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Note

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Increasing structural diversity of natural products by Michael addition with *ortho*-quinone methide as the acceptor

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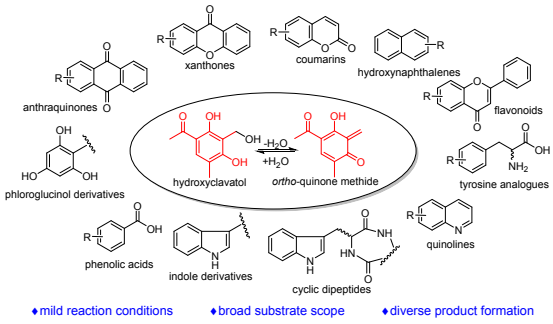
Supporting Information Placeholder

ABSTRACT: The active form of clavatol, *ortho*-quinone methide, can be generated from hydroxyclavatol in an aqueous system and used as a highly reactive intermediate for coupling with diverse natural products under very mild conditions. These include flavonoids, hydroxynaphthalenes, coumarins, xanthones, anthraquinones, phloroglucinols, phenolic acids, indole derivatives, tyrosine analogues, and quinolines. The clavatol moiety was mainly attached *via* C-C bonds to *ortho*- or *para*-position of phenolic hydroxyl/amino groups and the C2-position of the indole ring.



Ortho-quinone methides (*o*-QMs), as transient intermediates with remarkable reactivity, have been utilized as useful reactants in chemical synthesis.[1-5] A wide range of strategies, *e.g.* thermally driven,[6,7] photolytically induced tautomerization,[8,9] and benzylic oxidation[10,11] were developed to generate *o*-QMs. However, *o*-QMs can also be formed by spontaneous elimination of a stable molecule with concomitant dearomatization.[12,13]

Recently, we reported the formation of penilactones A and B by two-step non-enzymatic Michael additions between a γ-butyrolactone and two *o*-QM molecules. The key precursor hydroxyclavatol was the oxidation product of clavatol by the non-heme Fe^{II}/2-oxoglutarate dependent oxygenase ClaD and undergoes spontaneous water elimination, resulting in the active *o*-QM intermediate (Figure 1i).[12]

In addition to penilactones A and B from *Penicillium crustosum*,[14] a number of natural products containing a clavatol unit are found in fungi, especially in *Penicillium* species.[14-20] These include a clavatol-flavanone adduct from *Penicillium griseoroseum*,[16] coupling products of clavatol with α-pyrone (communol A) and indole (communol B) from *Penicillium commune*[17] (Figure 1ii). More coupling products of clavatol with diverse lactones, phenols, and quinones are listed in Figure S1 (see Supporting Information (SI)).

The occurrence of these natural products implies the involvement of clavatol, very likely *via* the *o*-QM intermediate, in their formation. Inspired by the post-biosynthetic non-enzymatic event in the formation of penilactones A and B, we wondered whether these clavatol-containing compounds are also pseudo-natural products.

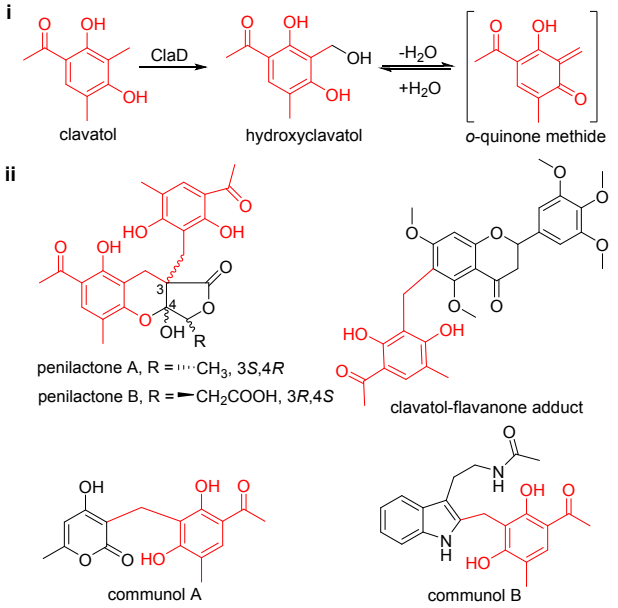


FIGURE 1. The formation of hydroxyclavatol and its equilibration with the *o*-QM intermediate (i). Representative examples of clavatol-containing natural products (ii). See Figure S1 for more examples.

This hypothesis triggered our interest to prove the reactivity of the *o*-QM intermediate derived from hydroxyclavatol with diverse natural products. Encouraged by accumulation of the clavatol-flavanone adduct in *P. griseoroseum*,[16] we synthesized hydroxyclavatol chemically (Scheme S1)[6,21] and screened its reactivity with 16 flavonoids (**1a** – **16a**) under mild conditions (Figures S2 – S4). Both hydroxyclavatol and reactants at a final

concentration of 0.4 mM in 50 µL H_2O were incubated at 25 °C for 16 h without pH adjustment. LC-MS analysis of the incubation mixtures showed that, with the exception for **10a**, $[M+H]^+$ ions being 178 Da larger than the corresponding reactants were detected. These proved the formation of the coupling products of flavonoids with clavatol. Masses of products harboring two clavatol units were also detected when using **4a**, **5a**, **8a**, **9a**, and **12a** – **15a** as reactants.

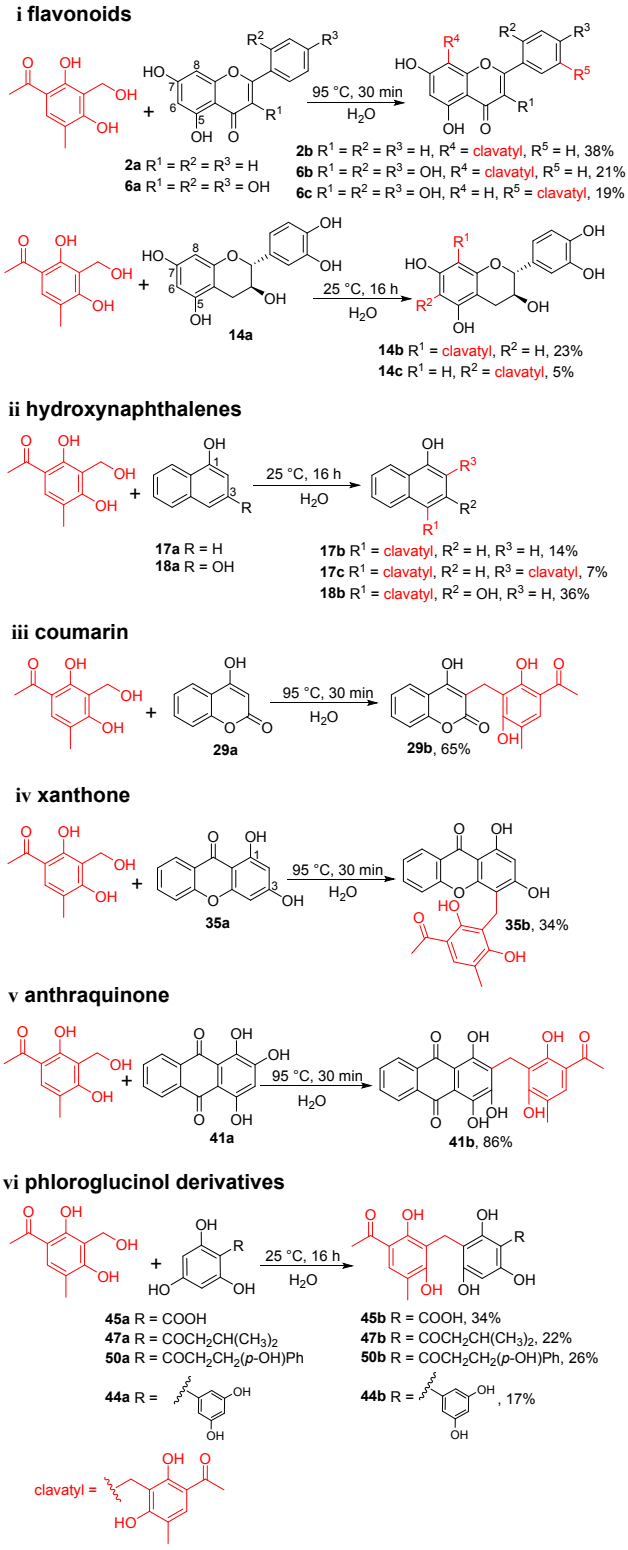
Subsequent assays of hydroxyclavatol with other phenolic substances, including hydroxynaphthalenes (**17a** – **27a**), coumarins (**28a** – **32a**), xanthones (**33a** – **38a**), anthraquinones (**39a** – **42a**), phloroglucinol derivatives (**43a** – **51a**), and phenolic acids (**52a** – **60a**) were carried out in a similar way as mentioned above. Products were detected in incubation mixtures of hydroxyclavatol with nine of eleven tested hydroxynaphthalenes. This proved hydroxynaphthalenes as suitable reactants for coupling with the *o*-QM (Figure S2 – S4). Coumarins with **29a** as an exception, xanthones, and anthraquinones were relatively poor reaction partners for the *o*-QM and gave no product or only trace amount of products in their reaction mixtures (Figures S2 – S5). Among all the tested phenolic substances, phloroglucinol derivatives were found to be the most favorable Michael donors for the *o*-QM intermediate, with 10 % to 55 % conversion (Figures S2, S5 and S6). In addition, coupling products of benzoic acids (**52a** – **54a**) were also observed by LC-MS analysis, while products from hydroxyphenyl acetic acid (**55a**), propionic acids (**56a** and **57a**), and acrylic acids (**58a** – **60a**) were not detectable (Figures S2 – S4).

