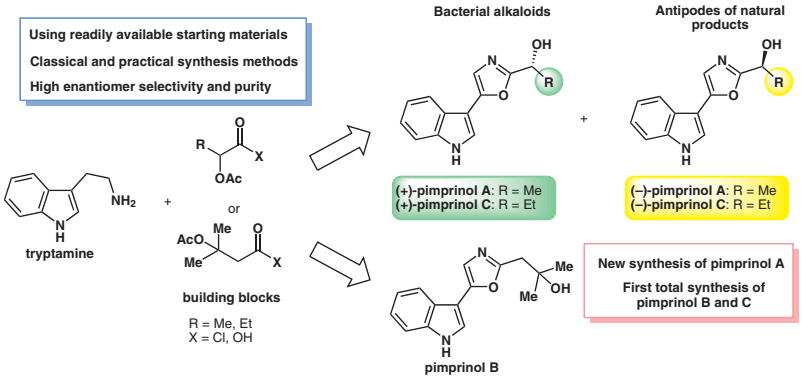
Total Synthesis of Bacterial 5-(3-Indolyl)oxazole Alkaloids: Pimprinols A–C

Tímea Szabó
Róbert Kormány
András Dancsó
Balázs Volk
Mátyás Milen*

Egis Pharmaceuticals Plc., Directorate of Drug Substance Development, P. O. Box 100, 1475 Budapest, Hungary
milen.matyas@egis.hu

This paper is dedicated to the memory of Professor József Reiter.



Received: 16.10.2019
Accepted after revision: 05.11.2019
Published online: 28.11.2019
DOI: 10.1055/s-0039-1690336; Art ID: so-2019-d0030-op

Abstract Pimprinols A, B, and C are bacterial 5-(3-indolyl)oxazole alkaloids that have been isolated from *Streptomyces* sp. Lv3–13. In this paper, we report a new synthesis of pimprinol A and the first total synthesis of pimprinol B and pimprinol C. In addition, antipodes of the naturally occurring pimprinols A and C, as well as the racemates of these two alkaloids were also prepared. In the pivotal step, the 1,3-oxazole ring was constructed by a Nicolaou's modified Robinson–Gabriel cyclization.

Key words oxazole, natural products, bacterial alkaloids, pimprinols A–C, total synthesis

Oxazole ring-containing compounds are significant representatives of natural products and synthetic pharmaceuticals.[1–5] The bacterial alkaloids pimprinols A–C [(*R*)-**1**, **2**, (*R*)-**3**; Figure 1], which belong to the 5-(3-indolyl)oxazole family, were isolated from the rare actinomycetes, *Streptomyces* sp. Lv3–13 by Müller and co-workers in 2012.[6] All three extracted alkaloids [(*R*)-**1**, **2**, (*R*)-**3**] were described as yellow oils and their structures were elucidated by UV, 1D and 2D NMR spectroscopy, and by HRMS (ESI, +) analysis. The absolute configurations of pimprinol A [(*R*)-**1**] and C [(*R*)-**3**] were determined by Mosher ester analysis.

The only known synthesis of pimprinol A [(*R*)-**1**] was described in 2014 by Wu et al. (Scheme 1).[7] In this one-pot method, compound (*R*)-**1** was prepared by treatment of 1-(1*H*-indol-3-yl)ethanone (**4**) with L-threonine (**5**; 2 equiv) in the presence of I_2 in DMSO at 110 °C. The product was

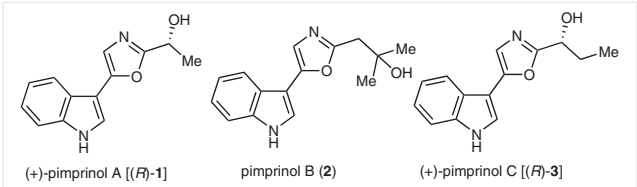
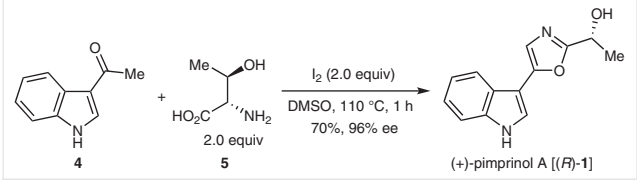


Figure 1 Chemical structures of pimprinols A–C

obtained in 70% yield and 96% enantiomeric excess as a pale-brown solid. The alkaloids pimprinol B (**2**) and C [(*R*)-**3**] have not yet been synthesized.



Scheme 1 Wu's synthesis of natural (+)-pimprinol A

Herein, we would like to report a new total synthesis of pimprinol A [(*R*)-**1**] and the first total synthesis of pimprinol B (**2**) and C [(*R*)-**3**]. In addition, antipodes and racemates of pimprinol A and C were also prepared.

Initially, the synthesis of racemic pimprinol A [(*rac*)-**1**] was investigated starting from the easily available DL-alanine [(*rac*)-**6**; Scheme 2]. 2-Chloro-1-methyl-2-oxoethyl acetate [(*rac*)-**7**] was prepared as previously reported.[8–10] Reaction of (*rac*)-**6** with $NaNO_2$ in glacial acetic acid, followed by treatment with an excess of $SOCl_2$, afforded compound (*rac*)-**7**. Intermediate (*rac*)-**9** was obtained by acylation of tryptamine (**8**) with (*rac*)-**7** in the presence of Et_3N in 88% yield. Oxidation of (*rac*)-**9** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a THF–water solvent mixture at 0 °C led to the corresponding acylamino-ketone (*rac*)-**10** in

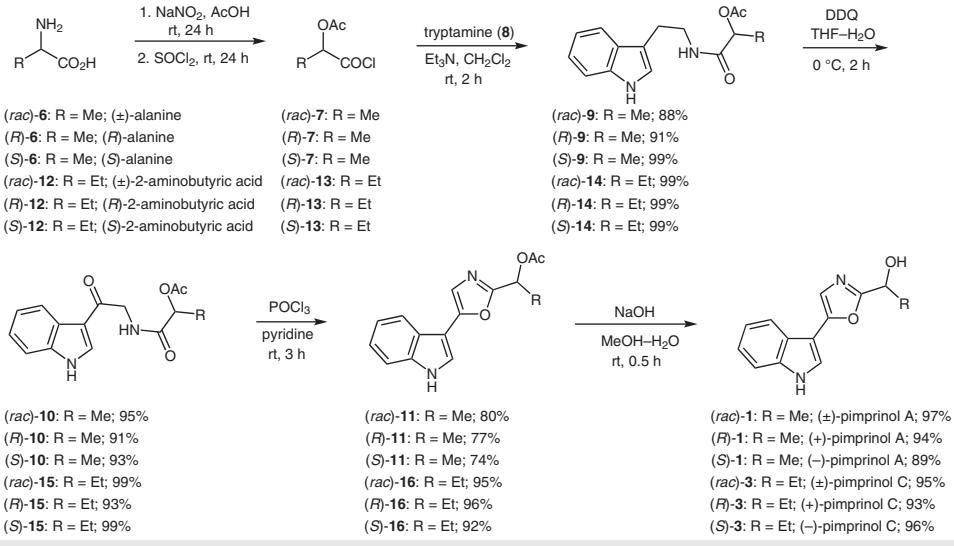
excellent yield. The Robinson–Gabriel cyclization of acylamino-ketone (*rac*)-**10** with propylphosphonic anhydride (T3P®) under microwave conditions[11] was unsuccessful, with the starting material being decomposed. Subsequently, the ring-closure reaction was attempted using Nicolaou's protocol with $POCl_3$ in pyridine at room temperature.[12] In this reaction, the desired 1,3-oxazole derivative (*rac*)-**11** was obtained in 80% yield. Removal of the acetyl group by alkaline hydrolysis furnished the target molecule, racemic pimprinol A [(*rac*)-**1**], in almost quantitative yield.

