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ARTICLE

Straightforward synthesis of enantiomerically pure 1,2,3-triazoles derived from amino esters

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A practical and straightforward approach that enables for the first time, the synthesis of enantiomerically pure 1,4,5-trisubstituted, 1,5-disubstituted, and fused 1,2,3 triazoles derivatives has been developed. The synthesis employs enantiomerically pure amino esters derived from amino acids and commercially available ketones under metal-free conditions.

Introduction

Amino acids represent a valuable enantiomerically pure source in organic chemistry, being widely employed as chiral starting materials for the synthesis of peptides^{1a} and more complex structures,^{2b} with broad biomedical implications.^{1c,d} In the last decades, the 1,2,3-triazole scaffold has received great attention from the scientist, due to its feasible synthesis and compatibility with diverse substrates.^{2a} In addition, triazoles play a crucial role in the drug discovery process owing to the ability of 1,2,3-triazole to mimic amide and ester groups which allows the expansion of the chemical space towards the synthesis of diverse triazole bioisosteres.^{2b} In the literature, most of the work reported to access the 1,4- and 1,5-disubstituted 1,2,3-triazole moiety has relied on Cu-^{3a} and Ru-catalyzed^{3b} azide-alkyne cycloaddition reactions respectively. Recently, the combination of amino acids and 1,5-di- and 1,4,5-trisubstituted triazoles has emerged as a powerful strategy to combat several diseases, for instance, apicidin analogues (**1a**),^{4a} glutamate analogues (**1b**)^{4b} and histone/protein deacetylase 8 inhibitors (**2**) (Fig. 1).^{4c} Despite of these exceptional results, the metal toxicity and side effects in biological systems produced by Cu and Ru are well known. As a consequence, such procedures have not been recommended in drug research programs.⁵ In this regard, metal free approaches towards 1,2,3-triazoles have emerged as a new alternative.⁶ Although metals are avoided, earlier methodologies relying on 1,3-dipolar cycloadditions have not

been further used due to (i) the generation of regioisomeric mixtures, (ii) the limited scope and (iii) the multistep reaction sequences required for the synthesis of the starting materials. Recently, the metal free organocatalytic synthesis of 1,2,3-triazoles⁷ has allowed a straightforward and highly regioselective manner to access diversely functionalized 1,2,3-triazoles, inaccessible by other means. Moreover, this methodology uses cheap and readily available building blocks, attractive advantages in the field of drug design.⁸ Lately, our group has reported a very general multicomponent triazolization strategy that can be applied to the synthesis of 1,4,5-trisubstituted, 1,5-disubstituted and 1,5-fused 1,2,3-triazoles.⁹ This method relies on using commercially available enolizable ketones, primary amines and *p*-nitrophenyl azide (PNA) as a dinitrogen source. Then, this method was successfully applied to obtain potential anti-HIV compounds derived from dihydroartemisinin.¹⁰ Building further on our previous work and driven by our interest in drug search, in this paper we describe for the first time the synthesis of enantiomerically pure 1,2,3-triazole derivatives of amino acids, using commercially available ketones and amino esters derived from natural amino acids.

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Table 1. Synthesis of derivative **5a** applying the previously reported conditions.^{9a}

Entry	T (°C)	additive	Time (h)	d.r. ^c	Yield (%)
1 ^b	100	AcOH	24	70/30	48
2 ^b	60	AcOH	24	80/20	45
3 ^b	50	AcOH	24	80/20	40
4	100	-----	24	>95	50
5	60	-----	24	>95	60
6	50	-----	24	>95	40

^aReactions conditions: Toluene (1.5 M), 1.0 equiv of **3**, 1.2 equiv of PNA and 1.4 equiv of **4a**. ^b 30% AcOH. ^cd.r. determined by ¹H-NMR analysis of the crude product **5a**.

Results and discussion

Initially, we started with the synthesis of 4,5- fused tri-substituted 1,2,3-triazoles. To achieve our goal, we used a reaction mixture composed of 5 α -cholestan-3-one (**3**), L-phenylalanine *tert*-butyl ester (**4a**), PNA and acetic acid (AcOH) as a catalyst in anhydrous toluene at 100 °C for 24 h^{9a}. It is important to mention that **3** was selected as a model reagent to easily detect any racemization which could take place during the reaction by ¹H-NMR spectroscopy due to the formation of diastereomers. To our delight, the triazole product **5a** was afforded in an isolated yield of 48%. However, a diastereomeric ratio (*d.r.*) about 70:30 was observed by ¹H-NMR spectroscopy of the crude reaction mixture (Table 1).¹¹ Reducing the temperature to 60 °C and 50 °C enhanced the *d.r.* to about 80:20. Nevertheless, a reduction in the yield of 45% and 40%, respectively, was obtained (Entry 2 and 3, Table 1). Based on the results, it was suspected that AcOH could play an important role in the observed racemization as well as in the reaction yields due to the formation of byproducts that were detected by inspection of the ¹H-NMR of the reaction crude. Hence, three new reaction conditions were performed without adding AcOH in toluene at 100 °C, 60 °C and 50 °C, 24 h. The desired products were formed in 50%, 60% and 40% yields, respectively, without racemization (Entry 5, 6 and 7, Table 1). Nevertheless some byproducts were detected when the reaction was performed at 100 °C. This result could explain the reduction in the yield at this temperature.

