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One-pot total synthesis: the first total synthesis of chiral alkaloid pimprinol A and the facile construction of its natural congeners from amino acids

Jiachen Xiang, Jungang Wang, Miao Wang, Xianggao Meng, Anxin Wu *

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

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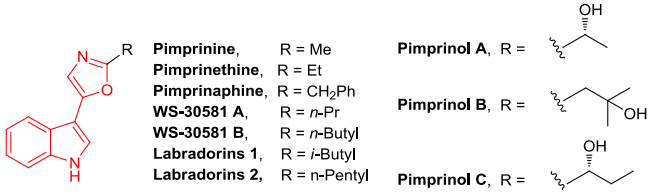
ABSTRACT

In this work, we accomplished the first total synthesis of chiral alkaloid pimprinol A and the facile construction of its natural congeners: pimprinine, pimprinethine, pimprinaphine, WS-30581A, WS-30581B, laboradorin 1, uguenenazole, balsoxine, texamine in one-pot from commercially available starting materials including amino acids. Further investigating into the mechanism revealed that this improved transformation was achieved by the integration of iodination, Kornblum oxidation, condensation, decarboxylation, annulation, and oxidation reaction sequence.

1. Introduction

During the last century, much research has concentrated on the isolation, biological activities, and synthesis of 5-(3-indolyl)oxazoles alkaloids (Scheme 1) due to their biological and pharmaceutical significance.[1] For example, pimprinine demonstrated good monoamine oxidase (MAO) inhibition, an antiepileptic effect, and promising anti-parkinsonian-like activity in mice.[1] The known synthesis of these alkaloids requires multi-steps to build up the oxazole core.[2–7] Kumar and co-workers described a five-step-synthetic route to form pimprinine and analogues in about 42% overall yield.[3] In addition, Horne and co-workers reported a three-step protocol for the construction of pimprinethine, WS-30581A, and WS-30581B, the overall yield was up to 70%.[4] Most recently, a group of new siblings of 5-(3-indolyl)oxazole family each containing a hydroxyl group on their side chains, named pimprinols A–C, have been isolated from *Streptomyces* sp. Lv3-13. As yet, reports have not been provided on the synthesis of pimprinol A. Development of expeditious and efficient protocols with fewer synthetic steps and inexpensive commercial starting materials still highly valuable for the synthesis of the 5-(3-indolyl)oxazole alkaloid family.



Scheme 1. Naturally occurring 5-(3-indolyl)oxazoles.

Amino acids are readily available and versatile organic building blocks ubiquitously masked in a broad range of natural products.[8] Employing amino acids as substrates to transform into natural products, which contain amino acid moieties promise higher efficiency in organic synthesis and hold value in inherently biomimetic significance yet still a hot topic in the total synthesis field.[9] We are pleased to recognize that side chains in the 5-(3-indolyl)oxazole alkaloids family were shown to accurately correspond to accessible amino acids. For example, the side chain of pimprinol A contains a two-carbon unit, a hydroxy group and more specifically, a chiral center. This fragment is identical with the side chain of L-threonine. Therefore, using amino acids as potential reagent becomes a selection priority. In 2013, Nachtsheim and co-workers developed a general synthetic method of oxazole containing compounds from amino acids using iodine and triple equivalents of strong oxidant Oxone.[10] In such transformation, Oxone played an essential role in the catalytic cycle and limited the scope of the substrates due to

* Corresponding author. Tel./fax: +86 (0)27 6786 7773; e-mail address: chwuax@mail.ccnu.edu.cn (A. Wu).

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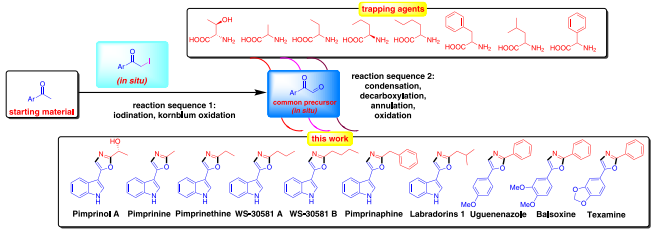
some side effects brought by this strong oxidant. Firstly, threonine, which branched sensitive hydroxyl groups could not afford the desired products pimprinol A (**3g**) with efficiency since the hydroxyl groups were easily to be oxidized to carbonyl group under the existence of Oxone.[11] Secondly, the author only used multi-substituted phenyl or naphthyl methyl ketones as substrates, however, 1*H*-indole rings may be poor tolerant in this harsh oxidant condition.[12] Thirdly, the author claimed clearly that phenylalanine can't afford the desired product, which means pimprinethine (**3e**) could not be obtained in this condition. Furthermore, the author didn't give results of using glycine as substrate and when using alanine as substrate the yield turned out poor (20% yield), which determined that pimprinine (**3a**) could not be installed in high yield. In fact, most of natural products including 5-(3-indolyl)oxazoles alkaloids contain sensitive groups, protecting group-free synthesis and relatively mild reaction need to be established. Inspired by Nachtsheim's outstanding work and based on our research interests in one-pot total synthesis,[14e,f] we herein detailed an improved method of using chemical equivalent iodine instead of Oxone to milden the reaction condition and successfully achieve the first accomplishment of oxidant sensitive chiral alkaloid pimprinol A and its natural congeners directly in one-pot (Scheme 2).