By following the above synthetic route, natural (+)-pimprinol A [(*R*)-**1**] and its enantiomer (–)-pimprinol A [(*S*)-**1**] were prepared starting from (*R*)-alanine [(*R*)-**6**] and (*S*)-alanine [(*S*)-**6**], respectively. It is important to note that the substitution of the amino group in alanine occurs by double inversion.[10,13] Natural (+)-pimprinol A [(*R*)-**1**] was obtained in four steps from known (1*R*)-2-chloro-1-methyl-2-oxoethyl acetate [(*R*)-**7**] in 60% overall yield and in 98% ee. (–)-Pimprinol A [(*S*)-**1**] was synthesized from the corresponding acid chloride (*S*)-**7** in a similar overall yield (61%). The enantiomeric purity was 98% also in the final product, which was determined by chiral chromatographic separation on a polysaccharide stationary phase (column: 150 × 4.6 mm Lux 5 µm amylose-1, temperature: 20 °C, mobile phase: acetonitrile with 0.1 % ethanolamine).

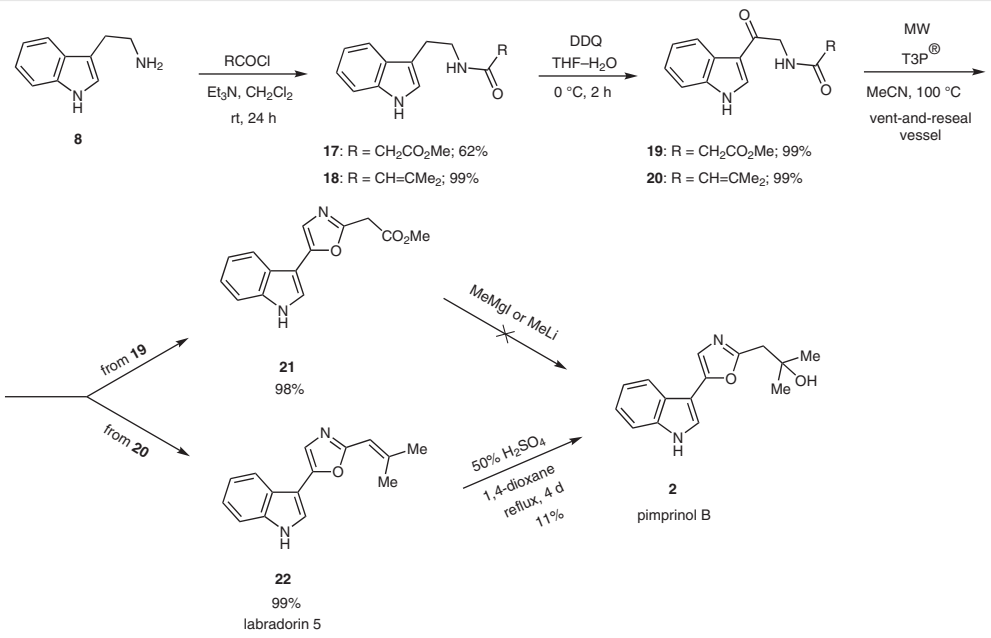
Racemic pimprinol C [(*rac*)-**3**] was prepared from the known 1-(chlorocarbonyl)propyl acetate [(*rac*)-**13**][8,14] by using an analogous procedure in four steps in 88% overall yield (Scheme 2). The natural alkaloid pimprinol C [(*R*)-**3**] and its enantiomer [(*S*)-**3**] were synthesized in a similar manner starting from (1*R*)- [(*R*)-**13**][15] and (1*S*)-1-(chlorocarbonyl)propyl acetate [(*S*)-**13**],[16] respectively. The latter compounds were obtained in more than 80% yield and in 98% ee.

Next, the synthesis of pimprinol B (**2**) was studied from two readily available oxazole derivatives; methyl [5-(1*H*-indol-3-yl)-1,3-oxazol-2-yl] acetate (**21**) and the natural product labradorin 5 (**22**; Scheme 3). First, tryptamine (**8**) was converted into compounds **21** and **22** through a three-step procedure involving acylation with the appropriate acyl chlorides, DDQ mediated oxidation, and T3P®-promoted Robinson–Gabriel cyclodehydration under microwave conditions in a vent-and-reseal vessel. The reaction of ester **21** with MeMgI or MeLi was unsuccessful. In both cases the starting material was recovered. It is hypothesized that the reaction of oxazole **21** with Grignard or organolithium reagent produced an inactive dianion by deprotonation of both the indole NH and the active methylene group. Water addition to, or epoxidation of, the isopropylidene double bond in labradorin 5 (**22**) was unsuccessful with various reagents, such as H_2SO_4/H_2O at room temperature,[17] polyphosphoric acid (PPA) at 90 °C,[18] $Hg(OAc)_2$/THF–H_2O then $NaOH/NaBH_4$,[19] HCl/THF–H_2O at reflux,[20] and *meta*-chloroperoxybenzoic acid (mCPBA) at 0 °C.[21] Finally, upon treatment of labradorin 5 (**22**) with 50% aqueous H_2SO_4 in boiling 1,4-dioxane[22] for 4 days, pimprinol B (**2**) was produced with 15% conversion and in 11% isolated yield. The main component of the residue was the starting material, with some decomposition detected. It is assumed that the poor reactivity of the isopropylidene double bond in compound **22** is caused by extensive conjugation.

