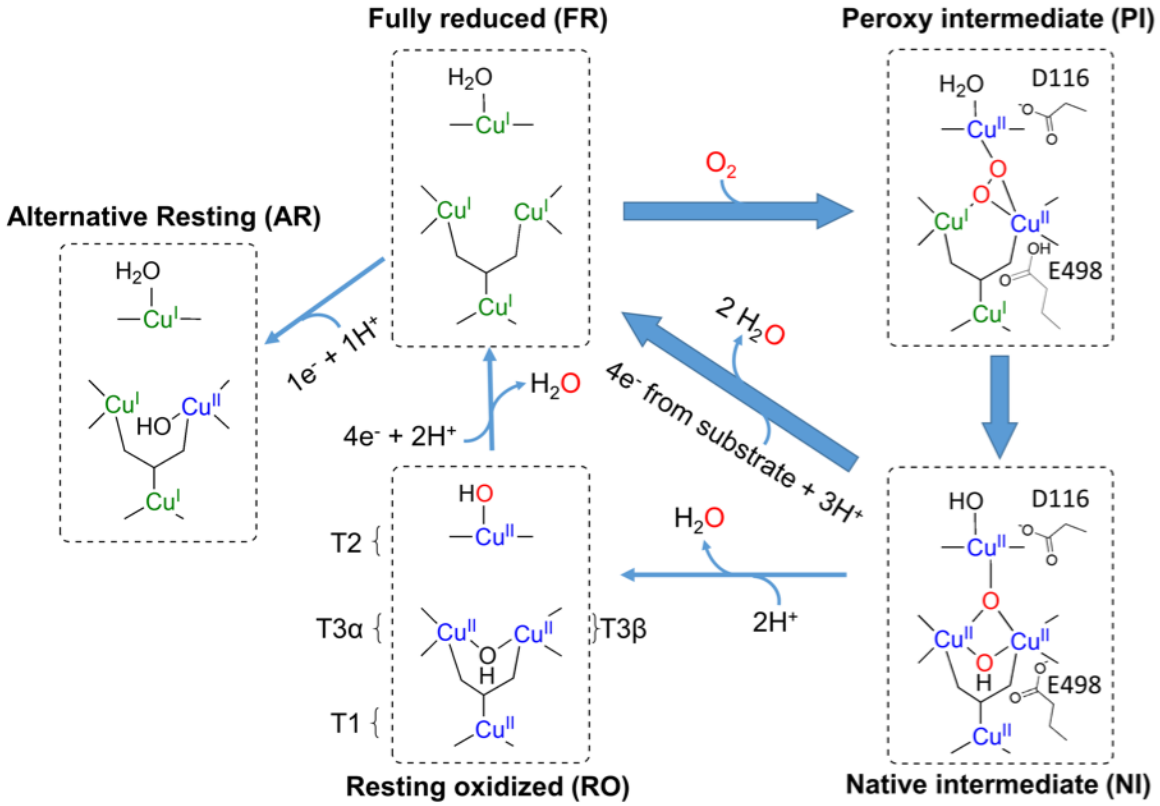


Figure S1. O_2 reduction reaction mechanism in MCOs. Thick arrows indicate the steps included in the catalytic cycle while the thinner arrows indicate slower processes found outside the catalytic cycle. Oxygen atoms that originate from the O_2 substrate are colored in red. Reduced coppers (+1 oxidation state) are in green and oxidized coppers (+2 oxidation state) are in blue. Residue numbers correspond to the sequence of CotA from *Bacillus subtilis*. Adapted with permission from reference [14] (Copyright 2008, The Royal Society of Chemistry) and reference [15] (Copyright 2015, American Chemical Society).