It is important to note that the acidic catalyst is not really needed for these reactions to proceed provided enough time is given (24h). The racemization might be attributed to the protonation of diverse species under acidic conditions for instance, the carbonyl of the ester group, the intermediates enamine and imine or the triazole final product. All species have a relatively acidic hydrogen at the chiral center that may be susceptible to racemization. Then, further experiments were set up to study the influence of the ester group in the amino acid on the yield and the *d.r.* using **3** and the methyl (**4b**), ethyl (**4c**) or benzyl ester (**4d**) of L-phenylalanine.¹¹ In all cases, the desired products were obtained without racemization and also a dependence was determined between the size of the ester substituent and the yield of the reaction with *t*-Bu > Et > Me > Bn (see, Entry 1-3, Table S2, ESI).¹¹ Further screening of temperature and reaction times using 1.0 equivalent of β -tetralone (**6**) (readily available), 1.4 equiv of **4a** and 1.2 equiv of PNA (Table 2) led to the best reaction condition (entry 4). Moreover, the enantiomeric excess (*e.e.*), determined by chiral HPLC, was not affected neither by the reaction time nor the temperature. In addition, the yields (89-93%) were independent of the temperature for reaction times close to 24 hours (Entry 6-8, Table 2), nonetheless the yield was reduced to 75% at 50 °C. Moreover, for higher reaction times of around 48 hours a strong dependence of the temperature was observed and the yields dropped from 90% to 61% (entry 1-4, Table 2).

Table 3. Diverse libraries of 4,5-fused -1,2,3-triazoles.

Reaction conditions: Toluene (1.5 M), 1.0 equiv of the ketone, 1.2 equiv of PNA and 1.4 equiv of the amino ester at 60 °C 24h.

With the optimized reaction conditions in hand, we set out to explore the substrate scope of the reaction with a range of different amino esters and cyclic ketones (Table 3). Firstly, the reaction was performed using **4a** and a series of diverse commercially available ketones. It was demonstrated that this reaction showed good functionalization group compatibility obtaining the desired compounds in good yields of 56–71% (Table 3, **5b–5g**). Notably, we did not observe any effect produced by the presence of a heteroatom in the cyclic ketones, obtaining the triazoles **5f** and **5g** in 60% and 65% yields, respectively. In addition, we also did not observe any tendency related to the bulkiness of the substituent (**5b**, **5c**, **5d**). However, when **5b** was compared with **5c** a strong electron donating effect of the methoxy groups was detected. As a consequence, the yield was reduced from 93% (**5b**) to 56% (**5c**). We hypothesized that, the methoxy groups reduce the rate to form the enamine intermediate which is an initial and essential intermediate towards the triazole formation.^{9a}

Secondly, we proceeded to explore the scope of the amino acid derivatives using tyrosine, L-Phe-L-Phe, glutamic acid, and serine derivatives. The products were obtained in good to moderate yields (40–61%, **5h–5k**). It was found that when serine with the free -OH group was employed, the desired triazole product was obtained in only 10% yield, increasing the time and/or the temperature did not show any improvement, and at 100 °C for 48 h the yield was actually reduced to 2%. Gratifyingly, when Ot-Bu protected serine was employed the yield of the reaction reached 50% (**5i**) at 60 °C for 24 h. It is important to mention that this detrimental effect of a free

1,4,5-trisubstituted 1,2,3-triazole of 5-cholestan-3-one **1,4,5-trisubstituted 1,2,3-triazole of dihydrotestosterone** **Fig. 2.** Natural products triazole derivatives.

hydroxyl group was not observed when tyrosine was employed. As an example of the broad scope the dipeptide triazole derivative L-Phe-L-Phe (**5h**) was obtained in 61% yield.

Thirdly, since semisynthetic natural products have been highlighted as a potential source of molecular diversity in drug design strategies, we decided to embark on the synthesis of triazole derivatives of natural origin of triazole derivatives of ketones of natural origin. In this regard, we used as natural source **3** and dihydrotestosterone and as amino ester substrate **4a** and tyrosine *tert*-butyl ester. To our delight, the desired products were isolated in good yields (59–71%, **5a**, **5l–5p**, Fig. 2). Furthermore, the racemization did not take place as evidenced by the ¹H-NMR spectra of the crude reaction mixtures. The reaction was also shown to be compatible with natural ketones or/and amino esters containing a free hydroxy group (**5m–5p**) as well as not to be affected by using both enantiomers of **4a** (**5a** and **5l**, **5n** and **5o**). Next, we examined the scope of this protocol towards the synthesis of 1,5-disubstituted -1,2,3-triazoles starting from diversely

Table 2. Optimal reaction conditions screening.

Entry	T (°C)	Time (h)	e.e. ^b	Yield ^c (%)
1	50	48	>99	84
2	60	48	>99	90
3	70	48	>99	72
4	80	48	>99	61
5	50	24	>99	75
6	60	24	>99	93
7	70	24	>99	91
8	80	24	>99	89
9	RT	24	--	trace
10	RT	48	--	trace

^aReactions conditions: Toluene (1.5 M), 1.0 equiv of **6**, 1.2 equiv of PNA and 1.4 equiv of **4a**. ^be.e. determined by chiral HPLC analysis.¹¹ Isolated yield after purification by column chromatography.

substituted, commercially available acetophenones. In this regard, a reaction was performed, using the procedure described above, with

Table 4. Diverse libraries of 1,5-disubstituted 1,2,3-triazoles.

acetophenones, **4a** and PNA. Under these reaction conditions the product **8a** was obtained with a low yield around 10%. Apparently, the enamines derived from open chain ketones are less reactive than the highly strained cyclic enamines. Notably, when the temperature was increased to 80 °C and 100 °C the yield of the reaction increased to 56% and 71% respectively (Table S3, ESI).¹¹ In addition, a prolonged reaction time of 48 hours at 100 °C did not affect considerably the yield of the reaction (60%).