Finally, a more efficient total synthesis of pimprinol B (**2**) was elaborated starting from commercially available 3-hydroxy-3-methylbutanoic acid (**23**; Scheme 4). Protection of the tertiary hydroxyl group of **23** with acetyl chloride afforded carboxylic acid **24**.[23] The latter intermediate and tryptamine (**8**) were coupled according to Methods A and B. First carbonyldiimidazole (CDI) as coupling agent was used



Scheme 2 Synthesis of racemic and optically active pimprinol A and C

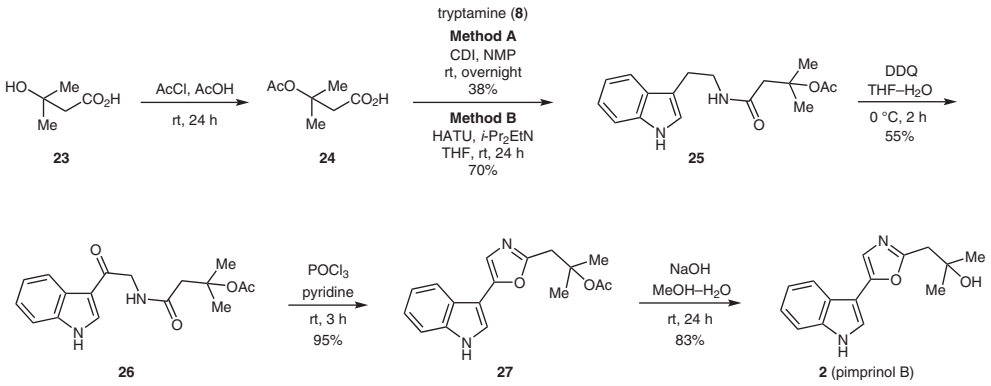


Scheme 3 Attempts at synthesis of pimprinol B (**2**)

in the amide formation but this resulted in the required product in only moderate yield. However, applying 1-[bis(dimethylamino)-methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) and Hünig's base, furnished the corresponding amide **25** in good yield. Although Method B resulted in a higher yield, the final product was contaminated with HATU, which was difficult to eliminate. Subsequent oxidation of intermediate **25** with DDQ in a THF–water solvent mixture provided β-keto amide **26**. Reaction of compound **26** with $POCl_3$ in pyridine, followed by alkaline hydrolysis of the ester group generated pimprinol B in 17% (Method A) and 30% (Method B) overall yields.

Pimprinols A–C were obtained as colorless crystals with sharp melting points, unlike the isolated samples.[6] The analytical data of these synthesized alkaloids are in agreement with those reported for the natural products. The only significant difference was found in the specific rotation values.[6]

In conclusion, a convergent synthesis of racemic and optically active pimprinols A and C has been developed from readily available amino acids in six steps using practical and convenient synthetic methodology. Furthermore, the first total synthesis of optically inactive pimprinol B was accomplished in five steps starting from commercially available 3-hydroxy-3-methylbutanoic acid. In addition, 25 new



Scheme 4 First total synthesis of pimprinol B

compounds were also synthesized as intermediates during the preparations. In each case, the modified Robinson–Gabriel cyclization was employed as the key step.

Reactions under microwave conditions were carried out with a MicroSYNTH T640 in 'vent-and-reseal' vessels with an ATC–FO automatic temperature control and limitation of maximum power to 200–300 W. All melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Bruker Alpha FT-IR spectrophotometer in KBr pellets or film. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6, $CDCl_3$ or CD_3OD in 5 mm tubes at r.t., with a Bruker Avance III HD 600 (600 and 150 MHz for ^{1}H and ^{13}C NMR spectra, respectively), or a Bruker Avance III 400 (400 and 100 MHz for ^{1}H and ^{13}C NMR spectra, respectively) spectrometer with the deuterium signal of the solvent as the lock and TMS as the internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively. The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sp = septet, m = multiplet, br = broad. Mass spectra were recorded with a Bruker O-TOF MAXIS Impact mass spectrometer coupled to a Dionex Ultimate 3000 RS HPLC system with a diode array detector. Reactions were monitored by thin-layer chromatography (TLC) carried out on silica gel plates (60 F_{254}) using UV light as visualizing agent. Purifications by flash column chromatography were carried out using Merck 107736 silica gel 60 H using a hexane–CH_2Cl_2 or CH_2Cl_2–MeOH solvent system. All reagents were purchased from commercial sources and used without further purification. Analytical samples of new compounds were obtained by recrystallization from the solvents or solvent mixtures given below in parentheses. The $[\alpha]_D$ values were determined as an average value of three measurements, measured in MeOH.

Compounds (*rac*)-**1**, (*R*)-**1**, **2**, (*R*)-**3**, (*rac*)-**9**, **17**, **18**, **20**, **22** are described in the literature, while compounds (*S*)-**1**, (*rac*)-**3**, (*S*)-**3**, (*R*)-**9**, (*S*)-**9**, (*rac*)-**10**, (*R*)-**10**, (*S*)-**10**, (*rac*)-**11**, (*R*)-**11**, (*S*)-**11**, (*rac*)-**14**, (*R*)-**14**, (*S*)-**14**, (*rac*)-**15**, (*R*)-**15**, (*S*)-**15**, (*rac*)-**16**, (*R*)-**16**, (*S*)-**16**, **19**, **21**, **25**, **26**, **27** are novel.

Chromatographic Separation and Conditions

During chiral separations, a polar organic mode was used on a polysaccharide stationary phase (150 × 4.6 mm Lux 5 µm amylose-1). The column was purchased from Phenomenex (Torrance, USA). The mobile phase used in this work was acetonitrile (gradient grade) with 0.1% diethylamine. Chemicals were purchased from Merck (Darmstadt, Germany). Chromatographic experiments were performed with a Waters Acquity UPLC H-Class system (Milford, USA) equipped with a quaternary solvent delivery pump, autosampler, photodiode array detector and Empower 3 software. The column temperature was 20 °C. This UHPLC system had a flow-through-needle (FTN) sample injector and 500 nL flow cell. Before analysis, samples were dissolved in pure acetonitrile (0.5 mg/mL); injection volume was 1 µL.

Preparation of Amides 9, 14, 17, 18; General Procedure

Tryptamine (**8**; 14 mmol) and triethylamine (21 mmol, 1.5 equiv) were dissolved in CH_2Cl_2 (80 mL) and cooled in an ice-water bath. To this solution, the appropriate acyl chloride (15.4 mmol) was added dropwise. After addition of the acyl chloride, the reaction mixture was allowed to warm to r.t. and stirred for 2 hours. After the reaction was complete, the mixture was washed with water (60 mL), 5% HCl solution (60 mL) and again with water (60 mL). The organic phase was dried over $MgSO_4$, filtered and evaporated to provide the amides (**9**, **14**, **17**, **18**). The crude products were purified by flash column chromatography (CH_2Cl_2–MeOH).

2-{[2-(1*H*-Indol-3-yl)ethyl]amino}-1-methyl-2-oxoethyl acetate [(*rac*)-9][24]

Yield: 3.047 g (88%); brown oil.

IR (KBr): 3405, 3311, 1738, 1667, 1537, 1232, 1096, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20 (br s, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.21 (t, *J* = 7.3 Hz, 1 H), 7.14 (t, *J* = 7.7 Hz, 1 H), 6.19 (br s, 1 H), 5.15 (q, *J* = 6.9 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.54 (m, 1 H), 3.00 (t, *J* = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.43 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 169.4, 136.3, 127.3, 122.23, 122.16, 119.6, 118.6, 112.7, 111.3, 70.6, 39.5, 25.0, 20.9, 17.9 ppm.

(1*R*)-2-{[2-(1*H*-Indol-3-yl)ethyl]amino}-1-methyl-2-oxoethyl acetate [(*R*)-9]

Yield: 3.151 g (91%); brown oil; $[\alpha]_D^{28}$ +13.7 (*c* 1.0, MeOH).