We speculated that the formation of the clavatol-indole adduct communol B from *P. commune*[17] was also a non-enzymatic event and therefore investigated the reaction activity of hydroxyclavatol with indole derivatives (**61a** – **72a**). The incubation mixture of L-tryptophan (**61a**) with hydroxyclavatol showed a coupling product with a conversion of 20 %, while replacement of the nitrogen of the indole ring by sulfur (**62a**) and methylation at N1 position (**63a**) significantly reduced the activity. Other indole derivatives carrying different side chains at C3 coupled with clavatol with up to 49 % conversion (Figures S2, S3, and S7).

Subsequently, cyclic dipeptides (**73a** – **82a**) were tested by co-incubation with hydroxyclavatol. All tryptophan-containing cyclic dipeptides (**73a** – **80a**) showed UV detectable product formation with 9 % to 29 % conversion. No product formation was detected for the incubation mixtures of *cyclo*-L-Tyr-L-Tyr (**81a**) and *cyclo*-L-Ser-L-Tyr (**82a**) (Figures S2 – 4, S7, and S8). In contrast to the easy coupling of L-tryptophan with the *o*-QM, L-tyrosine and its analogues (**83a** – **87a**) were generally poorly converted to their clavatol adducts. **88a** – **90a** with an amino group at the benzene ring showed UV detectable product formation (Figures S2 and S3). All selected quinolines (**91a** – **99a**) served as Michael donors to couple with the *o*-QM, especially **92a**, **94a**, **95a**, and **98a** with obvious product peaks in UV chromatograms (Figures S2**,** S3, and S8).

In addition, clear product formation was also detected for the *o*-QM with other nitrogen-containing reactants, including 2-aminobenzyl alcohol (**100a**), 2-aminobenzoic acid (**101a**), and even tris(hydroxymethyl)aminomethane (Tris, **102a**) prepared as Tris-HCl buffer (pH 7.5) (Figures S2 and S8).

SCHEME 1. The reactions of hydroxyclavatol with nitrogen free reactants.



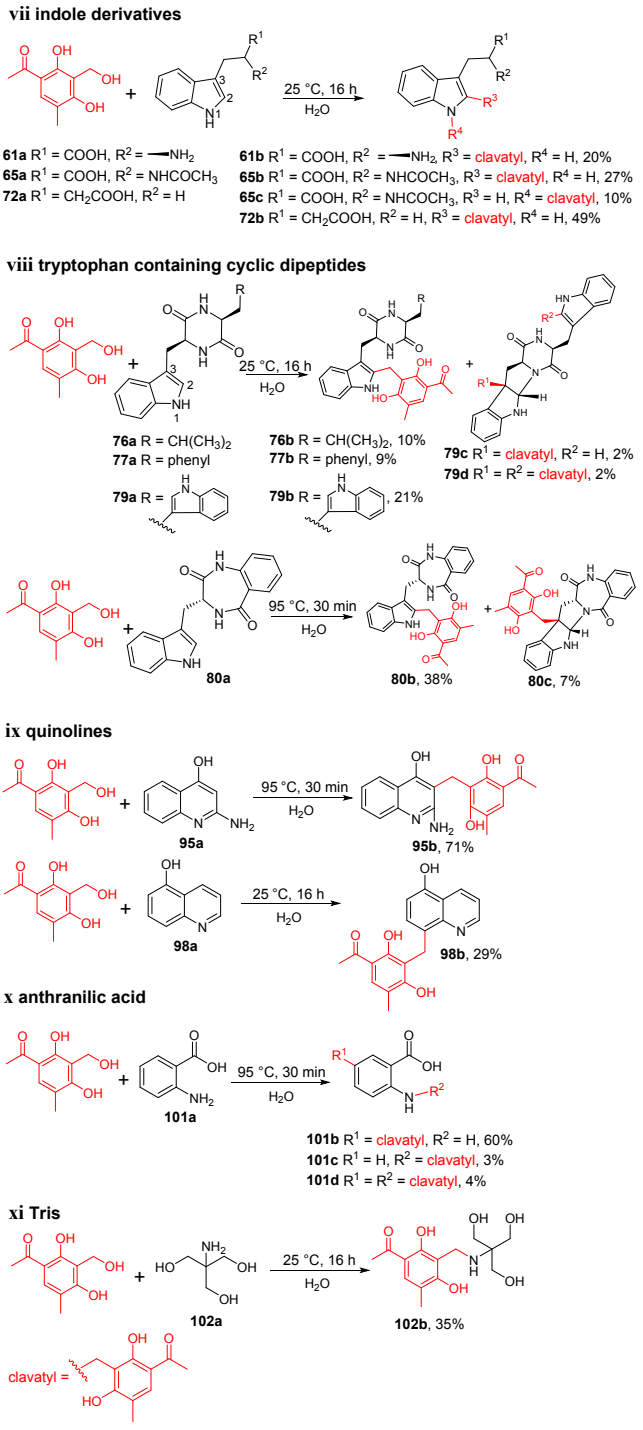
In summary, we demonstrated in a previous study that Michael additions between the *o*-QM and γ-butyrolactones took place easily under neutral or acidic conditions.[12] Therefore, hydroxyclavatol was incubated in this study with 101 natural products or natural product-like compounds at 25 °C and a nearly neutral pH value, which led to the detection of coupling products in 85 cases. Product formation with 10 to 55 % conversion was detected for 49 reactants (Schemes 1 and 2, Figures S5 – S10). To facilitate the isolation of the products for structural elucidation, we changed the reaction temperature for

all the incubations to 95 °C for 30 min to improve the product yields. As shown in Figures S5 – S10, the majority of the reactions was promoted by increased temperature, leading to generally two to ten-fold higher accumulation of the coupling products. Taking purpurin (**41a**) as an example, its coupling with clavatol was improved dramatically from trace amount to 86 %. In total, product formation with 30 to 99 % conversion was achieved for 58 reactants at 95 °C for 30 min. However, in a few cases, no significant change was observed for reactions performed at 25 °C and 95 °C (Figures S5 – S10). Therefore, large scaled reactions of hydroxyclavatol with 23 reactants of different structural skeletons were carried out at either 25 °C or 95 °C, resulting in the isolation of 32 products, which were further subjected to HR-ESI-MS and NMR analyses (Figures S12 – S86).

Structural elucidation of the coupling products of phenolic reactants confirmed the attachment of the clavatol unit to the *ortho*- or *para*-position of the hydroxyl group at the benzene ring. Herein, the *o*-QM formed from hydroxyclavatol in an aqueous system was proposed to act as the Michael acceptor for the phenolic substances (Figures S11i and ii). The formation of **17b** and **98b** represents examples for the attachment of a clavatol moiety onto the *para*-position of hydroxyl group (Schemes 1 and 2, Figures S5 and S8). For flavonoids with a 5,7-dihydroxyl feature (**2a**, **6a**, and **14a**), C8-adducts (**2b**, **6b**, and **14b**) were identified as main products and the C6-adduct (**14c**) as a byproduct (Scheme 1, Figure S5). The clavatol-containing flavanone from *P. griseoroseum* (Figure 1) was identified by feeding 5,7,3′,4′,5′-pentamethoxyflavanone into the culture.[16] The incorporation of clavatol unit into the exogenous flavanone might be also a non-enzymatic product. In analogy, **18b** and **35b** were identified as products of hydroxyclavatol with 1,3-dihydroxynaphthalene (**18a**) and 1,3-dihydroxyxanthone (**35a**) (Scheme 1, Figures S5 and S6). Additionally, formation of **29b** by the linkage between the clavatol unit and the α-pyrone moiety of **29a** suggests that communol A from *P. commune* could be formed in similar way (Scheme 1, Figure S5). Phloroglucinol derivatives harboring three hydroxyl groups at the benzene ring conjugated with a clavatol also *via* C-C bonds (**44b**, **45b**, **47b**, and **50b**) (Scheme 1, Figure S6).

