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Author manuscript

*Eur J Med Chem.* Author manuscript; available in PMC 2018 January 05.

Published in final edited form as:

*Eur J Med Chem.* 2017 January 05; 125: 130–142. doi:10.1016/j.ejmech.2016.09.034.

## Tetracyclic Indolines as A Novel Class of $\beta$ -Lactam-Selective Resistance-Modifying Agent for MRSA

Yugen Zhu<sup>a,‡</sup>, Lakota Cleaver<sup>a,‡</sup>, Wei Wang<sup>a</sup>, Jessica D. Podoll<sup>a</sup>, Shane Walls<sup>a</sup>, Austin Jolly<sup>a</sup>, and Xiang Wang<sup>a,\*</sup>

<sup>a</sup>Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309, USA

### Abstract

Antibiotic-resistant bacterial infections have seen a marked increase in recent years, while antibiotic discovery has waned. Resistance-modifying agents (RMA) offer an intriguing alternative strategy to fight against resistant bacteria. Here we report the discovery, antibiotic profiling, and structure-activity relationships of a novel class of RMAs, tetracyclic indolines. These selectively potentiate  $\beta$ -lactam antibiotics in methicillin-resistant *Staphylococcus aureus* (MRSA) without antibacterial or  $\beta$ -lactamase inhibitory activity on their own. The most potent analogue, **6a**, showed strong potentiation of amoxicillin/clavulanic acid in a variety of hospital-acquired and community-acquired MRSA strains with low mammalian toxicity. These compounds may be further developed to extend the clinic life span of  $\beta$ -lactam antibiotics.

### Graphical Abstract

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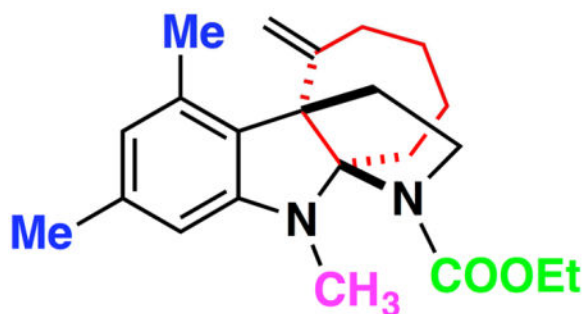
\*Corresponding Author: xiang.wang@colorado.edu. Phone: 303-492-6266. Fax: 303-492-5894.

‡These authors contributed equally.

#### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

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MRC (MRSA): 2  $\mu\text{g/mL}$   
MIC (MRSA): > 64  $\mu\text{g/mL}$   
GI<sub>50</sub> (HeLa): 61  $\mu\text{g/mL}$

### Keywords

$\beta$ -lactam; antibiotic resistance; methicillin-resistant *Staphylococcus aureus*; resistance-modifying agent; structure-activity relationship; indoline alkaloids

### Introduction

Antibiotics revolutionized medicine in the twentieth century not only by saving countless lives from succumbing to infectious diseases, but also by facilitating progressions in medicine, such as dialysis and organ transplantation [1]. The first of these “miracle drugs” was penicillin, which was discovered by Alexander Fleming in 1928. However, as predicted by Fleming himself [2], penicillin resistance arose;  $\beta$ -lactamase-mediated resistance was observed in *Staphylococcus aureus* in 1947, just four years after mass production of penicillin. In the light of this development, methicillin, a semi-synthetic penicillin analogue that was resistant to  $\beta$ -lactamase inactivation, came into favor. However, it was not long before *S. aureus* developed resistance to methicillin through expression of an alternative penicillin-binding protein, PBP2a, which can catalyze the transpeptidation step of cell wall synthesis in the presence of  $\beta$ -lactamases [3]. Multi-drug resistant bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE), and drug-resistant *Escherichia coli*, are continuing to emerge. Notably, MRSA is the most frequently identified resistant pathogen in US hospitals [4, 5]. In addition to potential loss of life, antibiotic resistant bacteria also present a heavy economic burden [6, 7]. These issues illustrate the necessity for continuous discovery of antibiotic classes with novel structures and mechanisms of action. However, very few new classes of antibiotics have been brought to market in the past 50 years, pointing to the need for novel approaches to antibiotic discovery [8, 9].

An alternative strategy to combat bacterial resistance is the use of resistance-modifying agents (RMAs) in combination with established clinical antibiotics [10]. Unlike traditional antibacterials, RMAs do not directly kill or inhibit the growth of bacteria, but target bacterial non-essential genes/gene products [11–19] (e.g., quorum sensing systems [20–22], two-

component system [23–27]). These are often metabolic burdens for bacteria and do not directly affect bacterial growth; hence, they pose no or little selective pressure on bacteria. The chance of developing resistance to this strategy is smaller than for conventional antibacterials [28]. For example, clavulanic acid is a  $\beta$ -lactamase inhibitor that was isolated from *Streptococcus clavuligerus* in 1972 [29]. Although lacking antibacterial activity itself, this molecule contains a  $\beta$ -lactam core and binds irreversibly to the active site of serine  $\beta$ -lactamases, thus deactivating the enzyme. When used in conjunction with  $\beta$ -lactam antibiotics (e.g., amoxicillin), it inhibits the breakdown of the antibiotic [29]. Although the synergistic effect of clavulanic acid is effective against serine  $\beta$ -lactamases, clavulanic acid is ineffective against metallo- $\beta$ -lactamase-producing bacteria and does nothing to combat  $\beta$ -lactam resistance mediated by PBP2a, a prominent resistance mechanism in MRSA [30]. While research is underway for novel RMAs targeting bacterial growth pathways, such as cell wall biosynthesis [31], and other bacterial resistance mechanisms, such as efflux pumps [32],  $\beta$ -lactamase inhibitors remain the only class of RMAs in clinical use.