On the base of the results obtained, we decided for further work with these less reactive open chain ketones to modify our initial reaction protocol, increasing the temperature from 60 °C to 100 °C at 24 h. It is important to mention that this change did not produce any effect on the *e.e.* of the product obtained as determined previously (ESI).¹¹ Then, the scope of the reaction was studied initially, using **4a** and diversely functionalized substituted aromatic ketones (Table 4). The results obtained showed that the reaction is independent of the electron rich (**8b**, **8c**) or electron deficient nature (**8d-8f**, **8h**) of the ketone. Besides, we also examined diverse

heterocyclic ketones (**8g-8j**). To our delight, various interesting heterocyclic moieties such as indole (**8g**) and furan (**8i**) were amenable to the reaction providing access to triazole derivatives with 41% and 69% yield respectively which are otherwise difficult to synthesize. The utility of this reaction was further demonstrated by the transformation of acetyl ferrocene. With a respect to the remaining acetylferrocene which was not consumed, the reaction conversion was about 20% (determined by ¹H-NMR); the desired product was isolated in 12% yield. Despite of the low yield, it is important to mention that this is the first time that an 1,5-disubstituted 1,2,3-triazole derivative of ferrocene, containing an amino acid is synthesized without using a protecting and deprotecting strategy.¹² The presented example represents a new alternative to synthesize novel unexplored ferrocene derivatives with potential biological applications in a straightforward manner.¹² Our interest in skeletal diversity also led us to investigate the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles using 5-nonanone and propiophenone under the same reaction conditions. In this regard, **8k** and **8l** were obtained in 20% and 61% yield, respectively. Then the amino ester diversity scope was examined, the reaction tolerated glycine ester without lateral chain (**8m**) in excellent yield (91%), and alkyl (**8n**) and aromatic (**8o**) lateral chains were also successfully introduced and the desired products were obtained with 71% and 63% yield respectively.

Finally, the free carboxylic acid derivative was prepared by hydrolysis of **5a** in acidic conditions. Fortunately, the carboxylic acid derivative **9a** (Fig. S39, ESI) was obtained with a 90% yield, besides no racemization was detected by ¹H-NMR spectra of the crude reaction mixture (see Fig. S40 ESI). Notably, attempts to prepare unprotected derivative **9a** directly from cholestanone **3** and phenylalanine failed due to the insolubility of the amino acid in toluene.

Conclusions

In summary, we have developed the synthesis of enantiomerically pure 1,4,5-trisubstituted, 1,5-disubstituted, and fused 1,2,3-triazole derivatives of enantiomerically pure amino acids, using commercially available ketones and amino esters derived from amino acids under metal-free conditions. The presented work provides an easy access to diversely functionalized 1,2,3-triazoles that are inaccessible by other means. The products were often obtained with very good yields and in all cases with retention of the chiral centre. Furthermore, the reaction showed to be widely tolerating aromatic and heteroaromatic substituted ketones, heterocycles, fused heterocycles and alkyl ketones. Besides, natural products such as 5 α -cholestan-3-one and dihydrotestosterone were also tolerated giving a new straightforward manner to modify biologically active compounds. In addition, the carboxylic acid was also obtained without racemization, making all the synthesized compounds valuable amino acid mimetic synthons to be further employed for medicinal syntheses as well as the construction of more complex structures for supramolecular chemistry.

Experimental Section

General experimental methods

NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz, Bruker AMX 400 MHz or Bruker Avance II+ 600 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^1H), or the internal (NMR) solvent signal (^{13}C). Exact mass spectra were acquired on a quadrupole orthogonal acceleration time-of-flight mass spectrometer (Synapt G2 HDMS, Waters, Milford, MA). Samples were infused at 3 $\mu\text{L}/\text{min}$ and spectra were obtained in positive (or: negative) ionization mode with a resolution of 15000 (FWHM) using leucine enkephalin as lock mass. Melting points (not corrected) were determined using a Reichert Thermovar apparatus. For column chromatography 70-230 mesh silica 60 (E. M. Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Dry- reaction solvents (toluene, DMF and DMSO) were used as received from commercial sources. Reactions were monitored using thin-layer chromatography (TLC) on aluminum packed percolated Silica Gel 60 F254 plates. Flash column chromatography was carried out with silica gel 60 (particle size less than 0.020 mm) by using appropriate mixtures of ethyl acetate and hexanes as eluent. Compounds were visualized on the TLC plates by use of UV light. Anhydrous magnesium sulfate was used for drying solutions. Chemical nomenclature was generated using Chem Bio Draw Ultra 13.0.

General procedure for the synthesis of 5a-5p

Ketone (1 eq.), amino ester (1.4 eq.), 4-nitrophenyl azide (1.2 eq), 4 Å molecular sieves (50 mg) and toluene (1.5 M) were mixed in a sealed reaction tube for 24 hours at 60 °C. After the solvent was removed under reduced pressure and the crude reaction mixture was purified by flash column chromatography.

5a. Yellow solid; M.p. 165 – 167 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 9:1). ^1H NMR (400 MHz, CDCl_3): δ 7.19 - 7.15 (m, 3H), 6.98 - 6.96 (m, 2H), 4.98 (t, J = 8.0 Hz, 1H), 3.53 (d, J = 7.8 Hz, 2H), 2.78 (d, J = 15.7 Hz, 1H), 2.26 - 2.20 (m, 2H), 2.04 - 2.01 (m, 1H), 1.85 - 1.77 (m, 1H), 1.69 - 1.65 (m, 1H), 1.57 - 1.50 (m, 4H), 1.43 (s, 9H), 1.34 - 0.97 (m, 17 H), 0.92 (d, J = 6.4 Hz, 4H), 0.88 - 0.85 (m, 7H), 0.65 (s, 3H), 0.44 (s, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 142.8, 136.4, 131.5, 129.0, 128.6, 127.0, 83.2, 63.2, 56.2, 53.5, 42.4, 42.0, 39.8, 39.5, 37.4, 36.7, 36.1, 36.0, 35.8, 35.5, 31.5, 29.7, 28.2, 28.0, 27.9, 24.5, 24.3, 23.8, 22.8, 22.6, 21.1, 18.7, 11.9, 11.3 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{40}\text{H}_{61}\text{N}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 616.4797; found 616.4836.