The indole ring in tryptophanyl moiety contributes greatly to structural complexity by enzymatic modifications and spontaneous rearrangement.[22,23] Communol B mentioned above represents a coupling example of clavatol moiety with indole skeleton.[17] Accordingly, incubation of L-tryptophan (**61a**) with hydroxyclavatol enabled us to obtain the product (**61b**) with similar structure to communol B (Scheme 2, Figure S7). Subsequent isolation of clavatol adducts with different indole derivatives ((±)-**65b** and **72b**) confirmed the spontaneous addition of the indole moiety *via* C2 to the *o*-QM (Scheme 2, Figure S7). Furthermore, a number of coupling products of clavatol with tryptophan-containing cyclic dipeptides were also identified. Among them, C2-adducts were obtained as main products (**76b**, **77b**, **79b**, and **80b**) and C3-adducts (**79c** and **80c**) as byproducts (Scheme 2, Figures S7 and S8). In addition, a *cyclo*-L-Trp-L-Trp derivative carrying two clavatol units (**79d**) was also identified (Scheme 2, Figure S7). The conjugation between the clavatol unit and indole skeleton indicates that the electron transfer in the indole ring enabled the Michael addition from C2 to the electrophilic methylene group of the *o*-QM (Figure S11iii).

SCHEME 2. The reactions of hydroxyclavatol with nitrogen containing reactants.



Steinmetz et al[24] reported C-N coupling compounds as Michael addition products of different nucleophiles *via* their amino groups to the *p*-quinone methide, *i.e.* elansolid A3. However, only a few coupling products were obtained *via* C-N bond formation in this study. Examples are (±)-**65c** as a byproduct from the incubation of hydroxyclavatol with N-acetyl-DL-tryptophan ((±)-**65a**), **101c** and **101d** from 2-

aminobenzoic acid (**101a**), and **102b** from Tris (**102a**) (Scheme 2, Figures S7, S8 and S11iv). It can be concluded that the cross-coupling between the nucleophiles tested above and the *o*-QM from hydroxyclavatol occurs preferentially *via* C-C bond formation. In addition, the C-N bond in **101d** seems instable and can be easily hydrolyzed, which was observed by inspection of the ^{1}H NMR spectrum of **101d** (Figure S83) and comparison of the impurity signals with those of **101b** (Figure S79).

After structure elucidation, the obtained clavatol-containing products were screened for their antibacterial, acetylcholinesterase, and α-glucosidase inhibition activities. Detailed evaluation of the α-glucosidase inhibitory activity revealed the clavatol-coupling products **2b**, **17b**, **18b**, **35b**, **72b**, and **95b** showed clear inhibition with IC_{50} values ranging from 43.8 ± 1.0 to 231.0 ± 7.5 μM, while their precursors showed no activity. These concentrations are significantly lower than that of the control substance acarbose with an IC_{50} at 766.2 ± 37.8 μM (Table 1), indicating that conjugation of low-molecular compounds with clavatol has the potential to increase the biological activity.

Table 1. Inhibitory effects of the selected compounds against α-glucosidase.

reactants	IC_{50} (μM)	products	IC_{50} (μM)
2a	n.i.	**2b**	60.1 ± 0.6
17a	n.i.	**17b**	167.8 ± 2.3
18a	n.i.	**18b**	231.0 ± 7.5
35a	n.i.	**35b**	43.8 ± 1.0
72a	n.i.	**72b**	140.1 ± 1.3
95a	n.i.	**95b**	52.0 ± 2.4
acarbose [a]	766.2 ± 37.8		

[a]positive control. n.i.: no inhibition. The IC_{50} data with standard deviation are mean values of three independent experiments.

In summary, our extended study on the utility of hydroxyclavatol proved that the *o*-QM generated from hydroxyclavatol can be considered as an excellent Michael acceptor for a variety of substances. The coupling reactions occurred under very mild condition, *i.e.* overnight incubation at 25 °C in water. Increasing the reaction temperature can accelerate the reaction rate and promote the product accumulation. Diverse clavatol-containing products were identified in this study by incorporation of a clavatol unit onto the *ortho*- or *para*-position of the hydroxyl group of different phenolic compounds as well as connection between the methylene group of clavatol unit and C2 of indole skeletons. Additional C-N bond formation of clavatol coupling products was also observed in a few cases.

Despite of the wide application of QMs in chemical synthesis,[1-5] QMs have also been reported to be involved in the assembly of natural products in recent years. For example, elansolid A3 acts as a key intermediate in the biosynthesis of elansolids.[25,26] Spontaneous Diels-Alder addition *via* an *o*-QM intermediate was suggested for the formation of leprins.[27] Another QM-like intermediate is likely responsible for the dimerization of benzofluorene-containing angucyclines.[13] In analogy, it is plausible that the clavatol-containing natural products listed in Figures 1 and S1 are formed by non-enzymatic Michael addition with involvement of the *o*-QM derived from hydroxyclavatol. Furthermore, it can be expected that more clavatol-coupling natural products will be discovered in the near future.

EXPERIMENTAL SECTION

Chemicals. 35a – 38a, **46a – 48a, 73a, 75a, 79a, 80a** were chemically synthesized as previously reported.[28-34] Other chemicals used in this study were purchased from Bachem (Bubendorf, Switzerland), ABCR (Karlsruhe, Germany), TCI Europe (Zwijndrecht, Belgium), Alfa Aesar (Kandel, Germany), Carl Roth (Karlsruhe, Germany), Sigma-Aldrich (St. Louis, USA), or Acros (Merelbeke, Belgium).

Reaction conditions of hydroxyclavatol with the tested aromatic compounds. Stock solutions of the tested compounds were prepared at 20 mM in DMSO or DMSO/H_2O (*v*/*v*, 1:1). Reactions were initiated by adding hydroxyclavatol (0.4 mM) and reactants (0.4 mM) into 50 μL distilled H_2O without pH adjustion. As a result, the reactions generally took place in the pH environment of 5.0 – 7.5. After incubation at 25 °C for 16 h, 50 μL ACN were added into the reaction mixture. 5 μL of supernatant were injected into LC-MS for analysis after centrifuging at 13,000 rpm for 30 min. Conversions were calculated from peak areas of products and reactants with UV detection. Two independent experiments were performed. In addition, reactions of all reactants were also carried out at 95 °C for 30 min.

LC-MS analysis of reaction mixtures. LC-MS analysis was performed on a microTOF-Q III spectrometer (Bruker, Bremen, Germany) with an Agilent 1260 HPLC system (Agilent Technologies, Böblingen, Germany), using the Multospher 120 RP18-5□ column (250 × 2 mm, 5 μm) (CS-Chromatographie Service GmbH). H_2O (A) and ACN (B), both with 0.1 % (*v*/*v*) HCOOH, were used as solvents at flow rate of 0.25 mL/min. The substances were eluted with a linear gradient from 5 – 100 % (*v*/*v*) B in 15 min. The column was then washed with 100 % (*v*/*v*) solvent B for 5 min and equilibrated with 5 % (*v*/*v*) solvent B for 5 min. Detection was carried out on a photodiode array detector and UV absorptions at 280 nm are illustrated in this study. Electrospray ionization at positive or negative mode was set for the determination of the accuracy masses. HCOONa was used in each run for mass calibration. The capillary voltage was set to 4.5 kV and a collision energy of 8.0 eV. Data were evaluated with the Compass DataAnalysis 4.2 software (Bruker Daltonik, Bremen, Germany). The masses were scanned in the range of *m/z* 100 – 1500.

Isolation and identification of the reaction products. To isolate the reaction products for structural elucidation, reactions were carried out in large scaled incubations (40 or 200 mL) containing hydroxyclavatol (0.4 mM), different reactants (0.4 – 0.8 mM), and up to 2 % (*v*/*v*) DMSO. After incubation at 25 °C for 16 h or heating at 95 °C for 30 min, the reaction mixtures were extracted with double volume of EtOAc for three times. The organic phases were combined and concentrated under vacuum. The resulted residues were dissolved in MeOH and centrifuged at 13,000 rpm for 20 min. The products were then purified by silica gel column chromatography with stepwise gradient of petroleum ether/EtOAc, or on Sephadex LH20 column with MeOH as elution solvent. A semi-preparative HPLC equipped with an Agilent ZORBAX Eclipse XDB-C18 HPLC column (250 × 9.4 mm, 5 μm) was also applied for purification by using isocratic elution with H_2O and ACN containing 0.1 % trifluoroacetic acid (TFA). NMR spectra were recorded on a JEOL ECA-500 MHz spectrometer (JEOL,

Tokyo, Japan). The spectra were processed with MestReNova 6.1.0 (Metrelab). Chemical shifts are referenced to those of the solvent signals.