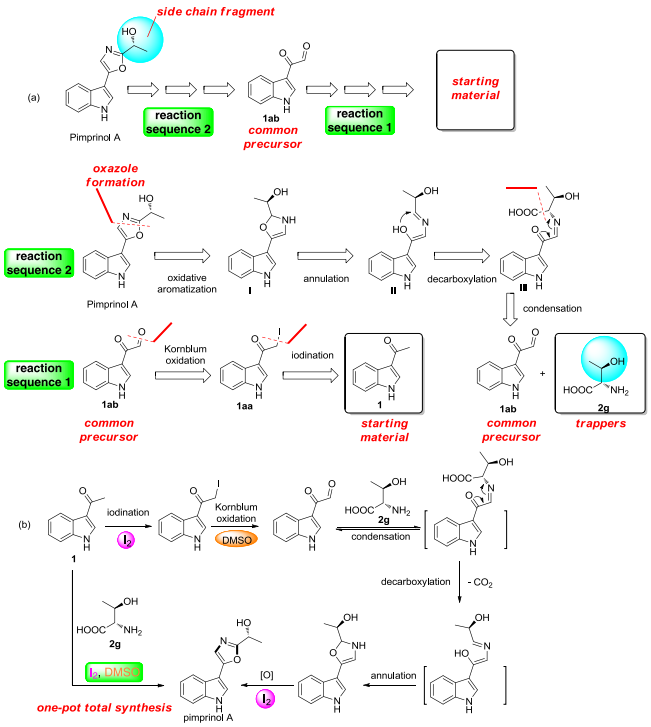


Scheme 2. Our synthesis of oxazole alkaloids from amino acid.

2. Results and discussion

The retrosynthetic analysis as applied to pimprinol A is depicted in Scheme 3a. According to extensive literature research including our original work,[13,14] the unstable intermediates 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde (**1ab**) was chosen as a common precursor. The oxazole ring, which presents as a core fragment in the desired product can be obtained from oxazoline **I** via an iodine-mediated oxidation.[15] Furthermore, **I** is generated smoothly through an annulation reaction of **II**, which is a decarboxylation product by intermediate **III**.[16] **III** can be produced by condensation of common precursor **1ab** and L-threonine, in a word, reaction sequence 2 was determinated. Furthermore, the iodination/Kornblum oxidation reaction sequence to afford **1ab** from 1-(1*H*-indol-3-yl)ethanone (**1**) can be seen as reaction sequence 1. The forward synthetic process is described in Scheme 3b and we envision the integration of reaction sequences 1 and 2 is possible to be executed in one-pot.

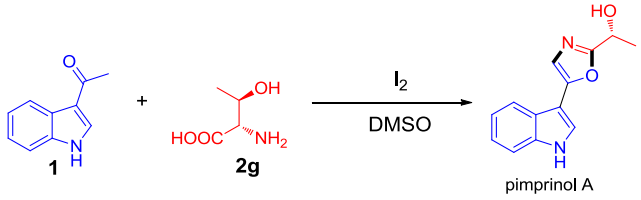
In order to optimize the reaction, 1-(1*H*-indol-3-yl)ethanone (**1**) and L-threonine (**2g**) were selected as model reagents. As the catalyst iodine and the oxidant DMSO were indispensable in the reaction, **1**, **2g**, I_2, and DMSO were added together and heated at 100 °C. Unfortunately, the desired 5-(3-indolyl)oxazole products were not observed. Then some extra oxidants were used as additives (Table 1, entries 2–5), the reaction did proceed in the presence of Oxone or $K_2S_2O_8$, but the efficiency was unsatisfactory as we predicted (entries 2 and 3, yields 49% and 44%). We were pleased to find that using one-pot two-stage method could enhance the yield significantly at the temperatures higher that 100 °C (entries 7–9). I_2 (2 equiv) was optimal (entry 10) and shown to provide the best outcome in pimprinol A. However, an extended reaction time was shown to be slightly detrimental to the yield.



Scheme 3. Retrosynthetic analysis and the forward process for one-pot synthesis of pimprinol A.