IR (film): 3405, 3308, 1735, 1664, 1540, 1233, 1096, 744 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.34 (br s, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.13 (t, *J* = 7.8 Hz, 1 H), 7.03 (d, *J* = 2.0 Hz, 1 H), 6.21 (br s, 1 H), 5.15 (q, *J* = 6.8 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.54 (m, 1 H), 3.00 (t, *J* = 6.7 Hz, 2 H), 1.92 (s, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 169.4, 136.2, 127.3, 122.20, 122.15, 119.5, 118.5, 112.6, 111.3, 70.5, 39.6, 25.0, 20.8, 17.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1396; found: 275.1390.

(1*S*)-2-{[2-(1*H*-Indol-3-yl)ethyl]amino}-1-methyl-2-oxoethyl acetate [(*S*)-9]

Yield: 3.428 g (99%); brown oil; $[\alpha]_D^{28}$ –17.5 (*c* 1.0, MeOH).

IR (KBr): 3405, 3306, 1737, 1665, 1537, 1233, 1096, 745 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 7.14 (t, *J* = 7.2 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 6.19 (br s, 1 H), 5.15 (q, *J* = 6.8 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.54 (m, 1 H), 3.00 (t, *J* = 6.6 Hz, 2 H), 1.93 (s, 3 H), 1.43 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 169.4, 136.3, 127.3, 122.23, 122.16, 119.6, 118.6, 112.7, 111.3, 70.6, 39.5, 25.0, 20.9, 17.9.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}N_2O_3$: 275.1396; found: 275.1390.

1-{[2-(1*H*-Indol-3-yl)ethyl]carbamoyl}propyl acetate [(*rac*)-14]

Yield: 3.994 g (99%); brown oil.

IR (film): 3406, 3299, 1739, 1660, 1537, 1233, 745, 426 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.2 Hz, 1 H), 7.26 (br s, 1 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 7.03 (d, *J* = 2.2 Hz, 1 H), 6.14 (br s, 1 H), 5.09 (q, *J* = 4.7 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.53 (m, 1 H), 3.00 (t, *J* = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.91–1.85 (m, 1 H), 1.84–1.77 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.61, 169.57, 136.3, 127.3, 122.3, 119.5, 118.6, 112.7, 111.3, 74.9, 39.5, 25.1, 25.0, 20.7, 9.0.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1552; found: 289.1546.

(1*R*)-1-{[2-(1*H*-Indol-3-yl)ethyl]carbamoyl}propyl acetate [(*R*)-14]

Yield: 3.994 g (99%); brown oil; $[\alpha]_D^{28}$ +17.1 (*c* 1.0, MeOH).

IR (KBr): 3405, 3306, 1738, 1666, 1536, 1232, 745, 426 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.17 (br s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.2 Hz, 1 H), 7.26 (br s, 1 H), 7.23 (t, *J* = 7.9 Hz, 1 H), 7.18 (t, *J* = 7.9 Hz, 1 H), 7.04 (d, *J* = 2.3 Hz, 1 H), 6.13 (br s, 1 H), 5.10 (q, *J* = 4.7 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.53 (m, 1 H), 3.00 (t, *J* = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.91–1.85 (m, 1 H), 1.84–1.77 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.59, 169.56, 136.3, 127.3, 122.23, 122.19, 119.6, 118.6, 112.7, 111.3, 74.9, 39.4, 25.1, 25.0, 20.8, 9.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1552; found: 289.1547.

(1*S*)-1-{[2-(1*H*-Indol-3-yl)ethyl]carbamoyl}propyl acetate [(*S*)-14]

Yield: 3.994 g (99%); brown oil; $[\alpha]_D^{28}$ –20.9 (*c* 1.0, MeOH).

IR (KBr): 3405, 3307, 1738, 1664, 1536, 1232, 744, 427 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.17 (br s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.22 (t, *J* = 7.3 Hz, 1 H), 7.14 (t, *J* = 7.8 Hz, 1 H), 7.04 (d, *J* = 1.9 Hz, 1 H), 6.13 (br s, 1 H), 5.10 (q, *J* = 4.8 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.53 (m, 1 H), 2.99 (t, *J* = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.91–1.85 (m, 1 H), 1.84–1.77 (m, 1 H), 0.88 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.60, 169.57, 136.3, 127.3, 122.23, 122.20, 119.6, 118.6, 112.7, 111.3, 74.9, 39.5, 25.1, 25.0, 20.8, 9.0.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_3$: 289.1552; found: 289.1547.

Methyl 3-{[2-(1*H*-Indol-3-yl)ethyl]amino}-3-oxopropanoate (17)[25]

Yield: 2.259 g (62%); brown oil.

IR (film): 3393, 3307, 1738, 1655, 1437, 830, 746, 559 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.50 (br s, 1 H), 7.59–7.56 (m, 1 H), 7.34–7.31 (m, 1 H), 7.19–7.14 (m, 1 H), 7.11–7.07 (m, 1 H), 7.02 (br s, 1 H), 6.98 (d, *J* = 2.3 Hz, 1 H), 3.65 (s, 3 H), 3.59 (q, *J* = 6.9 Hz, 2 H), 3.21 (s, 2 H), 2.89–2.94 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 169.5, 165.0, 136.3, 127.1, 122.2, 121.9, 119.2, 118.5, 112.4, 111.2, 52.3, 41.2, 39.9, 24.9.

***N*-[2-(1*H*-Indol-3-yl)ethyl]-3-methylbut-2-enamide (18)**[26]

Yield: 3.359 g (99%); colorless crystals; mp 73–75 °C (EtOH).

IR (KBr): 3296, 2885, 1626, 1548, 1457, 1222, 931, 799 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.17 (br s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.38 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.21 (t, *J* = 7.4 Hz, 1 H), 7.13 (t, *J* = 7.5 Hz, 1 H), 7.02 (s, 1 H), 5.82 (br s, 1 H), 4.88 (s, 1 H), 4.78 (s, 1 H), 3.60 (q, *J* = 6.4 Hz, 2 H), 2.97 (t, *J* = 6.7 Hz, 2 H), 2.91 (s, 1 H), 1.71 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.2, 140.3, 136.3, 127.3, 122.2, 122.0, 119.4, 118.7, 115.5, 112.9, 111.2, 46.3, 39.7, 25.2, 22.4.

Preparation of Amide 25; General Procedure

Method A: 3-Acetoxy-3-methylbutyric acid (**24**; 10 mmol) and carbonyldiimidazole (CDI; 10 mmol) were dissolved in *N*-methyl-2-pyrrolidine (10 mL) and the mixture was stirred for 1 h. Tryptamine (**8**; 10 mmol) was then added in one portion and the reaction mixture was stirred at r.t. overnight. After the conversion was complete, the reaction was quenched with water (50 mL) and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude product was purified with flash column chromatography (*n*-hexane–EtOAc) for analytical measurements.