Structural elucidation. Characteristic signals of the clavatol moiety were observed in ^{1}H NMR spectra of all the isolated products as a set of signals for an aromatic proton at approximately 7.5 ppm, a singlet between 12 – 14 ppm, a methylene group mostly between 3 – 4 ppm, and two methyl groups at around 2.5 and 2.1 ppm. The clavatol-coupling products generally belong to two major groups. The majority is with clavatol unit attached to the *ortho*- or *para*-position of a phenolic hydroxyl group at the benzene ring and other products carrying clavatol moieties attached to C2 or C3 of the indole skeleton.

In the cases of **17b** and **98b**, the linkage between the methylene group of the clavatol unit and the *para*-position of the hydroxy group was proved by HMBC correlations (Figures S27 – S30 and S76 – S78). In analogy, correlations of the methylene group to different aromatic carbons in the HMBC spectra supported the linkage between the clavatol part and *meta*-dihydroxylated benzene ring, such as **2b** (Figures S12–S14), **6b** (Figures S15 – S17), **6c** (Figures S18 – S20), **14b** (Figures S21 – S25), **18b** (Figures S32 – S34), **35b** (Figures S38 – S40), and **41b** (Figures S41 – S43). **14c** obtained as the byproduct from the reaction mixture of (+)-catechin (**14a**) with hydroxyclavatol is an analogue of isopilosanols A – C. Its structure was confirmed by comparison of ^{1}H NMR spectra with those of reported data (Figure S26).[35,36] Since **44b**, **45b**, **47b**, and **50b** are formed *via* coupling of clavatol unit with phloroglucinol derivatives, the attachment of clavatol to the phloroglucinol moiety in **44b** and **47b** was proved by HMBC correlations as examples (Figures S44 – S46 and S48 – S50). The structures of **45b** and **50b** are deduced according to their molecular weight and ^{1}H NMR data (Figures S47 and S51). **29b** and **95b** showed two sets of signals in their ^{1}H NMR, one set for clavatol subunit, and one set of four coupling aromatic protons for *ortho*-disubstituted benzene ring, suggesting the attachment of clavatol unit to the α-pyrone ring in **29b** (Figures S35 – S37) and to the pyridine ring in **95b** (Figures S73 – S75).

61b, (±)-**65b**, and **72b** are indole derivatives with clavatol unit linked at C2 position and differ only at the side chain of C3 position. Therefore, their structures were determined by comparison of the NMR data (Figures S52 – S54, and S60) with the known compound communol B.[17] (±)-**65c** is an example of C-N bond formation between clavatol moiety and the indole skeleton, which was confirmed by HMBC correlations (Figures S55 – S59). **76b**, **77b**, **79b**, **79c**, **79d**, **80b**, and **80c** are coupling products of clavatol with tryptophan-containing cyclic dipeptides (Figures S61 – S72). The structures of **79b** and **80b** were unequivocally confirmed by ^{1}H and ^{13}C NMR data, as well as HMBC correlations (Figures S63 – S66 and S69 – S71). Other products are analogues of **79b** and their structures were determined according to the C2- and C3-substitution patterns of the indole ring as reported before.[37]

In the cases of **101b** – **101d** obtained from 2-aminobenzoic acid (**101a**), detailed inspection of the ^{1}H NMR revealed that **101b** and **101c** are products with one clavatol moiety and **101d** harboring two clavatol units. The presence of one set of characteristic signals for an ABX system in the ^{1}H NMR spectrum of **101b** revealed a *para*-substitution of the amino group at the benzene ring. The structure of **101b** was further confirmed by ^{13}C NMR and HMBC analyses (Figures S79 – S81). In the ^{1}H NMR spectrum of **101c**, the coupling pattern consisting of four protons at the benzene ring and a downfield shift of the methylene group from 3.95 to 4.51 ppm (Figure S82) indicated clavatol attachment to the amino group of **101a**. Similarly, one clavatol at *para*-position of the amino group and one at the amino group can be concluded for the structure of **101d** (Figure S83). **102b** is another clavatol coupling derivative *via* C-N linkage, which was supported by the slightly downfield shifts of the methylene group at 4.49 ppm in the ^{1}H NMR spectrum and confirmed by HMBC correlations (Figure S84 – S86).

Characterization data. *8-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-5,7-dihydroxy-2-phenyl-4H-chromen-4-one (**2b**)*. The title compound was prepared using **2a** (0.106 mmol, 32.0 mg) and hydroxyclavatol (0.102 mmol, 20.0 mg) as reactants. The product was isolated in 39 % yield (17.3 mg) as yellow amorphous solid. Eluent: petroleum ether/EtOAc (5 : 1, *v*/*v*). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.00 (s, 1H), 8.00 (dd, J = 8.4, 1.5 Hz, 2H), 7.59 (tt, J = 7.5, 1.5 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.52 (s, 1H), 6.91 (s, 1H), 6.25 (s, 1H), 4.10 (s, 2H), 2.49 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.2, 182.2, 163.4, 162.2, 160.9, 160.9, 159.1, 155.0, 131.8, 131.1, 130.8, 128.9, 128.9, 126.5, 126.5, 115.8, 113.1, 112.1, 105.5, 104.8, 103.8, 98.4, 26.1, 16.6, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{21}O_7$ 433.1282; Found 433.1272.

*8-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2-(2,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one (**6b**)*. The title compound was prepared using **6a** (0.108 mmol, 32.9 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 17 % yield (5.5 mg) as yellow amorphous solid. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.82 (s, 1H), 12.64 (s, 1H), 9.74 (s, 1H), 7.48 (s, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 6.30 (dd, J = 8.5, 2.3 Hz, 1H), 6.20 (s, 1H), 3.95 (s, 2H), 2.49 (s, 3H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 202.8, 176.3, 160.9, 160.9, 160.4, 160.4, 158.4, 156.5, 154.5, 148.7, 135.4, 131.1, 130.5, 115.6, 113.1, 112.0, 109.5, 107.0, 104.7, 103.4, 102.9, 97.5, 26.1, 16.2, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{21}O_{10}$ 481.1129; Found 481.1151.

*2-(5-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one (**6c**)*. The title compound was prepared using **6a** (0.108 mmol, 32.9 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 21% yield (6.7 mg) as yellow amorphous solid. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (s, 1H), 10.66 (s, 1H), 7.58 (s, 1H), 6.79 (s, 1H), 6.50 (s, 1H), 6.18 (d, J = 2.2 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 3.78 (s, 2H), 2.52 (s, 3H), 2.15 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.2, 176.0, 163.6, 160.9, 160.7, 160.6, 157.4, 156.7, 154.4, 148.9, 136.0, 131.1, 129.9, 117.6, 116.0, 113.2, 112.3, 109.0, 103.4, 102.6, 98.0, 93.1, 26.1, 21.1, 16.1. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{21}O_{10}$ 481.1129; Found 481.1147.

*1-(3-(((2R,3S)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-8-yl)methyl)-2,4-dihydroxy-5-methylphenyl)ethan-1-one (**14b**)*. The title compound was prepared using **14a** (0.106 mmol, 30.8 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 28 % yield (8.6 mg) as brown oil. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 14.26 (s, 1H), 7.59 (s, 1H), 6.99 (d, J = 1.2 Hz, 1H), 6.86 (s,

1H), 6.86 (s, 1H), 6.11 (s, 1H), 4.81 (d, *J* = 7.8 Hz, 1H), 4.15 (ddd, J =8.5, 7.8, 5.5 Hz, 1H), 3.81 (d, *J* = 15.6 Hz, 1H), 3.77 (d, *J* = 15.6 Hz, 1H), 2.97 (dd, *J* = 16.3, 5.5 Hz, 1H), 2.61 (dd, *J* = 16.3, 8.5 Hz, 1H), 2.53 (s, 3H), 2.09 (s, 3H). ^{1}H NMR (500 MHz, pyridine-d_6) δ 7.62 (d, *J* = 2.1 Hz, 1H), 7.47 (s, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.25 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.67 (s, 1H), 5.31 (d, *J* = 7.7 Hz, 1H), 4.57 (ddd, *J* = 8.4, 7.7, 5.4 Hz, 1H), 4.47 (d, *J* = 15.1 Hz, 1H), 4.35 (d, *J* = 15.1 Hz, 1H), 3.63 (dd, *J* = 16.1, 5.4 Hz, 1H), 3.31 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.46 (s, 3H), 2.20 (s, 3H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.90 (s, 1H), 9.67 (s, 1H), 9.11 (s, 1H), 8.95 (s, 1H), 7.48 (s, 1H), 6.66 (d, *J* = 2.0 Hz, 1H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.46 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.03 (s, 1H), 4.54 (d, *J* = 7.1 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.76 (d, *J* = 14.8 Hz, 1H), 3.68 (d, *J* = 14.8 Hz, 1H), 2.62 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.49 (s, 3H), 2.37 (dd, *J* = 16.2, 7.7 Hz, 1H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 202.6, 160.6, 160.4, 154.0, 153.0, 152.8, 144.6, 144.5, 130.3, 130.2, 117.9, 115.6, 114.9, 114.4, 113.5, 112.2, 103.2, 99.8, 94.8, 81.2, 66.0, 30.6, 27.7, 26.2, 15.8. [α]20 D = +25 (*c* 0.1, MeOH); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{25}O_9$ 469.1493; Found 469.1493.