5l. Yellow solid; M.p. 165 – 167 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 9:1). ^1H NMR (400 MHz, CDCl_3) δ 7.21 - 7.18 (m, 3H), 7.07 - 7.05 (m, 2H), 5.10 (dd, J = 6.2, 9.4 Hz, 1H), 3.58 - 3.54 (m, 2H), 2.80 (d, J = 15.7 Hz, 1H), 2.29 - 2.20 (m, 2H), 2.08 - 2.01 (m, 2H), 1.84 - 1.80 (m, 1H), 1.71 - 1.67 (m, 2H), 1.58 - 1.50 (m, 4H), 1.39 (s, 9H), 1.34 - 0.98 (m, 15H), 0.91 (d, J = 6.5 Hz, 4H), 0.86 (d, J = 5.9 Hz, 7H), 0.65 (d, J = 7.18 Hz, 6H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 11.4, 11.9, 18.7, 21.1, 22.6, 22.8, 23.8, 24.3, 24.8, 27.8, 28.0, 28.2, 20.0, 31.6, 35.5, 35.8, 36.0, 36.1, 36.7, 39.5, 39.9, 39.9, 42.1, 42.4, 53.5,

56.2, 63.3, 83.1, 127.0, 128.6, 128.9, 131.4, 136.2, 143.2, 167.1 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{40}\text{H}_{61}\text{N}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 616.4797; found 616.4836.

5b. Red brown solid M.p. 82 - 84 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 8:2). ^1H NMR (400 MHz, CDCl_3) δ 7.92 (d, J = 7.6 Hz, 1H), 7.31 - 7.27 (m, 1H), 7.20 - 7.17 (m, 5H), 7.06 - 7.04 (m, 2H), 5.22 (dd, J = 6.2, 9.3 Hz, 1H), 3.62 - 3.52 (m, 2H), 2.96 - 2.80 (m, 2H), 2.68 (ddd, J = 7.3, 9.0, 16.1 Hz, 1H), 2.58 - 2.50 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 143.2, 135.9, 133.4, 133.3, 129.0, 128.7, 128.0, 127.3, 127.2, 127.2, 122.1, 83.5, 63.6, 37.3, 28.5, 27.8, 19.5 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 376.2025 found 376.2034.

5c. Brown solid M.p. 91 - 93 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 8:2). ^1H NMR (400 MHz, CDCl_3) δ 7.48 (s, 1H), 7.23 - 7.16 (m, 3H), 7.06 - 7.04 (m, 2H), 6.71 (s, 1H), 5.22 (dd, J = 6.2, 9.2 Hz, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.62 - 3.52 (m, 2H), 2.91 - 2.75 (m, 2H), 2.72 - 2.64 (m, 1H), 2.57 - 2.50 (m, 1H), 1.43 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.8, 148.2, 148.1, 143.4, 135.9, 132.4, 129.0, 128.7, 127.2, 125.6, 121.4, 111.6, 105.6, 83.5, 63.7, 56.1, 56.0, 37.3, 28.2, 27.9, 12.97 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_4$ [$\text{M}+\text{H}$] $^+$ 436.2236; found 436.2226.

5d. Yellow semi-solid. (CH_2Cl_2 followed by petroleum ether/EtOAc = 8:2). ^1H NMR (400 MHz, CDCl_3) δ 7.33 - 7.18 (m, 8H), 7.08 - 7.01 (m, 2H), 5.13 - 5.05 (m, 1H), 3.60 - 3.56 (m, 2H), 3.12 - 3.03 (m, 1H), 2.89 - 2.75 (m, 2H), 2.58 - 2.37 (m, 1H), 2.19 - 1.74 (m, 3H), 1.43 + 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 167.0, 166.9, 144.9, 144.8, 143.3, 143.1, 136.2, 132.6, 132.4, 129.0, 128.9, 128.6, 128.5, 127.1, 126.9, 126.8, 126.5, 83.3, 63.4, 63.3, 40.5, 40.2, 37.1, 37.0, 30.0, 29.8, 29.6, 29.3, 27.8, 20.1, 19.7 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_{24}$ [$\text{M}+\text{H}$] $^+$ 404.2293; found 404.2336.

5e. Yellow oil. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.22-7.19 (m, 3H), 7.04 - 7.02 (m, 2H), 5.03 (dd, J = 7.3, 8.8 Hz, 1H), 3.57 - 3.56 (m, 2H), 2.74 - 2.65 (m, 2H), 2.41 - 2.36 (m, 1H), 2.14 - 2.09 (m, 1H), 1.76 - 1.62 (m, 4H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 20.2, 21.9, 22.4, 22.6, 27.8, 37.1, 63.1, 83.1, 127.0, 128.5, 129.0, 132.8, 136.3, 143.0, 167.0 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{19}\text{H}_{25}\text{N}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 328.1980; found 328.2019.

5f. Brown solid M.p. 80 - 81 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.28-7.18 (m, 3H), 7.04-7.01 (m, 2H), 5.15 (dd, J = 6.3, 9.6 Hz, 1H), 4.77 (ABsyst, J = 13.8 Hz, 2H), 3.89-3.84 (m, 1H), 3.71-3.66 (m, 1H), 3.49-3.60 (m, 2H), 2.57 (dt, J = 5.7, 5.8 Hz, 1H), 2.33 (dt, J = 4.9, 15.8 Hz, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 22.0, 27.8, 37.2, 63.6, 63.8, 63.9, 83.5, 127.3, 128.7, 128.9, 130.4, 135.9, 141.3, 166.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 330.1773; found 330.1808.

5g. Yellow solid. M.p. 98 - 100 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (300 MHz, CDCl_3) δ 7.32 - 7.20 (m, 8H), 7.05 - 7.03 (m, 2H), 5.10 (dd, J = 6.3, 9.3 Hz, 1H), 3.74 - 3.59 (m, 4H), 3.57 - 3.50 (m, 2H), 2.77 - 2.72 (m, 1H), 2.61 - 2.47 (m, 2H), 2.32 - 2.26 (m, 1H), 1.41 (s, 9H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ 166.9,

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142.0, 138.0, 136.1, 131.4, 129.0, 128.9, 128.4, 127.3, 127.1, 83.4, 63.5, 61.2, 49.6, 49.0, 37.2, 27.8, 20.8 ppm. HRMS (ESI⁺): m/z calcd for C₂₅H₃₀N₄O₂ [M+H]⁺: 419,2402 found 419,2439.