Method B: Tryptamine (**8**; 20 mmol), 3-acetoxy-3-methylbutyric acid (**24**; 20 mmol), *i*-Pr_2EtN (40 mmol, 2 equiv), and HATU (24 mmol, 1.2 equiv) were dissolved in THF (200 mL) and the reaction mixture was stirred at r.t. overnight. After the reaction was complete, the mixture was evaporated. The residue was taken up in CH_2Cl_2 (100 mL) and the organic extract was washed with water (3 × 50 mL). The organic phase was dried over Na_2SO_4, filtered and evaporated to provide amide **25**. The crude product was purified by flash column chromatography (*n*-hexane–EtOAc).

3-{[2-(1*H*-Indol-3-yl)ethyl]amino}-1,1-dimethyl-3-oxopropyl acetate (25)

Yield (Method A): 1.149 g (38%); Yield (Method B): 3.387 g (70%); pale-brown oil.

IR (KBr): 3406, 2935, 1730, 1658, 1369, 1253, 833, 743 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.33 (br s, 1 H), 7.60 (d, *J* = 7.9 Hz, 1 H), 7.36 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 7.12 (t, *J* = 7.6 Hz, 1 H), 7.02 (d, *J* = 1.8 Hz, 1 H), 5.80 (br s, 1 H), 3.61 (q, *J* = 6.5 Hz, 2 H), 2.96 (t, *J* = 6.8 Hz, 2 H), 2.64 (s, 2 H), 1.73 (s, 3 H), 1.51 (s, 6 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.9, 169.4, 136.4, 127.1, 122.2, 122.0, 119.4, 118.6, 112.6, 111.2, 80.6, 47.2, 39.4, 26.5, 25.3, 22.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}N_2O_3$: 303.1709; found: 303.1703.

Preparation of Ketoamides 10, 15, 19, 20, 26; General Procedure

The appropriate amide **9**, **14**, **17**, **18**, **25** (4 mmol) was dissolved in THF–H_2O (9:1, 60 mL). To this solution was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 8 mmol, 2 equiv) in several portions at 0 °C. After addition was complete, the mixture was stirred at the same temperature for 2 h (until the consumption of the starting material as indicated by TLC). The mixture was then poured into EtOAc (150 mL), extracted with 10% aq. $NaHCO_3$ (4 × 85 mL), dried over $MgSO_4$, filtered, and evaporated to give the desired ketoamide. Analytical samples were obtained by recrystallization from EtOH.

2-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]amino}-1-methyl-2-oxoethyl acetate [(*rac*)-10]

Yield: 1.096 g (95%); colorless crystals; mp 128–130 °C (EtOH).

IR (KBr): 3278, 3116, 1737, 1666, 1633, 1243, 1048, 756 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 8.43 (d, *J* = 3.1 Hz, 1 H), 8.30 (t, *J* = 5.6 Hz, 1 H), 8.16 (d, *J* = 7.4 Hz, 1 H), 7.49 (d, *J* = 7.9 Hz, 1 H), 7.36–7.27 (m, 2 H), 5.07 (q, *J* = 6.9 Hz, 1 H), 4.48 (d, *J* = 6.9 Hz, 2 H), 2.10 (s, 3 H), 1.39 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.5, 169.9, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.1, 112.4, 69.8, 45.6, 21.0, 18.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_4$: 289.1188; found: 289.1183.

(1*R*)-2-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]amino}-1-methyl-2-oxoethyl acetate [(*R*)-10]

Yield: 1.049 g (91%); colorless crystals; mp 128–130 °C (EtOH); $[\alpha]_D^{28}$ +31.6 (c 1.0, MeOH).

IR (KBr): 3386, 3258, 1743, 1662, 1631, 1528, 1230, 745 cm^{-1}.

^1H NMR (600 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 8.44 (d, *J* = 3.1 Hz, 1 H), 8.31 (t, *J* = 5.6 Hz, 1 H), 8.17 (d, *J* = 7.5 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.26–7.17 (m, 2 H), 5.07 (q, *J* = 6.8 Hz, 1 H), 4.48 (d, *J* = 5.8 Hz, 2 H), 2.10 (s, 3 H), 1.40 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.6, 169.9, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.1, 112.4, 69.8, 45.6, 21.0, 18.1.

HRMS: m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_4$: 289.1188; found: 289.1183.

(1*S*)-2-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]amino}-1-methyl-2-oxoethyl acetate [(*S*)-10]

Yield: 1.072 g (93%); colorless crystals; mp 134–136 °C (EtOH); $[\alpha]_D^{28}$ –30.9 (c 1.0, MeOH).

IR (KBr): 3332, 3260, 1744, 1659, 1621, 1228, 1120, 746 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 8.44 (s, 1 H), 8.30 (t, J = 5.7 Hz, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.26–7.17 (m, 2 H), 5.07 (q, J = 6.8 Hz, 1 H), 4.48 (d, J = 5.7 Hz, 2 H), 2.09 (s, 3 H), 1.39 (d, J = 6.8 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.5, 169.9, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.1, 112.4, 69.8, 45.6, 21.0, 18.1.

HRMS: m/z [M + H]$^+$ calcd for $C_{15}H_{17}N_2O_4$: 289.1188; found: 289.1183.

1-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]carbamoyl}propyl acetate [(*rac*)-15]

Yield: 1.197 g (99%); colorless crystals; mp 152–153 °C (EtOH).

IR (KBr): 3275, 3106, 1733, 1664, 1631, 1580, 1236, 757 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.02 (br s, 1 H), 8.44 (d, J = 3.1 Hz, 1 H), 8.29 (t, J = 5.7 Hz, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 7.48 (d, J = 7.9 Hz, 1 H), 7.26–7.17 (m, 2 H), 4.96 (q, J = 4.9 Hz, 1 H), 4.55–4.46 (m, 2 H), 2.11 (s, 3 H), 1.88–1.71 (m, 2 H), 1.39 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.1, 169.7, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.2, 112.4, 74.4, 45.6, 25.1, 21.0, 9.5.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_2O_4$: 303.1345; found: 303.1339.

(1*R*)-1-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]carbamoyl}propyl acetate [(*R*)-15]

Yield: 1.247 g (93%); colorless crystals; mp 154–157 °C (EtOH); $[\alpha]_D^{28}$ +36.5 (c 1.0, MeOH).

IR (KBr): 3346, 3277, 1746, 1628, 1520, 1431, 1232, 746 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.02 (br s, 1 H), 8.44 (d, J = 3.2 Hz, 1 H), 8.29 (t, J = 5.7 Hz, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.26–7.17 (m, 2 H), 4.96 (q, J = 4.9 Hz, 1 H), 4.52–4.48 (m, 2 H), 2.11 (s, 3 H), 1.88–1.71 (m, 2 H), 0.95 (t, J = 7.6 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.1, 169.7, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.2, 112.4, 74.4, 45.6, 25.1, 21.0, 9.5.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_2O_4$: 303.1345; found: 303.1339.

(1*S*)-1-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]carbamoyl}propyl acetate [(*S*)-15]

Yield: 1.197 g (99%); colorless crystals; mp 151–154 °C (EtOH); $[\alpha]_D^{28}$ –34.8 (c 1.0, MeOH).