1-(3-(((2R,3S)-2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychroman-6-yl)methyl)-2,4-dihydroxy-5-methylphenyl)ethan-1-one ***(14c)***. The title compound was prepared using **14a** (0.106 mmol, 30.8 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 6 % yield (1.8 mg) as brown oil. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 14.5 (s, 1H), 7.67 (s, 1H), 6.85 (d, *J* = 2.0 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.71 (dd, *J* = 8.1, 2.0 Hz, 1H), 6.10 (s, 1H), 4.57 (d, *J* = 7.5 Hz, 1H), 3.98 (ddd, *J* = 8.5, 7.5, 5.3 Hz, 1H), 3.86 (s, 2H), 2.87 (dd, *J* = 16.2, 5.3 Hz, 1H), 2.60 (s, 3H), 2.54 (dd, *J* = 16.2, 8.5 Hz, 1H), 2.15 (s, 3H). [α]20 D = +23 (*c* 0.1, MeOH); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{25}O_9$ 469.1493; Found 469.1496.

1-(2,4-dihydroxy-3-((4-hydroxynaphthalen-1-yl)methyl)-5-methylph-enyl)ethan-1-one ***(17b)***. The title compound was prepared using **17a** (0.179 mmol, 25.9 mg) and hydroxyclavatol (0.076 mmol, 14.9 mg) as reactants. The product was isolated in 21 % yield (5.0 mg) as yellow amorphous solid. Eluent: ACN/H_2O (70 : 30, *v*/*v*). ^{1}H NMR (500 MHz, acetone-d_6) δ 13.09 (s, 1H), 8.28 (dd, *J* = 8.6, 1.5, Hz, 1H), 8.23 (dd, *J* = 8.6, 1.5, Hz, 1H), 7.71 (s, 1H), 7.56 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.6, 7.0, 1.5 Hz, 1H), 6.71 (s, 1H), 6.71 (s, 1H), 4.38 (s, 2H), 2.60 (s, 3H), 2.25 (s, 3H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.95 (s, 1H), 9.78 (s, 1H), 9.54 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.66 (s, 1H), 7.55 (dd, *J* = 8.5, 6.8 Hz, 1H), 7.46 (dd, *J* = 8.5, 6.8 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6. 63 (d, *J* = 8.0 Hz, 1H), 4.26 (s, 2H), 2.57 (s, 3H), 2.19 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.2, 161.1, 160.9, 151.4, 132.8, 131.3, 125.8, 125.6, 124.8, 124.1, 124.0, 123. 6, 122.4, 116.0, 113.1, 112.3, 107.3, 26.2, 24.3, 16.2. HRMS (ESI-TOF) *m/z*: [M - H]$^-$ Calcd for $C_{20}H_{17}O_4$ 321.1132; Found 321.1159.

1,1'-(((4-hydroxynaphthalene-1,3-diyl)bis(methylene))bis(2,4-dihyd-roxy-5-methyl-3,1-phenylene))bis(ethan-1-one) ***(17c)***. The title compound was prepared using **17a** (0.179 mmol, 25.9 mg) and hydroxyclavatol (0.076 mmol, 14.9 mg) as reactants. The product was isolated in 6 % yield (1.5 mg) as yellow amorphous solid. Eluent: ACN/H_2O (70 : 30, *v*/*v*). ^{1}H NMR (500 MHz, acetone-d_6) δ 13.11 (s, 1H), 13.00 (s, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.54 (s, 1H), 7.50 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.47 (dd, *J* = 8.4, 6.8 Hz, 1H), 7.00 (s, 1H), 4.30 (s, 2H), 3.98 (s, 2H), 2.63 (s, 3H), 2.55 (s, 3H), 2.24 (s, 3H), 2.15 (s, 3H). HRMS (ESI-TOF) *m/z*: [M - H]$^-$ Calcd for $C_{30}H_{27}O_7$ 499.1762; Found 499.1773.

1-(3-((2,4-dihydroxynaphthalen-1-yl)methyl)-2,4-dihydroxy-5-meth-ylphenyl)ethan-1-one ***(18b)***. The title compound was prepared using **18a** (0.161 mmol, 25.9 mg) and hydroxyclavatol (0.089 mmol, 17.4 mg) as reactants. The product was isolated in 24 % yield (7.3 mg) as white amorphous solid. Eluent: ACN/H_2O (65 : 35, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.66 (s, 1H), 10.11 (s, 1H), 8.32 (d, *J* = 8.9 Hz, 1H), 8.00 (d, *J* = 8.9 Hz, 1H), 7.55 (s, 1H), 7.37 (dd, *J* = 8.9, 6.7 Hz, 1H), 7.19 (dd, *J* = 8.9, 6.7 Hz, 1H), 6.71 (s, 1H), 4.18 (s, 2H), 2.54 (s, 3H), 2.04 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.4, 160.9, 159.9, 153.1, 150.9, 134.1, 131.0, 126.6, 123.5, 122.2, 121.5, 120.8, 116.1, 113.3, 112.1, 107.9, 99.6, 26.2, 17.1, 15.7. HRMS (ESI-TOF) *m/z*: [M - H]$^-$ Calcd for $C_{20}H_{17}O_5$ 337.1081; Found 337.1097.

3-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-4-hydroxy-2H-chromen-2-one ***(29b)***. The title compound was prepared using **29a** (0.173 mmol, 28.1 mg) and hydroxyclavatol (0.076 mmol, 14.9 mg) as reactants. The product was isolated in 43 % yield (11.2 mg) as white amorphous solid. Eluent: ACN/H_2O (90 : 10, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.70 (s, 1H), 10.28 (s, 1H), 10.23 (s, 1H), 7.93 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 7.43 (s, 1H), 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 3.87 (s, 2H), 2.58 (s, 3H), 2.21 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 203.6, 168.4, 163.4, 162.0, 158.9, 152.3, 132.6, 131.1, 124.8, 123.9, 119.8, 116.7, 116.3, 112.6, 112.3, 103.5, 26.0, 18.2, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{19}H_{17}O_6$ 341.1020; Found 341.1013.

4-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1,3-dihydroxy-9H-xanthen-9-one ***(35b)***. The title compound was prepared using **35a** (0.122 mmol, 27.9 mg) and hydroxyclavatol (0.071 mmol, 13.9 mg) as reactants. The product was isolated in 31 % yield (9.1 mg) as white amorphous solid. Eluent: ACN/H_2O (80 : 20, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 12.76 (s, 1H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.83 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.52 (s, 1H), 7.42 (ddd, *J* = 8.0, 7.2, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.28 (s, 1H), 4.06 (s, 2H), 2.50 (s, 3H), 2.16 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.1, 179.9, 161.0, 161.0, 160.3, 160.3, 155.3, 154.8, 135.5, 130.7, 125.1, 124.1, 119.4, 117.3, 115.7, 113.4, 112.0, 105.5, 102.1, 97.5, 26.1, 16.3, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{19}O_7$ 407.1125; Found 407.1116.

2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1,3,4-trihydroxy anthracene-9,10-dione ***(41b)***. The title compound was prepared using **41a** (0.094 mmol, 24.1 mg) and hydroxyclavatol (0.058 mmol, 11.4 mg) as reactants. The product was isolated in 33% yield (8.3 mg) as red amorphous solid. Eluent: ACN/H_2O (75 : 25, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 14.24 (s, 1H), 13.46 (s, 1H), 12.95 (s, 1H), 8.27 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.26 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.93 (td, *J* = 7.6, 1.3 Hz, 1H), 7.89 (td, *J* = 7.6, 1.3 Hz, 1H), 7.51 (s, 1H), 3.97 (s, 2H), 2.50 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 202.9, 184.8, 181.8, 161.2, 160.9, 160.9, 155.8, 134.7, 133.7, 133.6, 132.4, 130.7, 126.3, 126.2, 123.2, 115.8, 112.5, 112.2, 112.0, 109.8, 26.2, 17.5, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{19}O_8$ 435.1074; Found 435.1069.

*1-(2,4-dihydroxy-5-methyl-3-((2,3',4,5',6-pentahydroxy-[1,1'-biphenyl]-3-yl)methyl)phenyl)ethan-1-one (**44b**)*. The title compound was prepared using **44a** (0.128 mmol, 30.0 mg) and hydroxyclavatol (0.076 mmol, 14.9 mg) as reactants. The product was isolated in 28 % yield (8.9 mg) as brown oil. Eluent: ACN/H_2O (60 : 40, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.96 (s, 1H), 13.89 (s, 1H), 8.90 (s, 1H), 8.87 (s, 1H), 7.64 (s, 1H), 6.10 (s, 1H), 6.06 – 6.04 (m, 3H), 3.73 (s, 2H), 2.56 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.8, 160.6, 158.7, 157.4, 157.4, 154.2, 152.9, 152.8, 136.3, 131.1, 117.2, 113.2, 112.2, 110.1, 109.4, 109.4, 103.4, 100.5, 94.9, 48.6, 26.1, 15.7. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{21}O_8$ 413.1231; Found 413.1242.