5h. Yellow semisolid solid. (CH₂Cl₂ followed by petroleum ether/EtOAc = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.92 (dd, *J* = 0.7, 7.6 Hz, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.32-7.12 (m, 10H), 6.91 - 6.89 (m, 2H), 4.93 (dd, *J* = 4.0, 11.3 Hz, 1H), 4.87 (td, *J* = 5.3, 15.8, 1H), 3.69 (s, 3H), 4.70 (dd, *J* = 4.0, 13.8 Hz, 1H), 3.26 (m, 2H), 3.03 (dd, *J* = 8.0, 13.8 Hz, 1H), 2.82 - 2.74 (m, 1H), 2.61 - 2.51 (m, 2H), 2.04 - 1.96 (m, 1H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 167.2, 143.3, 135.9, 135.5, 134.5, 133.6, 129.2, 128.8, 128.76, 128.73, 128.06, 127.7, 127.3, 127.27, 122.1, 65.1, 53.7, 52.5, 39.7, 37.8, 29.7, 28.1, 18.6 ppm; HRMS (ESI⁺): m/z calcd for C₂₉H₂₈N₄O₃ [M+H]⁺: 481.2195; found 481.2226.

5i. Brown semi- solid. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.4 Hz, 1H), 7.30 (td, *J* = 1.7, 7.5 Hz, 1H), 7.24 - 7.18 (m, 2H), 5.44 (dd, *J* = 3.5, 5.7 Hz, 1H), 4.16 (dd, *J* = 5.6, 9.5 Hz, 1H), 3.88 (dd, *J* = 3.5, 9.5 Hz, 1H), 3.09 - 3.00 (m, 4H), 1.48 (s, 9H), 1.13 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 165.6, 143.6, 134.6, 133.9, 128.9, 127.9, 127.2, 127.1, 122.0, 83.3, 77.3, 77.0, 76.7, 73.9, 63.4, 62.2, 28.8, 27.9, 27.3, 20.9 ppm; HRMS (ESI⁺): m/z calcd for C₂₁H₂₉N₃O₃ [M+H]⁺: 372,2287; found 372,2275.

5j. Brown solid m.p. 100 - 102 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.27 - 7.23 (m, 1H), 7.17 - 7.15 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.66 (d, *J* = 8.6 Hz, 2H), 5.21 (dd, *J* = 6.8, 8.8 Hz, 1H), 3.51 - 3.49 (m, 2H), 2.98 - 2.86 (m, 2H), 2.78 - 2.61 (m, 2H), 1.42 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 155.5, 143.2, 133.6, 133.4, 130.0, 128.2, 128.0, 127.5, 127.3, 126.9, 122.2, 115.7, 83.6, 63.9, 36.2, 28.5, 27.9, 19.5 ppm. HRMS (ESI⁺): m/z calcd for C₂₃H₂₅N₃O₃ [M+H]⁺: 392,1974; found 392.1966.

5k. Brown semi-solid. (CH₂Cl₂ followed by petroleum ether/EtOAc = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.96 (d, *J* = 7.4 Hz, 1H), 7.32 (td, *J* = 2.4, 6.5 Hz, 1H), 7.25 - 7.19 (m, 2H), 5.41 (dd, *J* = 5.3, 10.6 Hz, 1H), 4.24 (q, *J* = 7.2 Hz, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.11 - 3.07 (m, 2H), 3.02 - 2.87 (m, 2H), 2.74 - 2.66 (m, 1H), 2.63 - 2.54 (m, 1H), 2.40 - 2.25 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 172.2, 168.1, 143.9, 133.4, 133.3, 128.5, 128.1, 127.5, 127.3, 122.1, 62.4, 60.8, 60.2, 29.9, 28.5, 26.0, 19.6, 14.1, 14.0 ppm; HRMS (ESI⁺): m/z calcd for C₁₉H₂₃N₃O₄ [M+H]⁺: 358.1722; found 358.1762.

5m. Brown solid M.p. 150 - 152 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.87 (br, 1H), 6.79 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.1 Hz, 2H), 5.05 (t, *J* = 7.8 Hz, 1H), 3.46 (d, *J* = 8.0 Hz, 2H), 2.73 (d, *J* = 15.6 Hz, 1H), 2.33 (dd, *J* = 4.4 Hz, 16.6 Hz, 1H), 2.20 (d, *J* = 15.9 Hz, 1H), 2.01 - 1.98 (m, 1H), 1.84 - 1.66 (m, 4H), 1.55 - 0.85 (m, 39H), 0.64 (s, 3H), 0.48 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 155.9, 142.9, 131.9, 129.8, 126.9, 115.6, 83.3, 63.5, 56.2, 53.5, 42.4, 42.0, 39.8, 39.5, 36.7, 36.2, 35.8, 35.7, 35.5, 31.5, 28.9, 28.2, 28.0, 27.9, 24.7, 24.2, 23.8, 22.8, 22.6,

21.1, 18.7, 12.0, 11.2 ppm; HRMS (ESI⁺): m/z calcd for C₄₀H₆₁N₃O₃ [M+H]⁺: 632,4791, found 632,4797.

5n. Yellow solid M.p. 160 - 162 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.31-7.17 (m, 3H), 6.98 - 6.96 (m, 2H), 4.98 (t, *J* = 8.0 Hz, 1H), 3.64 (t, *J* = 8.6 Hz, 1H), 3.53 (d, *J* = 7.7 Hz, 2H), 2.79 (d, *J* = 15.8 Hz, 1H), 2.27 - 2.21 (m, 2H), 2.07 - 2.03 (m, 1H), 1.86 - 1.83 (m, 1H), 1.69 - 1.48 (m, 6H), 1.43 (s, 9H), 1.39 - 0.79 (m, 10H), 0.74 (s, 3H), 0.45 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 142.7, 136.3, 131.5, 128.9, 128.6, 127.0, 83.2, 81.8, 63.2, 53.6, 50.8, 42.8, 42.1, 37.5, 36.8, 36.6, 36.0, 35.5, 31.1, 30.4, 28.8, 27.9, 24.5, 23.4, 20.7, 11.3, 11.0 ppm; HRMS (ESI⁺): m/z calcd for C₃₂H₄₅N₃O₃ [M+H]⁺: 520.3494, found 520.3531.