IR (KBr): 3346, 3276, 1746, 1627, 1519, 1430, 1232, 746 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.02 (br s, 1 H), 8.44 (d, J = 3.2 Hz, 1 H), 8.29 (t, J = 5.7 Hz, 1 H), 8.16 (d, J = 7.2 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.26–7.17 (m, 2 H), 4.96 (q, J = 4.9 Hz, 1 H), 4.52–4.48 (m, 2 H), 2.11 (s, 3 H), 1.88–1.71 (m, 2 H), 0.95 (t, J = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.1, 169.7, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.2, 112.4, 74.4, 45.6, 25.1, 21.0, 9.5.

HRMS: m/z [M + H]$^+$ calcd for $C_{16}H_{19}N_2O_4$: 303.1345; found: 303.1339.

Methyl 3-{[2-(1*H*-Indol-3-yl)-2-oxoethyl]amino}-3-oxopropanoate (19)

Yield: 1.086 g (99%); pale-brown crystals; mp 173–176 °C (EtOH).

IR (KBr): 3302, 3219, 1741, 1667, 1625, 1437, 1208, 743 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.86 (br s, 1 H), 8.35 (t, J = 3.7 Hz, 1 H), 7.96 (d, J = 3.1 Hz, 2 H), 7.49–7.43 (m, 1 H), 7.37–7.30 (m, 2 H), 4.70 (d, J = 4.3 Hz, 2 H), 3.80 (s, 3 H), 3.45 (s, 2 H), 3.59 (q, J = 6.9 Hz, 2 H), 3.21 (s, 2 H), 2.89–2.94 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 188.4, 169.2, 165.1, 136.1, 131.1, 125.2, 124.1, 123.1, 122.2, 115.4, 111.6, 52.6, 46.6, 41.3.

HRMS: m/z [M + H]$^+$ calcd for $C_{14}H_{14}N_2O_4$: 275.0954; found: 275.1024.

***N*-[2-(1*H*-Indol-3-yl)-2-oxoethyl]-3-methylbut-2-enamide (20)**

Yield: 1.015 g (99%); colorless crystals; mp 243–245 °C (EtOH, decomp.) (lit.[7] mp 230–233 °C).

IR (KBr): 3335, 3221, 1624, 1536, 1515, 1435, 926, 742 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.99 (br s, 1 H), 8.43 (s, 1 H), 8.22–8.12 (m, 1 H), 8.05 (t, J = 5.6 Hz, 1 H), 7.53–7.45 (m, 1 H), 7.28–7.16 (m, 2 H), 5.81 (s, 1 H), 4.48 (d, J = 5.8 Hz, 1 H), 2.10 (s, 3 H), 1.81 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 190.8, 166.4, 149.0, 136.6, 133.7, 125.6, 123.0, 122.0, 121.3, 119.1, 114.3, 112.3, 45.6, 27.0, 19.5.

3-{[2-(1*H*-Indol-3-yl)ethyl]amino}-1,1-dimethyl-3-oxopropyl acetate (26)

Yield: 696 mg (55%); colorless crystals; mp 169–171 °C (EtOH, decomp.).

IR (KBr): 3328, 3243, 1737, 1630, 1431, 1251, 1144, 746 cm^{-1}.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.01 (br s, 1 H), 8.43 (s, 1 H), 8.20–8.12 (m, 2 H), 7.52–7.47 (m, 1 H), 7.25–7.17 (m, 2 H), 4.47 (d, J = 5.6 Hz, 1 H), 2.74 (s, 2 H), 1.93 (s, 3 H), 1.51 (s, 6 H).

^{13}C NMR (150 MHz, DMSO-d_6): δ = 190.4, 170.1, 169.1, 136.6, 133.8, 125.6, 123.1, 122.0, 121.4, 114.2, 112.4, 80.2, 45.9, 45.2, 26.5, 22.5.

HRMS: m/z [M + H]$^+$ calcd for $C_{17}H_{21}N_2O_4$: 317.1501; found: 317.1496.

Formation of Oxazoles 11, 16, 27 in the Presence of $POCl_3$ and Pyridine; General Procedure

Ketoamide (**10**, **15**, **26**; 0.6 mmol) was dissolved in pyridine (2 mL), $POCl_3$ (3.24 mmol, 5.4 equiv) was added at r.t. and the reaction mixture was stirred 3 hours. After the reaction was complete (TLC monitoring), EtOAc (40 mL) and 10% aq. $NaHCO_3$ (60 mL) were added to the mixture, the phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with water (60 mL) and brine (60 mL), then dried ($MgSO_4$), filtered and evaporated to afford the appropriate products. Analytical samples were obtained by recrystallization from aqueous EtOH.

1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethyl acetate [(*rac*)-11]

Yield: 130 mg (80%); pale-brown crystals; mp 139–141 °C (EtOH–H_2O).

IR (KBr): 3473, 3171, 1750, 1634, 1495, 1221, 1044, 741 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.80 (dd, ^1J = 0.4 Hz, ^2J = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, J = 8.1 Hz, 1 H), 7.25 (s, 1 H), 7.20 (t, J = 7.1 Hz, 1 H), 7.16 (t, J = 7.8 Hz, 1 H), 6.01 (q, J = 6.8 Hz, 1 H), 2.12 (s, 3 H), 1.69 (d, J = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.6, 161.3, 151.0, 138.2, 125.4, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 66.2, 20.8, 18.6 ppm.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1077.

(1*R*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethyl acetate [(*R*)-11]

Yield: 125 mg (77%); pale-brown crystals; mp 164–166 °C (EtOH–H_2O); $[\alpha]_D^{28}$ +87.2 (c 1.0, MeOH).

IR (KBr): 3472, 3169, 1753, 1637, 1494, 1222, 1066, 749 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.81 (d *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.25 (s, 1 H), 7.24–7.19 (m, 1 H), 7.18–7.14 (m, 1 H), 6.02 (q, *J* = 6.8 Hz, 1 H), 2.13 (s, 3 H), 1.69 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.6, 161.3, 151.0, 138.2, 125.3, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 66.2, 20.8, 18.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1077.

(1*S*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethyl acetate [(*S*)-11]

Yield: 120 mg (74%); pale-brown crystals; mp 164–167 °C (EtOH–H_2O); $[\alpha]_D^{28}$ –89.4 (c 1.0, MeOH).

IR (KBr): 3473, 3169, 1753, 1637, 1451, 1222, 1066, 749 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.80 (d *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.46 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.24–7.19 (m, 1 H), 7.18–7.14 (m, 1 H), 6.02 (q, *J* = 6.8 Hz, 1 H), 2.13 (s, 3 H), 1.69 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.6, 161.3, 151.0, 138.2, 125.3, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 66.2, 20.8, 18.6.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}N_2O_3$: 271.1083; found: 271.1077.

1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]propyl acetate [(*rac*)-16]

Yield: 162 mg (95%); pale-yellow crystals; mp 131–133 °C (EtOH–H_2O).

IR (KBr): 3454, 3184, 1750, 1636, 1453, 1230, 1119, 739 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.79 (d *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.21 (t, *J* = 7.7 Hz, 1 H), 7.16 (t, *J* = 7.9 Hz, 1 H), 5.82 (t, *J* = 6.9 Hz, 1 H), 2.14 (s, 3 H), 2.13–2.03 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.8, 160.7, 150.9, 138.2, 125.3, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 71.0, 27.1, 20.7, 9.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1234.