With the optimal conditions in hand, the improved method was applied to the synthesis of 5-(3-indolyl)oxazoles in one-pot (Table 2). Including pimprinol A (**3g**), both the natural products and unnatural analogues with different side chains were obtained in moderate to good yields except **3o**. Specifically, the functional group tolerability of hydroxyl groups (**3g** and **3k**) and active methylene groups like **3e** and **3l** is acceptable. Those kinds of 2-arylmethylene oxazoles were failed to construct in the reported literature, which were attributed to the unavoidable side reaction

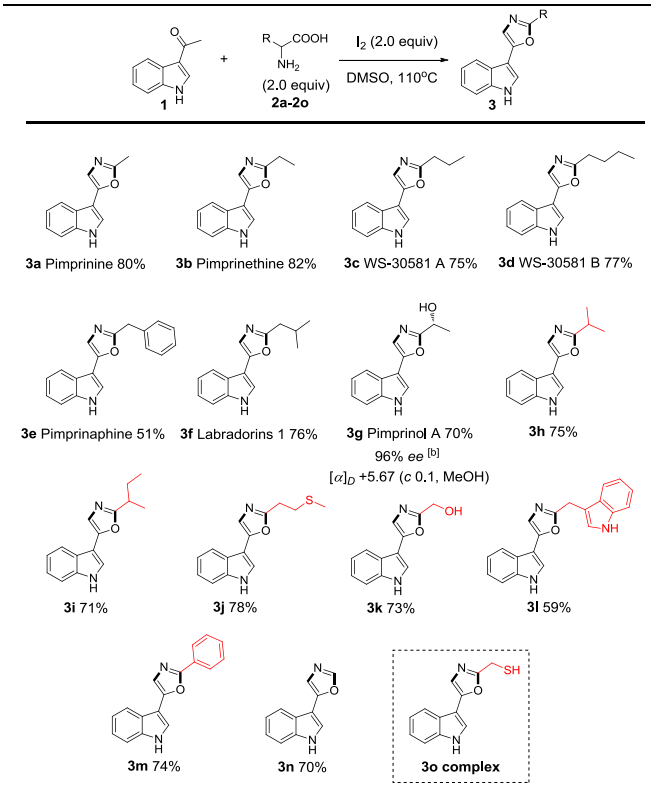
Table 1
Optimization of the reaction conditions[a]



Entry	I_2 (equiv)	Additive (equiv)	Temp (°C)	Time (h)	Yield[d] (%)
1[a]	1.5	—	100	1	0
2	0.2	Oxone (3.0)	95	2	49
3	1.5	$K_2S_2O_8$ (1.0)	100	1	44
4	1.5	H_2O_2 (3.0)	100	1	0
5	1.5	TBHP (3.0)	100	1	0
6[b]	1.5	—	80	1	0
7	1.5	—	100	1	68
8	1.5	—	110	1	66
9	1.5	—	120	1	62
10	*2.0*	—	*110*	*1*	*70*
11	3.0	—	110	1	66
12[c]	2.0	—	110	2	65

[a] Reaction conditions (entries 1–5): **1** (0.5 mmol), **2g** (1.0 mmol), I_2, DMSO (3.0 mL).
[b] Reaction conditions (entries 6–11): **1** (0.5 mmol), I_2, DMSO (3.0 mL), heat for 45 min, then add **2g** (1.0 mmol), heat at the same temperature for 15 min.
[c] Add **2g** (1.0 mmol), heat at the same temperature for 30 min.
[d] Isolated yields.

Table 2
Synthesis of natural 5-(3-indolyl)oxazoles and their unnatural analogues[a]



[a] Reaction conditions: **1** (0.5 mmol), I_2 (1.0 mmol), DMSO (3.0 mL), heat for 45 min, then add **2** (1.0 mmol) , heat at the same temperature for 15 min (for **3e** and **3l**, 5min). Isolated yields. [b] Please see the Supporting Information for the details of the optical purity measurement.

of amino acids homocondensation.[10] Moreover, the bis-indole product **3l** could be constructed directly, providing potential significance for synthesis research and bioactive study.[17] 5-(1*H*-Indol-3-yl)oxazole (**3n**) has also been obtained from glycine, which means this transformation can be applied as an alternative method to access to 5-aryloxazoles.[18] We can see clearly that using chemical equivalent of iodine instead of strong oxidant Oxone the functional group tolerability of the reaction enhanced. So this improved method with relatively mild condition featured powerful in the synthesis of this kind of alkaloids and achieved reasonable improvement. Unfortunately, cysteine cannot afford the desired product smoothly since the active thiol group disturbs the reaction approach (**3o**). The structure of pimprinol A (**3g**) and pimprinethine (**3b**) was further determined by X-ray crystal single diffraction analysis,[19] **3g** as an example was shown in Fig. 1.