5o. Yellow solid M.p. 160 - 162 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.23 - 7.18 (m, 3H), 7.07 - 7.05 (m, 2H), 5.11 (dd, *J* = 6.2, 9.3 Hz, 1H), 3.65 (t, *J* = 8.51 Hz, 1H), 3.58 - 3.55 (m, 2H), 2.82 (d, *J* = 15.4 Hz, 1H), 2.30 - 2.22 (m, 2H), 2.09 - 2.02 (m, 2H), 1.87 - 1.84 (m, 1H), 1.68 - 1.52 (m, 4H), 1.43 - 1.35 (m, 11H), 1.28 - 1.10 (m, 4H), 0.96 - 0.85 (m, 4H), 0.75 (s, 3H), 0.66 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 143.1, 136.2, 131.3, 128.9, 128.6, 127.0, 83.2, 81.8, 63.4, 53.6, 50.8, 42.8, 42.1, 36.8, 36.7, 36.1, 36.0, 35.5, 31.1, 30.4, 28.8, 27.8, 24.8, 23.4, 20.7, 11.4, 11.0 ppm; HRMS (ESI⁺): m/z calcd for C₃₂H₄₅N₃O₃ [M+H]⁺: 520.3494, found 520.3531.

5p. Yellow solid M.p. 155 - 156 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 8.62 (br, 1H), 6.75 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 4.98 (t, *J* = 8.0 Hz, 1H), 3.66 (t, *J* = 8.5 Hz, 1H), 3.45 (d, *J* = 7.8 Hz, 2H), 2.72 (d, *J* = 15.6 Hz, 1H), 2.32 (dd, *J* = 4.7, 15.7 Hz, 1H), 2.19 (d, *J* = 15 Hz, 1H), 2.08 - 2.00 (m, 1H), 1.83 (d, *J* = 11.4 Hz, 1H), 1.70 - 1.18 (m, 20H), 1.07 (td, *J* = 4.0, 13.0 Hz, 1H), 0.97-0.77 (m, 3H), 0.73 (s, 3H), 0.47 (s, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 155.9, 142.6, 131.9, 129.8, 16.8, 115.6, 83.3, 81.8, 63.5, 53.6, 50.8, 42.8, 42.0, 36.8, 36.6, 36.3, 35.8, 35.5, 31.1, 30.3, 28.8, 27.9, 24.6, 23.4, 20.7, 11.3, 11.1 ppm; HRMS (ESI⁺): m/z calcd for C₃₂H₄₅N₃O₄ [M+H]⁺: 536,3488; found 536,3483.

General procedure for the synthesis of 8a-8p

Ketone (1 eq.), amino ester (1.3 eq.), 4-nitrophenyl azide (1.1 eq) 4 Å molecular sieves (50 mg) and toluene 1.5 M were mixed in a sealed reaction tube for 24 hours at 100 °C. After the solvent was removed under reduced pressure, the crude reaction mixture was purified by flash column chromatography.

8a. Yellow solid M.p. 94 - 96 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.56 (s, 1H), 7.45 - 7.35 (m, *J* = 7.4 Hz, 1H), 7.35 - 7.28 (m, *J* = 7.4 Hz, 2H), 7.23 - 7.10 (m, *J* = 7.0 Hz, 3H), 6.88 (d, *J* = 7.2 Hz, 2H), 6.77 (d, *J* = 7.2 Hz, 2H), 4.91 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.79 - 3.67 (m, 1H), 3.55 (dd, *J* = 14.0, 4.2 Hz, 1H), 1.41 (s, 9H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 166.8, 139.4, 136.3, 132.3, 129.4, 129.1, 129.0, 128.7, 128.5, 127.0, 126.6, 83.3, 62.4, 37.3, 27.8 ppm; HRMS (ESI⁺): m/z calcd for C₂₁H₂₃N₃O₂ [M+H]⁺: 350.1824; found 350.1859.

8b. Orange solid M.p. 82 - 84 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 7:3). ¹H NMR (400 MHz, CDCl₃) δ 7.53 (s, 2H), 7.21 -

7.14 (m, 3H), 7.12 (d, $J = 7.8$ Hz, 2H), 6.89 (d, $J = 6.1$ Hz, 2H), 6.65 (d, $J = 7.8$ Hz, 2H), 4.91 (dd, $J = 11.3$, 4.2 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.55 (dd, $J = 14.1$, 4.1 Hz, 1H), 2.37 (s, 3H), 1.40 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 139.6, 139.5, 136.4, 132.3, 129.4, 129.0, 129.0, 128.5, 126.9, 123.5, 83.2, 62.3, 37.3, 27.8, 21.3 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 364.1980; found 364.2016.

8c. Yellow-brown oil. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.51 (s, 1H), 7.23 – 7.11 (m, 3H), 6.89 (d, $J = 6.4$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 6.68 (d, $J = 8.4$ Hz, 2H), 4.89 (dd, $J = 11.4$, 4.1 Hz, 1H), 3.82 (s, 3H), 3.77 – 3.67 (m, 1H), 3.54 (dd, $J = 14.0$, 4.1 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 160.5, 139.3, 136.4, 132.3, 130.5, 129.1, 128.5, 127.0, 118.5, 114.2, 83.2, 62.3, 55.3, 37.3, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$: 380.1929; found 380.1967.