(1*R*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]propyl acetate [(*R*)-16]

Yield: 163 mg (96%); pale-brown crystals; mp 115–117 °C (EtOH–H_2O); $[\alpha]_D^{28}$ +97.3 (c 0.5, MeOH).

IR (KBr): 3379, 3183, 1735, 1631, 1460, 1220, 1016, 743 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.80 (d *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.23–7.19 (m, 1 H), 7.18–7.14 (m, 1 H), 5.83 (t, *J* = 6.7 Hz, 1 H), 2.14 (s, 3 H), 2.13–2.03 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.8, 160.7, 150.9, 138.2, 125.3, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 71.0, 27.1, 20.7, 9.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1234.

(1*S*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]propyl acetate [(*S*)-16]

Yield: 157 mg (92%); pale-yellow crystals; mp 116–117 °C (EtOH–H_2O); $[\alpha]_D^{28}$ –102.4 (c 0.5, MeOH).

IR (KBr): 3379, 3183, 1735, 1631, 1460, 1221, 1016, 743 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.80 (d, *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.23–7.19 (m, 1 H), 7.18–7.14 (m, 1 H), 5.83 (t, *J* = 6.7 Hz, 1 H), 2.14 (s, 3 H), 2.13–2.03 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 171.8, 160.7, 150.9, 138.2, 125.3, 124.3, 123.5, 121.5, 120.4, 119.5, 112.9, 105.0, 71.0, 27.1, 20.7, 9.7.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{17}N_2O_3$: 285.1239; found: 285.1234.

2-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]-1,1-dimethylethyl acetate (27)

Yield: 170 mg (95%); colorless crystals; mp 145–147 °C (EtOH–H_2O).

IR (KBr): 3445, 3209, 1731, 1604, 1428, 1255, 1172, 735 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.60 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.24–7.18 (m, 2 H), 7.17–7.13 (m, 1 H), 3.41 (s, 2 H), 1.97 (s, 3 H), 1.56 (s, 6 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 172.4, 160.3, 150.7, 138.2, 125.3, 123.7, 123.5, 121.4, 120.5, 119.3, 112.8, 105.4, 81.6, 49.1, 38.8, 26.8, 22.4.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_3$: 299.1396; found: 299.1390.

Preparation of Oxazoles 21 and 22 with MW Technique in the Presence of Propylphosphonic Anhydride (T3P®); General Procedure

Ketoamide (**19** or **20**; 0.5 mmol), T3P® reagent (10 equiv, 2.98 mL, 50% EtOAc solution) and CH_3CN (12 mL) were measured into a vent-and-reseal vessel and the reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. After cooling to r.t., the mixture was evaporated, the residue was taken up in CH_2Cl_2 (50 mL) and extracted with sat. aq. $NaHCO_3$ (2 × 25 mL) and water (4 × 25 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated to afford the appropriate product. Analytical samples were obtained by recrystallization from aqueous EtOH.

Methyl [5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]acetate (21)

Yield: 126 mg (98%); brown crystals; mp 158–160 °C (EtOH–H_2O).

IR (KBr): 3170, 2899, 1746, 1637, 1251, 1169, 1006, 739 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.79 (d, *J* = 7.9 Hz, 1 H), 7.63 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.24 (s, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.15 (t, *J* = 7.5 Hz, 1 H), 3.99 (s, 1 H), 3.98 (s, 1 H), 3.77 (s, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 169.8, 156.9, 151.1, 138.2, 125.3, 124.1, 123.5, 121.4, 120.5, 119.7, 112.8, 105.2, 53.1, 34.8.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{13}N_2O_3$: 257.0926; found: 257.0921.

3-[2-(2-Methylprop-1-en-1-yl)-1,3-oxazol-5-yl]-1*H*-indole (22, *labradorin 5*)

Yield: 188 mg (99%); brown crystals; mp 126–129 °C (EtOH–H_2O) (lit.[7] mp 128–131 °C).

IR (KBr): 3452, 3063, 1631, 1449, 1112, 1011, 978, 735 cm^{-1}.

^{1}H NMR (600 MHz, CD_3OD): δ = 7.81 (d, *J* = 7.9 Hz, 1 H), 7.62 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.27 (s, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 6.17 (s, 1 H), 2.27 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 160.7, 149.0, 146.5, 138.2, 125.3, 123.9, 123.5, 121.4, 120.5, 120.0, 112.8, 112.3, 105.5, 27.4, 20.7.

Preparation of Pimprinol Alkaloids 1–3; General Procedure

Acetoxy-protected oxazole (**11**, **16** or **27**; 0.7 mmol) was dissolved in MeOH (28 mL) and aq. NaOH (3.08 mmol in 0.5 mL water, 4.4 equiv) was added. The reaction mixture was stirred at r.t. until the reaction was complete, then the solvent was evaporated. The residue was taken up in a mixture of EtOAc (50 mL) and water (50 mL), and the phases were separated. The aqueous mixture was extracted with further EtOAc (3 × 30 mL), and the combined organic phases were dried over $MgSO_4$, filtered and evaporated. The products were purified by recrystallization from MeCN.

1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethanol [(*rac*)-1]

Yield: 155 mg (97%); pale-yellow crystals; mp 157–160 °C (MeCN) (lit.[6] mp 151–152 °C).

IR (KBr): 3221, 1638, 1445, 1338, 1241, 1084, 974, 751 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.66 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.22 (s, 1 H), 7.20 (t, *J* = 7.3 Hz, 1 H), 7.16 (t, *J* = 7.9 Hz, 1 H), 4.96 (q, *J* = 6.7 Hz, 1 H), 1.63 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 165.1, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.2, 112.8, 105.3, 64.2, 21.5.

(1*R*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethanol ([(*R*)-1], *pimprinol A*)

Yield: 157 mg (98%); 98% ee; pale-yellow crystals; mp 172–174 °C (MeCN) (lit.[6] mp 151–152 °C); $[\alpha]_D^{27}$ +8.2 (c 1.0, MeOH).

IR (KBr): 3267, 1680, 1440, 1385, 1128, 1098, 971, 732 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.84–7.81 (m, 1 H), 7.65 (s, 1 H), 7.46–7.43 (m, 1 H), 7.22 (s, 1 H), 7.24–7.18 (m, 1 H), 7.17–7.14 (m, 1 H), 4.96 (q, *J* = 6.7 Hz, 1 H), 1.63 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 165.1, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.2, 112.8, 105.3, 64.2, 21.5.

(1*S*)-1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]ethanol [(*S*)-1]

Yield: 142 mg (89%); 98% ee; pale-yellow crystals; mp 177–179 °C (MeCN); $[\alpha]_D^{28}$ –7.4 (c 1.0, MeOH).