*3-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2,4,6-trihydroxybenzoic acid (**45b**)*. The title compound was prepared using **45a** (0.024 mmol, 4.2 mg) and hydroxyclavatol (0.016 mmol, 3.1 mg) as reactants. The product was isolated in 44 % yield (2.5 mg) as white amorphous solid. Eluent: ACN/H_2O (60 : 40, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 14.42 (s, 1H), 7.64 (s, 1H), 6.04 (s, 1H), 3.82 (s, 2H), 2.59 (s, 3H), 2.13 (s, 3H). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{17}H_{17}O_8$ 349.0918; Found 349.0925.

*1-(3-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2,4,6-trihydroxyphenyl)-3-methylbutan-1-one (**47b**)*. The title compound was prepared using **29a** (0.142 mmol, 30.0 mg) and hydroxyclavatol (0.076 mmol, 14.9 mg) as reactants. The product was isolated in 31 % yield (9.1 mg) as yellow amorphous solid. Eluent: ACN/H_2O (90 : 10, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.09 (s, 1H), 10.69 (s, 1H), 7.51 (s, 1H), 5.96 (s, 1H), 3.74 (s, 2H), 2.87 (d, *J* = 6.7 Hz, 1H), 2.51 (s, 3H), 2.14 (m, 1H), 2.08 (s, 3H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 205.1, 203.0, 163.4, 162.3, 160.8, 160.7, 160.3, 130.4, 115.7, 113.3, 112.0, 104.4, 103.7, 94.4, 51.8, 48.6, 26.1, 24.8, 22.6, 22.6, 15.9. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{25}O_7$ 389.1595; Found 389.1597.

*1-(3-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2,4,6-trihydroxyphenyl)-3-(4-hydroxyphenyl)propan-1-one (**50b**)*. The title compound was prepared using **50a** (0.028 mmol, 7.9 mg) and hydroxyclavatol (0.024 mmol, 4.7 mg) as reactants. The product was isolated in 19 % yield (2.0 mg) as white amorphous solid. Eluent: ACN/H_2O (80 : 20, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 14.53 (s, 1H), 7.66 (s, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 6.08 (s, 1H), 3.85 (s, 2H), 3.39 (t, *J* = 7.5 Hz, 2H), 2.90 (t, *J* = 7.5 Hz, 2H), 2.59 (s, 3H), 2.14 (s, 3H). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{25}H_{25}O_8$ 453.1544; Found 453.1561.

*(S)-3-(2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)-2-aminopropanoic acid (**61b**)*. The title compound was prepared using **61a** (0.160 mmol, 44.0 mg) and hydroxyclavatol (0.102 mmol, 20.0 mg) as reactants. The product was isolated in 27 % yield (10.4 mg) as yellow amorphous solid. Eluent: CH_2Cl_2. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.19 (s, 1H), 7.56 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.94 (dd, *J* = 8.0, 6.8 Hz, 1H), 6.90 (dd, *J* = 8.0, 6.8 Hz, 1H), 4.14 (d, *J* = 15.2 Hz, 1H), 4.07 (d, *J* = 15.2 Hz, 1H), 3.41 (dd, *J* = 6.8, 5.8, 1H), 3.18 (dd, *J* = 14.7, 5.8 Hz, 1H), 3.03 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.52 (s, 3H), 2.11 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 202.1, 171.2, 161.5, 136.1, 134.9, 130.8, 128.4, 119.8, 118.2, 118.0, 117.2, 111.9, 111.4, 110.9, 105.1, 55.0, 26.1, 25.9, 20.0, 16.5. [α]20 D = -6 (*c* 0.2, acetone); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{21}H_{23}N_2O_5$ 383.1601; Found 383.1609.

*2-acetamido-3-(2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)propanoic acid ((±)-**65b**)*. The title compound was prepared using (±)-**65a** (0.178 mmol, 44.0 mg) and hydroxyclavatol (0.069 mmol, 13.5 mg) as reactants. The product was isolated in 29 % yield (8.6 mg) as brown oil. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 13.26 (s, 1H), 7.66 (s, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 4.81 (ddd, *J* = 8.2, 7.7, 6.0 Hz, 1H), 4.21 (d, *J* = 15.0 Hz, 1H), 4.18 (d, *J* = 15.0 Hz, 1H), 3.45 (dd, *J* = 14.7, 6.0 Hz, 1H), 3.33 (dd, *J* = 14.7, 7.7 Hz, 1H), 2.57 (s, 3H), 2.26 (s, 3H), 1.85 (s, 3H). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{25}N_2O_6$ 425.1707; Found 425.1713.

*N^a-acetyl-1-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)tryptophan ((±)-**65c**)*. The title compound was prepared using (±)-**65a** (0.178 mmol, 44.0 mg) and hydroxyclavatol (0.069 mmol, 13.5 mg) as reactants. The product was isolated in 14 % yield (4.3 mg) as brown oil. Eluent: ACN/H_2O (55 : 45, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 13.31 (s, 1H), 7.71 (s, 1H), 7.70 (d, *J* = 8.2 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 1H), 7.29 (s, 1H), 7.09 (dd, *J* = 8.2, 7.0 Hz, 1H), 6.97 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.33 (s, 2H), 4.68 (ddd, *J* = 8.2, 7.5, 5.6 Hz, 1H), 3.27 (dd, *J* = 14.7, 5.6 Hz, 1H), 3.10 (dd, *J* = 14.7, 7.5 Hz, 3H), 2.56 (s, 3H), 2.27 (s, 3H), 1.83 (s, 3H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.69 (s, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.15 (s, 1H), 7.10 (dd, *J* = 8.2, 7.0 Hz, 1H), 6.98 (dd, *J* = 8.2, 7.0 Hz, 1H), 5.25 (s, 2H), 4.38 (td, *J* = 9.2, 5.1 Hz, 1H), 3.11 (dd, *J* = 15.0, 5.1 Hz, 1H), 2.90 (dd, *J* = 15.0, 9.2 Hz, 1H), 2.54 (s, 3H), 2.17 (s, 3H), 1.75 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.4, 173.4, 169.0, 161.0, 161.0, 136.0, 133.1, 127.3, 127.2, 120.8, 118.3, 118.1, 116.1, 112.4, 111.1, 110.2, 109.1, 52.8, 37.5, 26.9, 26.2, 22.2, 16.2. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{25}N_2O_6$ 425.1707; Found 425.1708.

*4-(2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)butanoic acid (**72b**)*. The title compound was prepared using **72a** (0.008 mmol, 1.6 mg) and hydroxyclavatol (0.008 mmol, 1.6 mg) as reactants. The product was isolated in 46 % yield (1.4 mg) as brown oil. Eluent: ACN/H_2O (65 : 35, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.30 (s, 1H), 8.57 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.40 (s, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.03 (dd, *J* = 8.0, 7.0 Hz, 1H), 4.14 (s, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.57 (s, 3H), 2.50 (t, *J* = 7.0 Hz, 2H), 2.18 (s, 3H), 2.07 – 2.01 (m, 2H). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{24}NO_5$ 382.1649; Found 382.1662.

*(3S,6S)-3-((2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)methyl)-6-isobutylpiperazine-2,5-dione (**76b**)*. The title compound was prepared using **76a** (0.016 mmol, 4.8 mg) and hydroxyclavatol (0.016 mmol, 3.2 mg) as reactants. The product was isolated in 13 % yield (1.0 mg) as white amorphous solid. Eluent: ACN/H_2O (60 : 40, *v*/*v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.40 (s, 1H), 8.77 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.46 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.12 (dd, *J* = 8.0, 7.1 Hz, 1H), 7.07 (dd, *J* = 8.0, 7.1 Hz, 1H), 6.39 (s, 1H), 5.99 (s, 1H), 4.40 (d, *J* = 8.9 Hz, 1H), 4.16 (d, *J* = 15.0 Hz, 1H), 4.13 (d, *J* = 15.0 Hz, 1H), 3.94 (d, *J* = 10.0 Hz, 1H), 3.65 (dd, *J* = 14.8, 3.2 Hz, 1H), 3.28 (dd, *J* = 14.8, 8.9 Hz, 1H), 2.60 (s, 3H), 2.23 (s, 3H), 1.68 – 1.60 (m, 1H), 1.61 – 1.56 (m, 1H), 1.17 (ddd, 13.7,

10.0, 4.5 Hz, 1H), 0.86 (d, *J* = 6.2 Hz, 1H), 0.85 (d, *J* = 6.2 Hz, 1H). [α]20 D = -41 (*c* 0.1, $CHCl_3$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{27}H_{32}N_3O_5$ 478.2336; Found 478.2339.