8d. Yellow solid M.p. 62 – 64 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.56 (s, 1H), 7.30 (dd, $J = 14.0$, 7.6 Hz, 1H), 7.23 – 7.13 (m, 3H), 7.13 – 7.06 (m, 1H), 6.87 (d, $J = 6.9$ Hz, 2H), 6.58 (d, $J = 7.6$ Hz, 1H), 6.41 (d, $J = 9.1$ Hz, 1H), 4.88 (dd, $J = 11.5$, 4.0 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.55 (dd, $J = 14.1$, 4.0 Hz, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.6, 163.7, 161.2, 138.3, 138.3, 136.2, 132.4, 130.5, 130.4, 129.0, 128.6, 128.5, 128.5, 127.1, 124.9, 124.9, 83.5, 62.6, 37.3, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 368.1730; found 368.1764.

8e. Yellow solid M.p. 87 – 89 °C (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.54 (s, 1H), 7.23 – 7.12 (m, 3H), 7.00 (t, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 6.9$ Hz, 2H), 6.73 – 6.67 (m, 2H), 4.82 (dd, $J = 11.5$, 4.0 Hz, 1H), 3.77 – 3.67 (m, 1H), 3.53 (dd, $J = 14.0$, 3.9 Hz, 1H), 1.42 (s, 9H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 166.7, 164.6, 162.1, 138.5, 136.4, 132.4, 131.2, 131.1, 129.0, 128.6, 127.0, 122.5, 122.5, 116.0, 115.8, 83.4, 62.5, 37.3, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{FN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$ 368.1730; found 368.1762.

8f. Yellow-brown oil. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 8.5$ Hz, 2H), 7.64 (s, 1H), 7.25 – 7.13 (m, 3H), 6.91 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 7.1$ Hz, 2H), 4.81 (dd, $J = 11.6$, 3.8 Hz, 1H), 3.79 – 3.67 (m, 1H), 3.55 (dd, $J = 14.1$, 3.7 Hz, 1H), 1.44 (s, 9H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 148.4, 137.5, 136.2, 133.1, 132.8, 130.1, 129.0, 128.8, 127.3, 123.9, 83.8, 63.0, 37.4, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{21}\text{H}_{22}\text{N}_4\text{O}_4$ $[\text{M}+\text{H}]^+$: 395.1675; found 395.1711.

8g. Off white solid. M.p. 155 – 156 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 8.92 (s, 1H), 7.68 (s, 1H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.28 – 7.22 (m, 1H), 7.21 – 7.05 (m, 5H), 6.88 (d, $J = 6.9$ Hz, 2H), 6.57 – 6.52 (m, 1H), 5.04 (dd, $J = 11.2$, 4.2 Hz, 1H), 3.79 – 3.69 (m, 1H), 3.56 (dd, $J = 14.0$, 4.2 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 136.6, 135.8, 133.4, 133.2, 129.2, 128.5, 126.9, 126.6, 124.7, 123.0, 120.8, 119.0, 111.5, 101.3, 83.2, 62.4, 37.6, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 389.1933; found 389.1965.

8h. Yellow-brown oil. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.94 – 7.83 (m, 2H), 7.65 (s, 1H), 7.60 – 7.33 (m, 3H), 7.26 – 7.04 (m, 4H), 6.93 – 6.73 (m, 2H), 5.84 (bs, 1H), 4.61 (bs, 1H), 3.90 – 3.60 (m, 1H), 3.49 (dd, $J = 13.9$, 3.7 Hz, 1H), 1.40 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 137.4, 136.4, 133.7, 133.2, 132.0, 130.2, 129.3, 128.8, 128.7, 128.6, 128.4, 128.2, 127.0, 126.4, 126.1, 125.9, 124.8, 113.4, 83.4, 62.6, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 400.2010; found 400.2012.

8i. Brown solid M.p. 63 – 65 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (s, 1H), 7.51 (dd, $J = 1.8$, 0.8 Hz, 1H), 7.20 – 7.14 (m, 3H), 7.11 – 7.06 (m, 2H), 6.49 (dd, $J = 3.4$, 1.8 Hz, 1H), 6.47 (dd, $J = 3.5$, 0.7 Hz, 1H), 5.53 (dd, $J = 9.3$, 6.1 Hz, 1H), 3.74 (d, $J = 5.7$ Hz, 1H), 3.71 (d, $J = 2.4$ Hz, 1H), 1.37 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 143.7, 141.2, 136.4, 132.0, 129.7, 129.0, 128.5, 127.0, 111.7, 110.5, 83.3, 64.1, 36.9, 27.7 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_3$ $[\text{M}+\text{H}]^+$ 340.1616; found 340.1647.

8j. Dark yellow solid M.p. 123 – 125 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.63 (s, 1H), 7.23 – 7.16 (m, 3H), 7.05 – 6.97 (m, 2H), 5.17 (dd, $J = 10.8$, 4.4 Hz, 1H), 4.30 – 4.22 (m, 3H), 4.03 (s, 5H), 3.88 (d, $J = 22.1$ Hz, 1H), 3.79 (dd, $J = 13.8$, 11.1 Hz, 1H), 3.61 (dd, $J = 14.1$, 4.4 Hz, 1H), 1.41 (s, 9H) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 167.1, 137.3, 136.6, 132.9, 129.2, 128.6, 127.0, 83.3, 70.8, 69.6, 69.4, 69.4, 68.9, 68.5, 62.6, 37.2, 27.8 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{25}\text{H}_{27}\text{FeN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 458.1486; found 458.1516.

8k. Yellow oil. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.17 – 1.16 (m, 3H), 7.00 – 6.97 (m, 2H), 4.78 (dd, $J = 4.3$, 10.7 Hz, 1H), 3.75 – 3.70 (m, 1H), 3.58 (dd, $J = 4.3$, 13.9 Hz, 1H), 2.56 – 2.48 (m, 2H), 2.30 – 2.23 (m, 1H), 2.16 – 2.08 (m, 1H), 1.72 – 1.63 (m, 3H), 1.39 (s, 9H), 1.13 – 1.03 (m, 4H), 0.89 (t, $J = 7.3$ Hz, 3H), 0.78 (t, $J = 6.6$ Hz, 3H) ppm; ^{13}C NMR (100 MHz, CDCl_3) δ 167.1, 144.0, 136.8, 134.2, 129.1, 128.5, 126.9, 83.0, 62.6, 37.3, 30.8, 27.8, 26.9, 22.8, 22.2, 21.7, 13.7, 13.6 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{22}\text{H}_{33}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 372.2606; found 372.2642.