The O_2 substrate can only bind to the fully reduced MCO (FR, all Cu atoms in +1 oxidation state), which occurs once the enzyme has received electrons from the one-electron oxidation of four electron-donor substrates at the T1 site (**Figure S1**). The reaction of O_2 with the reduced TNC results in two, two-electron steps to first produce a peroxy intermediate (PI), followed by the native intermediate (NI).[7] In the PI, the TNC is partially oxidized, with the two oxygen atoms found at the center of the TNC triangle.[16, 17] The transition from the PI to the NI requires the rearrangement of the oxygen atoms in the TNC, made possible by the transfer of an electron from the T1 site (which becomes oxidized) and a proton from a nearby glutamate (E498 in CotA from *B. subtilis*). Thus, all the Cu co-factors of the NI are oxidized.[18, 19] Three electrons coming sequentially from the T1 site, and three protons transferred from

the E498 residue, are required to protonate (and reduce) the TNC, releasing the two water products and completing the catalytic cycle (the fourth electron reduces the T1).[11, 12]

In the absence of a reducing substrate, the NI decays to a resting oxidized (RO) state (**Figure S1**). The oxidation state of the Cu co-factors is maintained through the transition from NI to RO, as both are fully oxidized forms (all Cu atoms in the +2 state).[20] In 2012, a second "alternative resting" (AR) form of bilirubin oxidases was characterized with EPR, UV-vis and X-ray absorption spectroscopy, and X-ray crystallography.[21] This form has no 330 nm peak and a longer distance between the T3 Cu ions than the RO state. These resting states sit outside the catalytic cycle, so most spectroscopic and crystallographic analyses of MCO inhibition have not studied catalytically active states of the enzyme.

S3. Tables of published solution-based inhibition measurements

Table S3. Summary of F^- inhibition constants obtained from solution-based spectrophotometric assays. The terms K_{ci} and K_{ui} are the inhibitor dissociation constants based on a competitive or uncompetitive inhibition model, respectively, and are equivalent to K_i and αK_i in the linear mixed scheme in **Table S1**. Abbreviations: F = Fungi (kingdom), P = Plantae (kingdom), B = Bacteria (kingdom/domain), Ba = Basidiomycota (phylum), As = Ascomycota (phylum), M = Myrothecium (genus), Ma = Magnoliophyte (phylum), Fi = Firmicutes (phylum), T. = Trametes (genus), B. = Bacillus (genus), BOD = bilirubin oxidase, ABTS = 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid), SGZ = syringaldazine, 2,6-DMP = 2,6-dimethylphenol, Abu62 = sodium 1-amino-4-(cyclohexylamino)-9,10-dihydro-9,10-dioxoanthracene-2-sulfonic acid, N.D. = not determined, HW = Hanes–Woolf,[22, 23] MM= Michaelis-Menten LB = Lineweaver-Burk, D = Dixon,[24] CB = Cornish-Bowden[25]

MCO (kingdom/phylum)	pH	Electron donor	Type of inhibition (plot type(s))	K_i or IC_{50}	Ref.
T. trogii laccase (F/Ba)	3.4	2,6-DMP	Mixed (HW)	IC_{50} = 9 µM K_{ci} = 9 µM K_{ui} = 10 µM	[26]
T. trogii laccase (F/Ba)	3.4	ABTS	Mixed (HW)	IC_{50} = 9 µM K_{ci} = 10 µM K_{ui} = 20 µM	[26]
P. sanguineus CS43 LAC1 laccase (F/Ba)	4	ABTS	Non-competitive (LB)	K_i = 72.4 µM	[27]
P. sanguineus CS43 LAC2 laccase (F/Ba)	4	ABTS	Non-competitive (LB)	K_i = 18.4 µM	[27]
Marasmius quercophilus laccase (F/Ba)	4	SGZ	N.D.	IC_{50} = 2.7 mM	[28]
T. villosa (Polyporus pinsitus) laccase isozyme 1 (F/Ba)	5	ABTS	Mixed	IC_{50} = 0.02 mM	[29]
Rhizoctonia solani laccase isozyme 4 (F/Ba)	5	ABTS	Mixed	IC_{50} = 0.02 mM	[29]
Coprinus cinereus laccase (F/Ba)	6	ABTS	N.D.	IC_{50} = 2 mM	[30]
Trachyderma tsunodae K-2593 BOD (F/Ba)	6.8	Bilirubin	Non-competitive (D)	K_i = 26 mM	[31]
Myceliophthora thermophila laccase (F/As)	5	ABTS	Mixed	IC_{50} = 0.05 mM	[29]
Mycothermus (*Scytalidium*) *thermophilum* laccase (F/As)	5	ABTS	Mixed	IC_{50} = 0.5 mM	[29]
M. verrucaria BOD (F/As)	5	ABTS	Mixed	IC_{50} = 1 mM	[29]
M. verrucaria BOD (F/As)	7	$[Fe(CN_6)]^{3-/4-}$	Competitive (LB, HW, D, CB)	K_i = 17 mM	[32]
Toxicodendron vernicifluum (*Rhus vernifera*) laccase (P/Ma)	5	ABTS	Mixed	IC_{50} = 0.02 mM	[29]

Table S4. Summary of Cl^- inhibition constants obtained from solution-based spectrophotometric assays. Symbols and abbreviations are the same as Table S3.