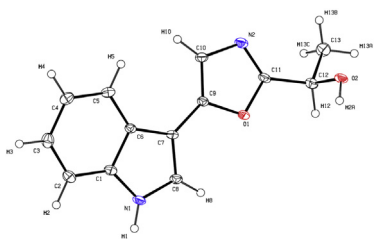
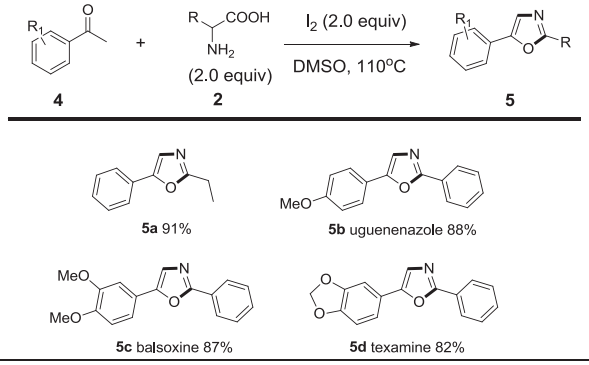


Fig. 1. Crystal structure of pimprinol A (**3g**).

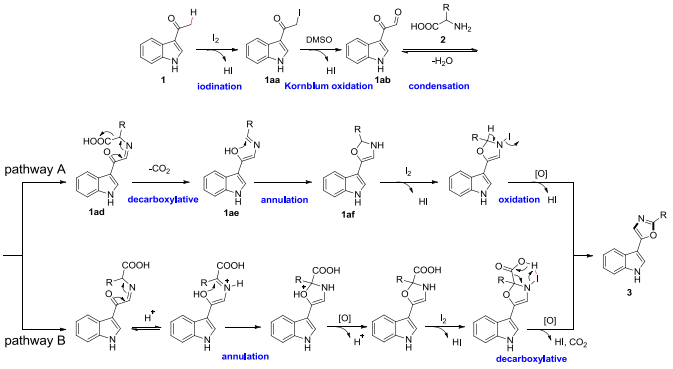
Table 3
A further application of this method using some simpler aryl methyl ketones as substrates[a]



[a] Reaction conditions: **4** (0.5 mmol), I_2 (1.0 mmol), DMSO (3.0 mL), heat for 45 min, then add **2** (1.0 mmol) , heat at the same temperature for 20 min. Isolated yields.

Some simpler aryl methyl ketones as substrates were further scanned (Table 3). Three natural 2,5-diaryloxazole alkaloids: uguenenazole (**5b**),[20] balsoxine (**5c**),[21] texamine (**5d**),[22] were obtained smoothly in high yields via this one-pot variation. To the best of our knowledge, those alkaloids have been constructed using at most seven linear-step sequence by others.[23]

According to our retrosynthetic analysis, the key intermediate in our reaction is the common precursor aromatic α-keto aldehyde (**1ab**) rather than α-hydroxylated aromatic ketone, so the mechanism is somehow different from the reported in the literature.[10] A possible reaction pathway was determined (Scheme 4) based on the control experiments (see Supplementary data) and previous reports.[14–16] The α-iodo ketone **1aa** was initially obtained by the iodination of **1**. Then, **1aa** was oxidized by DMSO via a classic Kornblum oxidation to provide **1ab** and its hydrated hemiacetal form **1ac** (not shown here). Following the addition of substrate **2**, intermediate **1ad** was formed through condensation. After the condensation, there may be two possible reaction pathways, which both make sense.[16b] In pathway A, after keto–enol tautomerization, decarboxylation reaction occurred. Then annulation product **1af** was formed through the attack of the hydroxyl group of **1ae**. Subsequently, **3** could be afforded by iodine-mediated oxidation reaction. In the pathway B, annulation reactions happened at the first place to form **1af'**, then desired product **3** was obtained through iodine-mediated decarboxylation and oxidation reactions. But after imine formation, the proton at the α-position of amino acid should be more acidic. The arrow showing the enol formation would be hard to reach. So we think pathway A is more optimistic. The construction of compounds **5** underwent an identical mechanism.



Scheme 4. Probable reaction pathways.

3. Conclusion

In conclusion, we described a synthesis of 5-(3-indolyl)oxazoles alkaloids from amino acids in one-pot. Such approach is inherently biomimetic and holds significant promise in the field of natural product total synthesis. We have accomplished the first total synthesis of chiral alkaloid pimprinol A and applied to the facile synthesis of pimprinine, pimprinethine, pimprinaphine, WS-30581A, WS-30581B, laboradorin 1, uguenenazole, balsoxine, texamine, directly. In the reaction process, the common precursor aromatic α-keto aldehydes, which were generated by iodination/Kornblum oxidation sequence from aromatic ketones, were trapped in situ by amino acids via condensation/decarboxylation/annulation/oxidation reaction sequence to eventually approach to natural products. Further exploration of the substrate scope is currently underway in our laboratory.