*(3S,6S)-3-((2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)methyl)-6-benzylpiperazine-2,5-dione (**77b**)*. The title compound was prepared using **77a** (0.032 mmol, 10.7 mg) and hydroxyclavatol (0.016 mmol, 3.1 mg) as reactants. The product was isolated in 24 % yield (2.0 mg) as white amorphous solid. Eluent: ACN/H_2O (55 : 45, *v/v*). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 9.96 (s, 1H), 9.63 (s, 1H), 7.94 (d, *J* = 3.0 Hz, 1H), 7.64 (d, *J* = 3.3 Hz, 1H), 7.62 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.16 – 7.10 (m, 3H), 6.95 (dd, *J* = 7.6, 6.5 Hz, 1H), 6.92 (dd, *J* = 7.6, 6.5 Hz, 1H), 6.62 (dd, *J* = 7.5, 2.3 Hz, 2H), 4.05 (d, *J* = 15.7 Hz, 1H), 4.07 – 4.04 (m, 1H), 4.01 (d, *J* = 15.7 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.05 (dd, *J* = 14.7, 4.7 Hz, 1H), 2.98 (dd, *J* = 14.7, 5.4 Hz, 1H), 2.55 (s, 3H), 2.47 (m, 1H), 2.18 (s, 3H), 1.61 (dd, *J* = 13.7, 7.9 Hz, 1H). [α]20 D = -49 (*c* 0.2, MeOH); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{30}H_{30}N_3O_5$ 512.2180; Found 512.2200.

*3-((1H-indol-3-yl)methyl)-6-((2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)methyl)piperazine-2,5-dione (**79b**)*. The title compound was prepared using **79a** (0.040 mmol, 14.9 mg) and hydroxyclavatol (0.033 mmol, 6.5 mg) as reactants. The product was isolated in 30 % yield (5.4 mg) as white amorphous solid. Eluent: ACN/H_2O (65 : 35, *v/v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.40 (s, 1H), 8.74 (s, 1H), 8.01 (s, 1H), 7.48 (s, 1H), 7.47 (d, *J* = 8.0, 1H), 7.46 (d, *J* = 8.2, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.11 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.08 (dd, *J* = 8.0, 7.1 Hz, 1H), 7.05 (dd, *J* = 8.0, 7.1 Hz, 1H), 6.58 (s, 1H), 6.48 (s, 1H), 5.84 (s, 1H), 4.36 (d, *J* = 7.7 Hz, 1H), 4.20 (d, *J* = 10.1 Hz, 1H), 4.08 (d, *J* = 15.1 Hz, 1H), 4.04 (d, *J* = 15.1 Hz, 1H), 3.45 (dd, *J* = 14.7, 3.2 Hz, 1H), 3.30 (dd, *J* = 14.5, 3.2 Hz, 1H), 3.08 (dd, *J* = 14.5, 7.7 Hz, 1H), 2.61 (s, 3H), 2.27 – 2.24 (m, 1H), 2.23 (s, 3H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.04 (s, 1H), 10.75 (d, *J* = 1.9 Hz, 1H), 9.92 (s, 1H), 9.61 (s, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.62 (s, 1H), 7.60 (d, *J* = 2.7 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.98 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.93 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.90 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.88 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.37 (d, *J* = 2.1 Hz, 1H), 4.02 (dd, *J* = 8.1, 3.8 Hz, 1H), 3.97 (d, *J* = 15.4 Hz, 1H), 3.91 (d, *J* = 15.4 Hz, 1H), 3.81 – 3.76 (m, 1H), 2.99 (dd, *J* = 14.4, 4.6 Hz, 1H), 2.88 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.71 (dd, *J* = 14.4, 3.8 Hz, 1H), 2.55 (s, 3H), 2.17 (s, 3H), 1.85 (dd, *J* = 14.4, 8.1 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.1, 167.0, 166.5, 160.7, 160.6, 136.1, 136.1, 135.2, 131.4, 128.4, 127.0, 124.2, 120.7, 119.8, 119.4, 118.2, 118.1, 118.0, 115.9, 112.5, 112.5, 111.1, 110.8, 108.8, 104.9, 55.9, 55.3, 30.6, 30.6, 26.2, 19.3, 16.2. [α]20 D = -38 (*c* 0.1, $CHCl_3$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{32}H_{31}N_4O_5$ 551.2289; Found 551.2313.

*(3S,5aS,10bS,11aS)-3-((1H-indol-3-yl)methyl)-10b-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2,3,6,10b,11,11a-hexahydro-4H-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4(5aH)-dione (**79c**)*. The title compound was prepared using **79a** (0.040 mmol, 14.9 mg) and hydroxyclavatol (0.033 mmol, 6.5 mg) as reactants. The product was isolated in 3 % yield (0.6 mg) as white amorphous solid. Eluent: ACN/H_2O (65 : 35, *v/v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.01 (s, 1H), 8.11 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.15 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 8.0, 7.0 Hz, 1H), 7.06 (s, 1H), 6.82 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 5.60 (s, 1H), 5.47 (s, 1H), 4.29 (d, *J* = 11.0 Hz, 1H), 3.92 (dd, *J* = 11.3, 5.8 Hz, 1H), 3.69 (dd, *J* = 15.0, 3.5 Hz, 1H), 3.21 (d, *J* = 14.0 Hz, 1H), 2.97 (d, *J* = 14.0 Hz, 1H), 2.90 (dd, *J* = 15.0, 11.0 Hz, 1H), 2.74 (dd, *J* = 13.2, 5.8 Hz, 1H), 2.57 (s, 3H), 2.37 (dd, *J* = 13.2, 11.3 Hz, 1H), 2.18 (s, 3H). [α]20 D = -58 (*c* 0.06, $CHCl_3$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{32}H_{31}N_4O_5$ 551.2289; Found 551.2314.

*(3S,5aS,10bS,11aS)-10b-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-3-((2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)methyl)-2,3,6,10b,11,11a-hexahydro-4H-pyrazino[1',2':1,5]pyrrolo[2,3-b] indole-1,4(5aH)-dione (**79d**)*. The title compound was prepared using **79a** (0.040 mmol, 14.9 mg) and hydroxyclavatol (0.033 mmol, 6.5 mg) as reactants. The product was isolated in 4 % yield (1.0 mg) as white amorphous solid. Eluent: ACN/H_2O (65 : 35, *v/v*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.98 (s, 1H), 12.92 (s, 1H), 8.18 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.21 (m, 1H), 7.19 (t, *J* = 7.5, 1H), 7.12 (dd, *J* = 8.0, 7.0 Hz, 1H) 7.12 (s, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.71 (t, *J* = 7.5 Hz, 1H), 5.69 (s, 1H), 5.52 (s, 1H), 4.76 (d, *J* = 15.2 Hz, 1H), 4.54 (d, *J* = 15.2 Hz, 1H), 4.46 (dd, *J* = 10.0, 3.4 Hz, 1H), 3.99 (dd, *J* = 11.9, 5.5 Hz, 1H), 3.70 (dd, *J* = 15.0, 3.4 Hz, 1H), 3.12 (dd, *J* = 15.0, 10.0 Hz, 1H), 2.78 (s, 2H), 2.69 (dd, *J* = 13.0, 5.5 Hz, 1H), 2.55 (s, 3H), 2.51 (s, 3H), 2.28 (s, 3H), 2.04 (dd, *J* = 13.0, 11.9 Hz, 1H), 1.99 (s, 3H). [α]20 D = -63 (*c* 0.1, $CHCl_3$); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{42}H_{41}N_4O_8$ 729.2919; Found 729.2932.

*(R)-3-((2-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-1H-indol-3-yl)methyl)-3,4-dihydro-1H-benzo[e][1,4]diazepine-2,5-dione (**80b**)*. The title compound was prepared using **80a** (0.080 mmol, 24.5 mg) and hydroxyclavatol (0.051 mmol, 10.0 mg) as reactants. The product was isolated in 21 % yield (5.3 mg) as white amorphous solid. Eluent: ACN/H_2O (55 : 45, *v/v*). ^{1}H NMR (500 MHz, acetone-d_6) δ 13.30 (s, 1H), 9.71 (s, 1H), 9.52 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.62 (s, 1H), 7.52 (dd, *J* = 8.0, 7.2 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.20 (dd, *J* = 8.0, 7.2 Hz, 1H), 6.93 (dd, *J* = 8.0, 7.0 Hz, 1H), 6.84 (dd, *J* = 8.0, 7.0 Hz, 1H), 4.28 (d, *J* = 15.0 Hz, 1H), 4.25 (dd, *J* = 9.0, 5.9 Hz, 1H), 4.22 (d, *J* = 15.0 Hz, 1H), 3.51 (dd, *J* = 15.0, 5.9 Hz, 1H), 3.34 (dd, *J* = 15.0, 9.0 Hz, 1H), 2.56 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ 203.9, 172.7, 168.5, 161.4, 161.4, 137.5, 136.6, 136.5, 133.3, 132.4, 131.8, 128.9, 127.1, 125.1, 121.9, 121.6, 119.5, 118.5, 117.0, 114.2, 113.8, 111.7, 106.3, 53.2, 26.4, 24.4, 20.2, 16.3. [α]20 D = -52 (*c* 0.1, acetone); HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{28}H_{26}N_3O_5$ 484.1867; Found 484.1870.