IR (KBr): 3266, 1681, 1440, 1376, 1128, 1098, 972, 732 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.84–7.81 (m, 1 H), 7.65 (s, 1 H), 7.46–7.42 (m, 1 H), 7.22 (s, 1 H), 7.24–7.18 (m, 1 H), 7.17–7.14 (m, 1 H), 4.96 (q, *J* = 6.7 Hz, 1 H), 1.63 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 165.1, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.2, 112.8, 105.3, 64.2, 21.5.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{13}N_2O_2$: 229.0977; found: 229.0972.

1-[5-(1*H*-Indol-3-yl)-1,3-oxazol-2-yl]-2-methylpropan-2-ol (2, *pimprinol B*)[6]

Yield: 149 mg (83%); colorless crystals; mp 149–150 °C (MeCN).

IR (KBr): 3222, 1636, 1441, 1338, 1257, 1107, 971, 741 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.81 (d, *J* = 7.7 Hz, 1 H), 7.61 (s, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 7.24–7.11 (m, 3 H), 3.00 (s, 1 H), 1.34 (s, 6 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 164.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.3, 69.7, 29.6, 10.1.

1-[5-(1-Indol-3-yl)-1,3-oxazol-2-yl]propan-1-ol [(*rac*)-3]

Yield: 161 mg (95%); colorless crystals; mp 159–160 °C (MeCN).

IR (KBr): 3222, 1636, 1441, 1338, 1257, 1107, 971, 741 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.82 (d, *J* = 7.8 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.20 (t, *J* = 7.2 Hz, 1 H), 7.16 (t, *J* = 7.8 Hz, 1 H), 4.70 (t, *J* = 6.9 Hz, 1 H), 2.07–1.93 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H) ppm.

^{13}C NMR (150 MHz, CD_3OD): δ = 164.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.3, 69.7, 29.6, 10.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found: 243.1128.

(1*R*)-1-[5-(1-Indol-3-yl)-1,3-oxazol-2-yl]propan-1-ol ([(*R*)-3], *pimprinol C*)[6]

Yield: 158 mg (93%); 98% ee; colorless crystals; mp 143–145 °C (MeCN); $[\alpha]_D^{27}$ +12.8 (c 1.0, MeOH).

IR (KBr): 3285, 1634, 1587, 1438, 1258, 1125, 966, 732 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.26–7.18 (m, 1 H), 7.17–7.13 (m, 1 H), 4.70 (t, *J* = 7.0 Hz, 1 H), 2.07–1.93 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 164.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.4, 69.7, 29.6, 10.1.

(1*S*)-1-[5-(1-Indol-3-yl)-1,3-oxazol-2-yl]propan-1-ol [(*S*)-3]

Yield: 162 mg (96%); 98% ee; pale-yellow crystals; mp 144–146 °C (MeCN); $[\alpha]_D^{27}$ –12.2 (c 1.0, MeOH).

IR (KBr): 3259, 1634, 1615, 1439, 1127, 977, 800, 732 cm^{-1}.

^1H NMR (600 MHz, CD_3OD): δ = 7.82 (d, *J* = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, *J* = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.26–7.18 (m, 1 H), 7.17–7.13 (m, 1 H), 4.70 (t, *J* = 7.1 Hz, 1 H), 2.07–1.93 (m, 2 H), 1.01 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 164.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.4, 69.7, 29.6, 10.1.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_2$: 243.1134; found: 243.1128.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690336.

References

(1) Jacobs, H. M.; Burke, B. A. *Alkaloids, Vol. 35*; Rossi, A., Ed.; Academic Press: San Diego, **1989**, 259–310.
(2) Davyt, D.; Serra, G. *Mar. Drugs* **2010**, *8*, 2755.
(3) Swellmeen, L. *Pharma Chem.* **2016**, *8*, 269.
(4) Joshi, S.; Bisht, A. S.; Juyal, D. *Pharma Innovation* **2017**, *6*, 109.
(5) Kakkar, S.; Narasimhan, B. *BMC Chem.* **2019**, *13*, 16.
(6) Raju, R.; Gromyko, O.; Fedorenko, V.; Luzhetskyy, A.; Müller, R. *Tetrahedron Lett.* **2012**, *53*, 3009.
(7) Xiang, J.; Wang, J.; Wang, M.; Meng, X.; Wu, A. *Tetrahedron* **2014**, *70*, 7470.
(8) Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4978.
(9) Testa, E.; Fontanella, L.; Mariani, L. *Justus Liebigs Ann. Chem.* **1962**, *660*, 135.
(10) Leśniak, S.; Rachwalski, M.; Jarzyński, S.; Obijalska, E. *Tetrahedron: Asymmetry* **2013**, *24*, 1336.
(11) Szabó, T.; Dancsó, A.; Ábrányi-Balogh, P.; Volk, B.; Milen, M. *Tetrahedron Lett.* **2019**, *60*, 1353.

(12) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y.-K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897.
(13) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry, 1st ed*; Oxford University Press: Oxford, **2001**, 1223.
(14) Crombie, L.; Jones, R. C. F.; Palmer, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 333.
(15) Oruganti, S.; Sen, S.; Dahanukar, V. H.; Ganorkar, R.; Chakka, R. PCT Int. Appl. WO 2016108206, **2016**; *Chem. Abstr.* **2016**, *165*, 176459.
(16) Claffey, M. M.; Helal, C. J.; Verhoest, P. R. PCT Int. Appl. WO 2010084438, **2010**; *Chem. Abstr.* **2010**, *153*, 260362.
(17) Suess, B.; Brockhoff, A.; Meyerhof, W.; Hofmann, T. *J. Agric. Food Chem.* **2018**, *66*, 2301.
(18) Moon, H. R.; Kim, S. Y.; Lim, J. W.; Kim, J. N. *Bull. Korean Chem. Soc.* **2015**, *36*, 2773.
(19) Morisaki, M.; Rubio-Lightbourn, J.; Ikekawa, N. *Chem. Pharm. Bull.* **1973**, *21*, 457.
(20) Almansour, A. I.; Arumugam, N.; Kumar, R. S.; Soliman, S. M. Altaf M.; Ghabbour, H. A. *Molecules* **2016**, *21*, 724.
(21) Chudasama, V.; Ahern, J. M.; Fitzmaurice, R. J.; Caddick, S. *Tetrahedron Lett.* **2011**, *52*, 1067.
(22) Nomura, T.; Fukai, T.; Sato, E.; Fukushima, K. *Heterocycles* **1981**, *16*, 983.
(23) Fedeor, L. R. *J. Am. Chem. Soc.* **1969**, *91*, 913.
(24) Nemet, I.; Varga-Defterdarovic, L. *Bioorg. Med. Chem.* **2008**, *16*, 4551.
(25) Muratore, M. E.; Shi, L.; Pilling, A. W.; Storer, R. I.; Dixon, D. J. *Chem. Commun.* **2012**, *48*, 6351.
(26) Broberg, A.; Bjerketorp, J.; Andersson, P.; Sahlberg, C.; Levenfors, J. J. *Molecules* **2017**, *22*, 1072.
(27) Miyake, F.; Hashimoto, M.; Tonsiengsom, S.; Yakushijin, K.; Horne, D. A. *Tetrahedron* **2010**, *66*, 4888.