4. Experimental

4.1. General

All substrates and reagents were commercially available and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). IR spectra were recorded on a Perkin–Elmer PE-983 infrared spectrometer as KBr pellets with absorption in cm^{-1}. ^1H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on 400/600 MHz NMR spectrometer and resonances (δ) are given in parts per million (ppm) relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet q=quadruple), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on 100/150 MHz NMR spectrometer and resonances (δ) are given in parts per million (ppm). HRMS were obtained on a Bruker 7-Tesla FT-ICR MS equipped with an electrospray source. The X-ray crystal-structure determinations of **3b** and **3g** were obtained on a Bruker SMART APEX CCD system. Melting points were determined using XT-4 apparatus and not corrected. Enantiomeric ratios were determined by chiral HPLC with different chiral columns (Chiralpak OD column) with hexane and *i*-PrOH as solvents. Optical rotation was measured with polarimeter: Atopol IV (an average value of three times parallel tests).

4.2. General procedure for synthesis of 3 and 5 (3b as an example)

A mixture of 1-(1*H*-indol-3-yl)ethanone **1** (0.5 mmol), I_2 (1.0 mmol) in DMSO (3.0 mL) was stirred at 110 °C for 45 min till almost full conversion of the substrates was indicated by TLC analysis, then added 2-aminobutanoic acid **2b** (1.0 mmol) and stirred at 110 °C for 15 min. Then added 50 mL water and 30 mL saturated brine solution to the mixture and extracted with EtOAc three times (3×50 mL). The extract was washed with 10% $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: petroleum ether/EtOAc=4:1) to afford the product **3b** as a yellow solid.

4.3. Characterization data

*4.3.1. 5-(1H-Indol-3-yl)-2-methyloxazole (**3a** pimprinine).* Yield 80%; light yellow solid; mp=203–204 °C; IR (KBr): 3133, 3116, 2929, 2898, 1637, 1585, 1453, 1364, 1350, 1123, 1024 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.61 (s, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.51 (s, 1H), 7.43 (d, *J*=7.8 Hz, 1H), 7.26 (m, 2H), 7.15 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.32, 147.40, 136.39, 123.55, 122.92, 122.13, 120.05, 119.49, 119.23, 112.07, 103.93, 13.60. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{12}H_{11}N_2O$: 199.0866; found: 199.0865.

*4.3.2. 2-Ethyl-5-(1H-indol-3-yl)oxazole (**3b** pimprinethine).* Yield 82%; yellow solid; mp=154–155 °C; IR (KBr): 3453, 3132, 2928, 2885, 1652, 1622, 1455, 1376, 1244, 1122, 1000 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.88 (s, 1H), 7.81 (d, *J*=7.8 Hz, 1H), 7.48 (d, *J*=2.4 Hz, 1H), 7.39 (d, *J*=7.8 Hz, 1H), 7.26–7.19 (m, 2H), 7.14 (s, 1H), 2.85 (q, 2H), 1.39 (t, *J*=7.8 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 163.69, 147.30, 136.27, 124.09, 122.88, 121.65, 120.73, 119.90, 119.60, 111.55, 105.81, 21.70, 11.31. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{13}H_{13}N_2O$: 213.1022; found: 213.1021.

*4.3.3. 5-(1H-Indol-3-yl)-2-propyloxazole (**3c** WS-30581A).* Yield 75%; yellow solid; mp=131–133 °C; IR (KBr): 3169, 2930, 2873, 1617, 1577, 1450, 1252, 1121, 1002 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.79 (s, 1H), 7.84 (d, *J*=7.8 Hz, 1H), 7.51 (d, *J*=1.8 Hz, 1H), 7.43 (d, *J*=7.8 Hz, 1H), 7.28–7.23 (m, 2H), 7.16 (s, 1H), 2.83 (t, *J*=7.2 Hz, 2H), 1.88 (m, 2H), 1.05 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 162.75, 147.30, 136.27, 124.06, 122.82, 121.67, 120.69, 119.86, 119.51, 111.55, 105.73, 30.08, 20.60, 13.72. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1179; found: 227.1179.

*4.3.4. 2-Butyl-5-(1H-indol-3-yl)oxazole (**3d** WS-30581B).* Yield 77%; light yellow solid; mp=125–126 °C; IR (KBr): 3099, 2950, 2926, 2868, 1632, 1612, 1571, 1452, 1239, 1122, 1098, 1009 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.06 (s, 1H), 7.83 (d, *J*=7.8 Hz, 1H), 7.49 (d, *J*=2.4 Hz, 1H), 7.40 (d, *J*=7.8 Hz, 1H), 7.24 (m, 2H), 7.15 (s, 1H), 2.84 (t, *J*=7.8 Hz, 2H), 1.81 (m, 2H), 1.44 (m, 2H), 0.95 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.96, 147.40, 136.34, 124.09, 122.83, 121.79, 120.70, 119.87, 119.40, 111.62, 105.66, 29.24, 27.90, 22.27, 13.72. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1335; found: 241.1334.