*(5aS,13aR,14aS)-14a-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-5a,13a,14,14a-tetrahydrobenzo[5',6'][1,4]diazepino[1',2':1,5]pyrrolo[2,3-b]indole-7,13(5H,12H)-dione (**80c**)*. The title compound was prepared using **80a** (0.080 mmol, 24.5 mg) and hydroxyclavatol (0.051 mmol, 10.0 mg) as reactants. The product was isolated in 4 % yield (1.0 mg) as white amorphous solid. Eluent: ACN/H_2O (55 : 45, *v/v*). ^{1}H NMR (500 MHz, acetone-d_6) δ 13.14 (s, 1H), 9.54 (s, 1H), 8.63 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.48 (dd, *J* = 8.0, 7.3 Hz, 1H), 7.20 (dd, *J* = 8.0, 7.3 Hz, 1H), 7.16 (dd, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.97 (dd, *J* = 8.2, 7.7 Hz, 1H), 6.67 (d, *J* = 8.2 Hz, 1H), 6.61 (dd, *J* = 8.2, 7.7 Hz, 1H), 6.31 (s, 1H), 5.65 (s, 1H), 4.01 (dd, *J* = 8.2, 7.0 Hz, 1H), 3.22 (d, *J* = 14.0 Hz, 1H), 3.17 (d, *J* =

14.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.56 (s, 3H), 2.47 (dd, *J* = 14.0, 8.2 Hz, 1H), 2.25 (s, 1H). [α]20 D = -47 (*c* 0.1, acetone); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{26}N_3O_5$ 484.1867; Found 484.1874.

*1-(3-((2-amino-4-hydroxyquinolin-3-yl)methyl)-2,4-dihydroxy-5-methylphenyl)ethan-1-one (**95b**)*. The title compound was prepared using **95a** (0.128 mmol, 20.6 mg) and hydroxyclavatol (0.058 mmol, 11.3 mg) as reactants. The product was isolated in 46 % yield (9.0 mg) as brown amorphous solid. Eluent: ACN/H_2O (75 : 25, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.93 (s, 1H), 11.52 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.56 (s, 1H), 7.55 (dd, *J* = 8.2, 7.1, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.25 (dd, *J* = 8.2, 7.1 Hz, 1H), 6.67 (s, 2H), 3.70 (s, 2H), 2.53 (s, 3H), 2.08 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 202.9, 174.0, 164.1, 159.4, 153.0, 136.9, 130.9, 130.8, 124.4, 122.3, 120.6, 117.7, 116.3, 113.1, 111.0, 101.0, 25.8, 17.6, 15.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{19}N_2O_4$ 339.1339; Found 339.1357.

*1-(2,4-dihydroxy-3-((5-hydroxyquinolin-8-yl)methyl)-5-methyl phenyl)ethan-1-one (**98b**)*. The title compound was prepared using **98a** (0.157 mmol, 22.9 mg) and hydroxyclavatol (0.059 mmol, 11.5 mg) as reactants. The product was isolated in 38 % yield (7.1 mg) as yellow amorphous solid Eluent: ACN/H_2O (80 : 20, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.19 (s, 1H), 10.59 (s, 1H), 9.01 (dd, *J* = 4.5, 1.7 Hz, 1H), 8.69 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (dd, *J* = 8.4, 4.5 Hz, 1H), 7.55 (s, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 4.23 (s, 2H), 2.51 (s, 3H), 2.12 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 203.1, 161.2, 160.9, 152.0, 148.6, 144.4, 133.7, 132.1, 130.7, 126.9, 120.2, 120.1, 117.3, 114.1, 112.0, 109.0, 26.1, 24.5, 15.9. HRMS (ESI-TOF) *m/z:* $[M + H]^+$ Calcd for $C_{19}H_{18}NO_4$ 324.1230; Found 324.1235.

*5-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2-aminobenzoic acid (**101b**)*. The title compound was prepared using **101a** (0.167 mmol, 23.0 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 23 % yield (4.7 mg) as brown amorphous solid. Eluent: ACN/H_2O (65 : 35, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 13.08 (s, 1H), 7.72 (d, *J* = 2.1 Hz, 1H), 7.62 (s, 1H), 7.37 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 2H), 2.56 (s, 3H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, acetone-d_6) δ 204.0, 163.7, 162.0, 161.6, 146.0, 136.8, 132.2, 132.1, 129.8, 116.4, 115.5, 114.0, 114.0, 112.6, 27.9, 26.4, 16.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_5$ 316.1179; Found 316.1169.

*2-((3-acetyl-2,6-dihydroxy-5-methylbenzyl)amino)benzoic acid (**101c**)*. The title compound was prepared using **101a** (0.167 mmol, 23.0 mg) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 6 % yield (1.2 mg) as brown amorphous solid. Eluent: ACN/H_2O (65 : 35, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 13.23 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.68 (s, 1H), 7.37 (dd, *J* = 8.0, 7.1 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.0, 7.1 Hz, 1H), 4.51 (s, 2H), 2.56 (s, 3H), 2.21 (s, 3H). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{18}NO_5$ 316.1179; Found 316.1181.

*5-(3-acetyl-2,6-dihydroxy-5-methylbenzyl)-2-((3-acetyl-2,6-dihydroxy-5-methylbenzyl)amino)benzoic acid (**101d**)*. The title compound was prepared using **101a** (0.167 mmol, 12.9 mg) and hydroxyclavatol (0.066 mmol, 13.0 mg) as reactants. The product was isolated in 3 % yield (0.9 mg) as yellow amorphous solid. Eluent: ACN/H_2O (65 : 35, *v*/*v*) supplied with 0.1% TFA. ^{1}H NMR (500 MHz, acetone-d_6) δ 13.21 (s, 1H), 13.06 (s, 1H), 7.89 (d, *J* = 2.1 Hz, 1H), 7.64 (s, 1H), 7.59 (s, 1H), 7.32 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.49 (s, 2H), 3.91 (s, 2H), 2.55 (s, 3H), 2.54 (s, 3H), 2.22 (s, 3H), 2.17 (s, 3H). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{28}NO_8$ 494.1809; Found 494.1823.

*1-(3-(((1,3-dihydroxy-2-(hydroxymethyl)propan-2-yl)amino)methyl)-2,4-dihydroxy-5-methylphenyl)ethan-1-one (**102b**)*. The title compound was prepared by using **102a** (1.0 mmol, 122.0 mg, prepared as Tris-HCl buffer, pH7.5) and hydroxyclavatol (0.066 mmol, 12.9 mg) as reactants. The product was isolated in 16 % yield (3.2 mg) as brown oil. Eluent: ACN/H_2O (70 : 30, *v*/*v*) supplied with 0.1 % TFA. ^{1}H NMR (500 MHz, CD_3OD) δ 7.72 (s, 1H), 4.49 (s, 2H), 3.82 (s, 6H), 2.56 (s, 3H), 2.22 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, CD_3OD) δ 204.9, 162.5, 162.4, 135.5, 117.3, 114.4, 107.3, 67.5, 59.7, 59.7, 59.7, 36.5, 26.3, 16.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{22}NO_6$ 300.1442; Found 300.1445.

α-Glucosidase inhibition assay. The α-glucosidase inhibition activity was evaluated by modified procedures reported previously.[38,39] The assays contained 100 mM phosphate buffer (pH 6.8), α-glucosidase (1.3 U/mL) (Sigma-Aldrich, St. Louis, USA), 10 µL of 2 mM DMSO solution of compounds to be tested. After pre-incubation at 37 °C for 15 min, the assays were initiated by addition of 40 µL of 2.5 mM *p*-nitrophenyl-α-D-glucopyranoside solution (Sigma-Aldrich, St. Louis, USA) to a final volume of 150 µL. After incubating at 37 °C for further 15 min, the absorbance at 405 nm was recorded on a microplate reader (BMG Labtech, Offenburg, Germany). DMSO was used as negative control and acarbose (TCI Europe, Zwijndrecht, Belgium) as positive control. All assays were performed in triplicate. The IC_{50} value was determined by regression analysis.[40,41]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Chemical synthesis of hydroxyclavatol, structural overview of all reactants, LC-MS chromatograms of selected reactions, NMR spectra of coupling products (PDF).

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Notes

The authors declare no competing financial interest.

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