MCO (kingdom/phylum)	pH	Electron donor	Type of inhibition (plot type(s))	K_i or IC_{50}	Ref.
T. versicolor laccase (F/Ba)	3	ABTS	Mixed (LB)	K_{ci} = 0.35 mM K_{ui} = 18.1 mM	33
T. trogii laccase (F/Ba)	3.4	2,6-DMP	Mixed (HW)	IC_{50} = 5 mM K_{ci} = 1.6 mM K_{ui} = 17.2 mM	26
T. trogii laccase (F/Ba)	3.4	ABTS	Mixed (HW)	IC_{50} = 70 mM K_{ci} = 0.47 mM K_{ui} = 52 mM	26
P. sanguineus CS43 LAC1 laccase (F/Ba)	4	ABTS	Competitive (LB)	K_i = 64.7 mM	27
P. sanguineus CS43 LAC2 laccase (F/Ba)	4	ABTS	Competitive (LB)	K_i = 15.2 mM	27
Marasmius quercophilus laccase (F/Ba)	4	SGZ	N.D.	IC_{50} = 7.5 mM	28
T. hirsuta laccase (F/Ba)	4.5	2,6-DMP	N.D.	IC_{50} = 50 mM	34
T. versicolor laccase isozyme IIIb (F/Ba)	5	ABTS	Mixed (CB)	IC_{50} = 40 mM K_{ci} = 1.8 mM K_{ui}= 17 mM	35
T. versicolor laccase isozyme IIIb (F/Ba)	5	Abu62	Mixed (other)[36]	IC_{50} = 10 mM K_i = 9.5 mM	35
T. versicolor laccase (F/Ba)	5	ABTS	Hyperbolic (LB)	K_i = 12.8 mM	6
T. versicolor laccase (F/Ba)	5	Reactive blue 19	Parabolic (LB)	K_i = 74 mM	6
T. villosa (Polyporus pinsitus) laccase isozyme 1 (F/Ba)	5	ABTS	Mixed	IC_{50} = 40 mM	29
Rhizoctonia solani laccase isozyme 4 (F/Ba)	5	ABTS	Mixed	IC_{50} = 50 mM	29
Fomes fomentarius laccase (F/Ba)	5	Ferulic acid	Competitive (MM)	K_i = 13.7 mM	37
Cyathus bulleri laccase (F/Ba)	5.5	ABTS	N.D.	IC_{50} = 0.6 M	38
Coprinus cinereus laccase (F/Ba)	6	ABTS	N.D.	IC_{50} = 200 mM	30
T. versicolor laccase (F/Ba)	6	ABTS	Mixed (LB)	K_{ci} = 23.7 mM K_{ui} = 324 mM	33
Trachyderma tsunodae K-2593 BOD (F/Ba)	6.8	Bilirubin	Non-competitive (D)	K_i = 0.11 M	31
Myceliophthora thermophila laccase (F/As)	5	ABTS	Mixed	IC_{50} = 0.6 M	29
Mycothermus (*Scytalidium*) *thermophilum* laccase (F/As)	5	ABTS	Mixed	IC_{50} = 0.4 mM	29
M. verrucaria BOD (F/As)	5	ABTS	Mixed	IC_{50} = 10 mM	29
M. verrucaria BOD (F/As)	5	$[Fe(CN_6)]^{3-/4-}$	Non-competitive (LB, HW, D, CB)	K_i = 220 mM	32
Toxicodendron vernicifluum (*Rhus vernifera*) laccase (P/Ma)	5	ABTS	Mixed	IC_{50} = 0.05 mM	29

Table S5. Summary of inhibition constants obtained from solution-based spectrophotometric assays for other inhibitors. IDA = 2,2′-iminodiacetate–terminated poly(2-oxazoline), DEA = diethylamine, C_2C_1Im = 1-ethyl-3-methylimidazolium, Ch = cholinium, Lys = lysinate. Other symbols and abbreviations are the same as Table S3. Dashed lines mark clusters of the same inhibitor.