*4.3.5. 2-Benzyl-5-(1H-indol-3-yl)oxazole (**3e** pimprinaphine).* Yield 51%; light red solid; mp=202–203 °C; IR (KBr): 3737, 2935, 1719, 1647, 1560, 1454, 1111, 1006 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.56 (s, 1H), 7.82 (d, *J*=7.8 Hz, 1H), 7.73 (d, *J*=2.4 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.36–7.34 (m, 3H), 7.21 (m, 5H), 4.20 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.07, 147.89, 136.41, 136.32, 128.81, 128.66, 126.86, 123.60, 123.18, 122.18, 120.13, 119.50, 119.39, 112.13, 103.80, 33.82. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{18}H_{15}N_2O$: 275.1179; found: 275.1178.

*4.3.6. 5-(1H-Indol-3-yl)-2-isobutyloxazole (**3f** laboradorin 1).* Yield 76%; yellow solid; mp=147–148 °C; IR (KBr): 2962, 1615, 1581, 1456, 1352, 1250, 1166, 1127 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.15 (s, 1H), 7.84 (d, *J*=7.7 Hz, 1H), 7.51 (s, 1H), 7.42 (d, *J*=7.9 Hz, 1H), 7.25 (m, 7.1 Hz, 2H), 7.17 (s, 1H), 2.73 (d, *J*=7.2 Hz, 2H), 2.26–2.20 (m, 1H), 1.03 (d, *J*=6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.26, 147.42, 136.27, 124.03, 122.81, 121.75, 120.68, 119.81, 119.29, 111.58, 105.61, 37.05, 27.63, 22.34. HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1335; found: 241.1334.

*4.3.7. (R)-1-(5-(1H-Indol-3-yl)oxazol-2-yl)ethanol (**3g** pimprinol A).* Yield 70%; light brown solid; $[\alpha]_D$ +5.67 (*c* 0.1, MeOH) (an average value of three times parallel tests). Mp=151–152 °C (according to the report pimprinol A exists as yellow oil in small amounts, but we find that when we added *n*-hexane as solvent it turned into light brown solid); IR (KBr): 3348, 3267, 2988, 2927, 1637, 1577, 1458, 1442, 1258, 1084 cm^{-1}. ^1H NMR (600 MHz, CD_3OD) δ (ppm) 7.82 (d, *J*=7.8 Hz, 1H), 7.65 (s, 1H), 7.44 (d, *J*=7.8 Hz, 1H),

7.21–7.14 (m, 3H), 4.96 (m, 1H), 1.63 (d, J=6.0 Hz, 3H). ^{13}C NMR (150 MHz, CD_3OD) δ (ppm) 165.02, 150.42, 138.13, 125.31, 124.02, 123.45, 121.39, 120.48, 119.13, 112.80, 105.31, 64.18, 21.49. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.57 (s, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.77 (s, 1H), 7.47 (d, J=7.8 Hz, 1H), 7.34 (s, 1H), 7.20 (t, J=7.2 Hz, 1H), 7.15 (t, J=7.2 Hz, 1H), 5.72 (d, J=5.4 Hz, 1H), 4.92–4.68 (m, 1H), 1.51 (d, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.52, 147.51, 136.36, 123.63, 123.21, 122.13, 120.08, 119.54, 118.87, 112.08, 103.83, 62.05, 21.44. HRMS (ESI): m/z $[M+H]^+$ calcd for C_{13} $H_{13}N_2O_2$: 229.0970; found: 229.0972. HPLC (Chiralpak OD column, hexane/2-propanol=90:10, 1.0 mL/min, 254 nm, 25 °C, t_1=6.48 min, t_2=10.25 min).

*4.3.8. 5-(1H-Indol-3-yl)-2-isopropyloxazole (**3h**).* Yield 75%; yellow solid; mp=125–126 °C; IR (KBr): 3171, 2975, 2927, 1636, 1616, 1570, 1449, 1256, 1123, 1106 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.01 (s, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.52 (s, 1H), 7.42 (d, J=7.8 Hz, 1H), 7.29–7.22 (m, 2H), 7.16 (s, 1H), 3.21–3.16 (m, 1H), 1.44 (d, J=7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.93, 147.17, 136.26, 124.13, 122.86, 121.66, 120.73, 119.91, 119.34, 111.53, 105.75, 28.43, 20.54. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2O$: 227.1179; found: 227.1177.