8l. Yellow solid M.p. 58 – 60 °C. (CH_2Cl_2 followed by petroleum ether/EtOAc = 7:3). ^1H NMR (400 MHz, CDCl_3) δ 7.53 (s, 2H), 7.21 – 7.14 (m, 3H), 7.12 (d, $J = 7.8$ Hz, 2H), 6.89 (d, $J = 6.1$ Hz, 2H), 6.65 (d, $J = 7.8$ Hz, 2H), 4.91 (dd, $J = 11.3$, 4.2 Hz, 1H), 3.78 – 3.68 (m, 1H), 3.55 (dd, $J = 14.1$, 4.1 Hz, 1H), 2.37 (s, 3H), 1.40 (s, 9H) ppm. ^{13}C NMR (100 MHz, CDCl_3) δ 166.9, 139.6, 139.5, 136.4, 132.3, 129.4, 129.1, 129.0, 128.5, 127.0, 123.5, 83.2, 62.3, 37.3, 27.8, 21.3 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 364.1980; found 364.2016.

8m. Off white semi solid. (CH_2Cl_2 followed by heptane/EtOAc = 6:4). ^1H NMR (300 MHz, CDCl_3) δ 7.75 (s, 1H), 7.49 – 7.47 (m, 3H), 7.41 – 7.37 (m, 2H), 5.04 (s, 1H), 1.39 (s, 9H) ppm; ^{13}C NMR (75 MHz, CDCl_3) δ 165.6, 138.7, 133.0, 129.8, 129.2, 128.7, 126.9, 83.6, 50.3, 27.9 ppm; HRMS (ESI^+): m/z calcd for $\text{C}_{14}\text{H}_{18}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$: 260.1393; found 260.1392.

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8n. Yellow oil. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.70 (s, 1H), 7.53 – 7.47 (m, 3H), 7.42 – 7.36 (m, 2H), 4.59 (d, *J* = 9.0 Hz, 1H), 2.77 – 2.68 (m, 1H), 1.44 (s, 9H), 1.28 – 1.17 (m, 1H), 1.09 – 0.96 (m, 4H), 0.77 (t, *J* = 7.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ 167.15, 139.20, 132.49, 129.64, 129.31, 129.07, 126.98, 82.92, 66.07, 36.62, 27.85, 25.45, 15.85, 10.81 ppm; HRMS (ESI⁺): *m/z* calcd for C₁₈H₂₅N₃O₂ [M+H]⁺: 316.1980; found 316.2021.

8o. Yellow solid. M.p. 140 – 142 °C. (CH₂Cl₂ followed by petroleum ether/EtOAc = 8:2). ¹H NMR (400 MHz, CDCl₃) δ 7.55 (s, 1H), 7.47 – 7.31 (m, 3H), 6.87 (d, *J* = 7.4 Hz, 2H), 6.80 – 6.73 (m, 2H), 6.71 – 6.63 (m, 2H), 4.98 – 4.90 (m, 1H), 3.74 – 3.63 (m, 1H), 3.51 – 3.43 (m, 1H), 1.41 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 166.9, 155.7, 139.8, 132.1, 130.1, 130.1, 129.7, 129.2, 128.8, 127.2, 126.3, 115.6, 83.4, 62.8, 36.3, 27.8 ppm; HRMS (ESI⁺): *m/z* calcd for C₂₁H₂₃N₃O₃ [M+H]⁺: 366.1773; found 366.1808.

9a. **5a** (20 mg, 0.03 mmol) was dissolved in 1,4-dioxane (1.0 mL), then 0.5 mL of 6M HCl (aq) was added at R.T. and the reaction was stirred 5h at 85 °C. After, the mixture was cooled to R.T. and water and ether were added. The mixture was then separated and the aqueous layer was extracted with ether 3 times. The combined organic fractions were recollected and dried over MgSO₄, filtered and the solvent was removed under reduced pressure affording a mixture of **9a** and *tert*-butanol (100% conversion). ¹H NMR (400 MHz, CDCl₃) δ 7.20 – 7.19 (m, 3H), 6.93 (m, 2H), 5.03 (dd, *J* = 3.4, 11.5 Hz, 1H), 3.65 (dd, *J* = 3.7, 13.7 Hz, 1H), 3.56 – 3.51 (m, 1H), 2.78 (d, *J* = 15.6 Hz, 1H), 2.22 – 2.17 (m, 2H), 2.05 – 2.03 (m, 2H), 1.87 – 1.84 (m, 2H), 1.67 – 1.66 (m, 2H), 1.56 – 1.51 (m, 4H), 1.41 – 1.32 (m, 7H), 1.20 – 1.09 (m, 5H), 1.06 – 0.98 (m, 4H), 0.94 – 0.88 (m, 11H), 0.67 (s, 3H), 0.38 (s, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 169.1, 143.0, 135.8, 133.0, 128.9, 128.8, 127.3, 62.8, 56.2, 56.1, 53.4, 42.4, 41.7, 39.8, 39.5, 39.07, 36.7, 36.2, 35.8, 35.6, 35.4, 31.4, 29.7, 28.8, 28.2, 28.0, 24.2, 23.8, 22.8, 22.6, 21.1, 18.7, 14.1, 11.9, 11.3. HRMS (ESI⁺): *m/z* calcd for C₃₆H₅₃N₃O₂ [M+H]⁺ 560.4171; found 560.4192.

Conflicts of interest

There are no conflicts to declare.

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