MCO (kingdom/phylum)	pH	Electron donor	Inhibitor	Type of inhibition (plot type(s))	K_i or IC_{50}	Ref.
Marasmius quercophilus laccase (F/Ba)	4	SGZ	Br^-	N.D.	IC_{50} = 20 mM	[28]
T. villosa (Polyporus pinsitus) laccase isozyme 1 (F/Ba)	5	ABTS	Br^-	Mixed	IC_{50} = 40 mM	[29]
Rhizoctonia solani laccase isozyme 4 (F/Ba)	5	ABTS	Br^-	Mixed	IC_{50} = 0.2 M	[29]
Trachyderma tsunodae K-2593 BOD (F/Ba)	6.8	Bilirubin	Br^-	Non-competitive (D)	K_i = 0.43 M	[31]
Myceliophthora thermophila laccase (F/As)	5	ABTS	Br^-	Mixed	IC_{50} = 1.6 M	[29]
Mycothermus (*Scytalidium*) *thermophilum* laccase (F/As)	5	ABTS	Br^-	Mixed	IC_{50} = 5 mM	[29]
M. verrucaria BOD (F/As)	5	ABTS	Br^-	Mixed	IC_{50} = 10 mM	[29]
Toxicodendron vernicifluum (*Rhus vernifera*) laccase (P/Ma)	5	ABTS	Br^-	Mixed	IC_{50} = 0.05 mM	[29]
T. trogii laccase (F/Ba)	3.4	2,6-DMP	I^-	N.D.	IC_{50} = 67 mM	[26]
T. trogii laccase (F/Ba)	3.4	ABTS	I^-	N.D.	IC_{50} = 70 mM	[26]
Marasmius quercophilus laccase (F/Ba)	4	SGZ	I^-	N.D.	IC_{50} = 3.3 mM	[28]
T. hirsuta laccase (F/Ba)	4.5	2,6-DMP	N_3^-	N.D.	IC_{50} = 2 µM	[34]
Trachyderma tsunodae K-2593 BOD (F/Ba)	6.8	Bilirubin	N_3^-	Non-competitive	IC_{50} = 19 µM	[31]
T. villosa laccase (F/Ba)	N.D.	ABTS	N_3^-	Mixed (LB)	K_{ci} = 17.6 µM K_{ui} = 10.6 µM	[39]
B. subtilis CotA (B/Fi)	4	ABTS	N_3^-	N.D.	IC_{50} = 2.3 mM (WT) = 2.3 mM (E498D) = 4.7 mM (E498T) = 9.8 mM (E498L)	[19]
Trachyderma tsunodae K-2593 BOD (F/Ba)	6.8	Bilirubin	SCN^-	Non-competitive (D)	K_i = 94 µM	[31]
M. verrucaria BOD (F/As)	7	$[Fe(CN_6)]^{3-/4-}$	SCN^-	Non-competitive (LB, HW, D, CB)	K_i = 120 mM	[32]
T. villosa laccase (F/Ba)	4	ABTS	Acetate	Mixed (LB)	K_{ic} = 38.8 mM K_{iu} = 117.5 mM	[39]
T. villosa laccase (F/Ba)	4	ABTS	Formate	Non-competitive (LB)	K_i = 7.7 mM	[39]
T. versicolor laccase (F/Ba)	4.5	ABTS, 2,6–DMP	IDA	Competitive (LB)	IC_{50} = 1–3 mM	[40]
T. versicolor laccase (F/Ba)	5	ABTS	$[DEA][HSO_4]$	Non-competitive (HW)	IC_{50} = >4% w/v	[41]
T. versicolor laccase (F/Ba)	5	ABTS	$[C_2C_1Im][OAc]$	Mixed (HW)	IC_{50} = 1–4% w/v	[41]
T. versicolor laccase (F/Ba)	5	ABTS	[Ch][Lys]	Mixed (HW)	IC_{50} = 1–2% w/v	[41]

S4. References

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