*4.3.9. 2-(sec-Butyl)-5-(1H-indol-3-yl)oxazole (**3i**).* Yield 71%; light yellow solid; mp=144–145 °C; IR (KBr): 3172, 3118, 2966, 2931, 1637, 1616, 1569, 1450, 1350, 1247, 1106, 1070, 1001 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 9.05 (s, 1H), 7.81 (d, J=7.2 Hz, 1H), 7.51 (s, 1H), 7.42 (d, J=8.4 Hz, 1H), 7.24 (m, 2H), 7.15 (s, 1H), 3.01 (dd, J=13.8, 7.2 Hz, 1H), 1.89 (dd, J=14.1, 6.6 Hz, 1H), 1.73 (dd, J=13.9, 7.8 Hz, 1H), 1.40 (d, J=7.2 Hz, 3H), 0.96 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.37, 147.32, 136.27, 124.07, 122.89, 121.81, 120.78, 119.84, 118.79, 111.59, 105.57, 35.23, 28.26, 17.99, 11.63. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{15}H_{17}N_2O$: 241.1335; found: 241.1334.

*4.3.10. 5-(1H-Indol-3-yl)-2-(2-(methylthio)ethyl)oxazole (**3j**).* Yield 78%; yellow solid; mp=149–150 °C; IR (KBr): 3169, 3136, 2933, 1637, 1615, 1572, 1454, 1434, 1264, 1274, 1111, 1010 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.82 (s, 1H), 7.83 (d, J=7.8 Hz, 1H), 7.51 (d, J=2.4 Hz, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.29–7.22 (m, 2H), 7.18 (s, 1H), 3.16 (t, J=7.8 Hz, 2H), 2.98 (t, J=7.8 Hz, 2H), 2.15 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.68, 147.72, 136.22, 123.99, 122.88, 121.84, 120.76, 119.79, 119.64, 111.57, 105.48, 31.27, 28.52, 15.44. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{14}H_{15}N_2OS$: 259.0900; found: 259.0898.

*4.3.11. (5-(1H-Indol-3-yl)oxazol-2-yl)methanol (**3k**).* Yield 73%; yellow solid; mp=189–190 °C; IR (KBr): 3440, 1637, 1427, 1386, 1115, 1079 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.55 (s, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.75 (d, J=2.4 Hz, 1H), 7.45 (d, J=7.8 Hz, 1H), 7.35 (s, 1H), 7.19 (t, J=7.2 Hz, 1H), 7.13 (t, J=7.2 Hz, 1H), 5.66 (t, J=6.6 Hz, 1H), 4.53 (d, J=6.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.92, 147.97, 136.42, 123.64, 123.32, 122.22, 120.17, 119.58, 119.16, 103.82, 56.03. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{11}N_2O_2$: 215.0815; found: 215.0813.

*4.3.12. 2,5-Di(1H-indol-3-yl)oxazole (**3l**).* Yield 59%; yellow solid; mp=199–200 °C; IR (KBr): 3391, 3184, 2923, 1836, 1699, 1654, 1627, 1447, 1113 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.50 (s, 1H), 10.99 (s, 1H), 7.78 (d, J=6.0 Hz, 1H), 7.67 (d, J=2.4 Hz, 1H), 7.62 (d, J=6.6 Hz, 1H), 7.44 (d, J=5.4 Hz, 1H), 7.39–7.35 (m, 1H), 7.34 (s, 1H), 7.30 (d, J=2.4 Hz, 1H), 7.17 (t, J=5.4 Hz, 1H), 7.09 (t, J=6.6 Hz, 2H), 7.01 (t, J=6.6 Hz, 1H), 4.27 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 160.67, 147.38, 136.28, 136.22, 126.88, 123.64, 123.48, 122.89, 122.03, 121.14, 119.95, 119.46, 119.16, 118.54, 111.99, 111.47, 108.74, 103.84, 24.38. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{16}N_3O$: 314.1293; found: 314.1289.

*4.3.13. 5-(1H-Indol-3-yl)-2-phenyloxazole (**3m**).* Yield 74%; white solid; mp=226–228 °C; IR (KBr): 3171, 3081, 2934, 2893, 1637, 1613, 1547, 1483, 1450, 1369, 1256, 1163, 1163, 1008 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.72 (s, 1H), 8.11 (s, 1H), 8.10 (s, 1H), 7.99 (s, 1H), 7.97 (s, 1H), 7.62 (s, 1H), 7.57–7.48 (m, 4H), 7.24 (d, J=7.8 Hz, 1H), 7.21 (d, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 158.10, 148.33, 136.48, 130.03, 129.16, 127.27, 125.57, 123.92, 123.57, 122.30, 120.86, 120.36, 119.60, 112.23, 103.69. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{13}N_2O$: 261.1022; found: 261.1021.

*4.3.14. 5-(1H-Indol-3-yl)oxazole (**3n**).* Yield 70%; light yellow solid; mp=156–157 °C; IR (KBr): 3174, 2986, 2930, 1632, 1576, 1526, 1449, 1352, 1297, 1244, 1164, 1110, 1090, 1010 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ (ppm) 11.61 (s, 1H), 8.35 (s, 1H), 7.87 (d, J=7.8 Hz, 1H), 7.82 (s, 1H), 7.50 (s, 1H), 7.47 (s, 1H), 7.21 (d, J=7.2 Hz, 1H), 7.16 (d, J=7.2 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 149.61, 147.69, 136.24, 123.53, 123.38, 122.21, 120.20, 119.43, 118.71, 112.09, 103.60. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_9N_2O$: 185.0709; found: 185.0710.

*4.3.15. 2-Ethyl-5-phenyloxazole (**5a**).* Yield 95%; yellow oil; IR (KBr): 3443, 3060, 2981, 2940, 2880, 1558, 1488, 1449, 1376, 1290, 1262, 1188, 1133, 1069, 1049 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.61 (d, J=6.0 Hz, 2H), 7.39 (s, 2H), 7.29 (s, 1H), 7.21 (s, 1H), 2.85 (d, J=5.4 Hz, 2H), 1.39 (t, J=5.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.30, 150.75, 128.72, 128.06, 123.84, 121.61, 77.32, 77.01, 76.84, 21.70, 11.11. HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{11}H_{12}NO$: 174.0914; found: 174.0913.

*4.3.16. 5-(4-Methoxyphenyl)-2-phenyloxazole (**5b** uguenenazole).-* Yield 88%; white solid; mp=78–79 °C. IR (KBr): 3057, 2969, 2840, 1656, 1607, 1498, 1252, 1173, 1021 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.09 (d, J=7.2 Hz, 2H), 7.64 (d, J=8.4 Hz, 2H), 7.50–7.41 (m, 3H), 7.32 (s, 1H), 6.96 (d, J=8.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.48, 159.76, 151.26, 130.08, 128.74, 127.47, 126.09, 125.69, 121.83, 120.79, 114.34, 55.31. HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{16}H_{14}NO_2$: 252.1019; found: 252.1021.

*4.3.17. 5-(3,4-Dimethoxyphenyl)-2-phenyloxazole (**5c** balsoxine).* Yield 87%; white solid; mp=95–97 °C. IR (KBr): 3079, 3000, 2955, 2929, 2831, 2055, 1827, 1638, 1545, 1508, 1455, 1350, 1281, 1285, 1228, 1138, 1007, 1027 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.10 (d, J=7.2 Hz, 2H), 7.47 (m, 3H), 7.34 (d, J=2.4 Hz, 1H), 7.30 (d, J=8.4 Hz, 1H), 7.19 (s, 1H), 6.93 (d, J=8.4 Hz, 1H), 3.98 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.55, 151.22, 149.37, 149.25, 130.12, 128.73, 127.41, 126.11, 122.14, 120.96, 117.19, 111.39, 107.33, 55.95. MS (EI): m/z (%)[14]=282.25 (19), 281.24 (100), 266.20 (26), 238.25 (11), 107.17 (9).

*4.3.18. 5-(Benzo[d][1,3]dioxol-5-yl)-2-phenyloxazole (**5d** texamine).* Yield 82%; light yellow solid; mp=135–137 °C. IR (KBr): 3063, 2916, 1602, 1547, 1493, 1328, 1240, 1104, 1036 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.08 (d, J=6.6 Hz, 2H), 7.45 (m, J=7.8 Hz, 3H), 7.30 (s, 1H), 7.23 (d, J=7.8 Hz, 1H), 7.16 (s, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.00 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 160.56, 151.09, 148.16, 147.85, 130.18, 128.76, 127.37, 126.13, 122.27, 122.15, 118.31, 108.81, 104.78, 101.36. HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{16}H_{12}NO_3$: 266.0812; found: 266.0814.

*4.3.19. 1-(1H-Indol-3-yl)-2-iodoethanone (**1aa**).* Yield 99%; light pink solid; mp=207–208 °C; IR (KBr): 3218, 1699, 1635, 1520, 1436, 1315, 1240, 1129, 1092, 1107 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6)

δ (ppm) 12.12 (s, 1H), 8.49 (d, J=3.0 Hz, 1H), 8.13 (d, J=7.2 Hz, 1H), 7.49 (d, J=7.8 Hz, 1H), 7.22 (t, J=7.8 Hz, 2H), 4.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 188.32, 136.75, 135.10, 125.47, 123.09, 122.0, 121.25, 112.83, 112.22, 6.06. MS: m/z=285.11.

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Supplementary data

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