Recently, our group reported a series of novel anti-MRSA compounds, which were discovered by synthesizing and screening a highly diverse collection of polycyclic indole derivatives [33–38]. Further biological profiling studies showed that some hits from the screens, such as the ring-opened fused indoline Of1 (**1**, Figure 1) and tetracyclic indolenine **2**, selectively re-sensitizes MRSA to  $\beta$ -lactam antibiotics [33]. Aza-tricyclic indoline **3** (Figure 1) was developed to optimize the physiochemical properties Of1 [39]. Herein, we report the antibiotic profiling and structure-activity relationship (SAR) studies of alkylated fused indoline Kf18 (**4**, Figure 1), another hit compound from our previous screens [33], with a distinct tetracyclic indoline scaffold. The SAR study of this compound shows promising developments in discovering novel RMAs for combatting epidemic of antibiotic resistance.

## Result and Discussion

### Antibiotic profiling of Kf18 (**4**)

To assess the scope of Kf18 to potentiate different classes of antibiotics, we used a nosocomial, multi-drug resistant MRSA strain, ATCC BAA-44, which was also used in our primary screen to identify methicillin potentiators [33]. The minimum inhibitory concentrations (MICs) of five  $\beta$ -lactam antibiotics (methicillin, amoxicillin/clavulanic acid, cefazolin, meropenem, and oxacillin) were determined in the absence of Kf18 and with the addition of 20  $\mu$ M of Kf18 (entries 1–5, Table 1). From this experiment we confirmed that BAA-44 is highly resistant to all  $\beta$ -lactam antibiotics tested, and that Kf18 can significantly potentiate all five  $\beta$ -lactams. In addition to  $\beta$ -lactams, strain BAA-44 is also resistant to a number of other classes of antibiotics, such as tetracycline, ciprofloxacin, and clindamycin. The MICs of these antibiotics in the presence and absence of Kf18 were also tested using our established protocols [33, 35, 38]. As shown in Table 1 (entries 6–12), Kf18 does not potentiate these classes of antibiotics. Furthermore, the MIC of Kf18 in ATCC BAA-44 alone was  $>128 \mu\text{g/mL}$ , the highest concentration tested. These results suggested that Kf18 is a selective potentiator of  $\beta$ -lactam antibiotics in MRSA with a novel tetracyclic indoline scaffold.

In order to investigate the SAR of tetracyclic indoline Kf18, several series of structural analogues were synthesized and evaluated for their biological activities. Our evaluation included determining the minimum inhibitory concentrations (MICs) and the minimum re-sensitizing concentrations (MRCs) for two  $\beta$ -lactam antibiotics in two representative MRSA strains (i.e., ATCC BAA-44 and NRS-100 (a.k.a., COL)), as well as assessing mammalian toxicity in human cervical adenocarcinoma (HeLa) cells. The two  $\beta$ -lactams used were cefazolin, a first-generation cephalosporin, and amox/clav (a.k.a., amoxicillin/clavulanic acid and Augmentin), an antibiotic/RMA combination. The MRC is defined as the minimum concentration of the test compound that, in combination with antibiotic, returned MRSA to below the Clinical Laboratory Standards Institutes (CLSI)-defined sensitive concentration [40]. The CLSI-defined sensitive concentrations used for our experiments were 8  $\mu\text{g/mL}$  for cefazolin and 4  $\mu\text{g/mL}$  for amox/clav (2:1 ratio).

### SARs of the D-ring nitrogen functionality

The SAR studies began with the preparation of analogues with changes to the methyl carbamate affixed to the nitrogen of the D ring in Kf18 (Scheme 1). The methyl carbamate was removed in excellent yield by employing  $\text{Me}_3\text{SiI}$  at an elevated temperature. The resulting amine **5** provided a facile entry point into a diverse array of analogues.

First, a few other carbamates were synthesized to explore the importance of methyl carbamate in Kf18. Ethyl and benzyl carbamates **6a** and **6b** were prepared from reacting **5** with their corresponding chloroformates. *Tert*-butyl carbamate, **6c**, was obtained by sequential treatment of **5** with triphosgene and *tert*-butyl alcohol. Switching the methyl carbamate of Kf18 to the ethyl carbamate, **6a**, improved the RMA activity by 8-fold for both cefazolin and amox/clav in both MRSA strains (entry 2, Table 2). **6a** also showed significantly decreased mammalian toxicity. Substituting methyl with benzyl carbamate **6b**, abolished activity (entry 3, Table 2). Further extension of the hydrophobic reach with *tert*-butyl carbamate **6c**, only showed a modest increase in activity compared to Kf18 (entry 4, Table 2).

Next, non-carbamate functional groups were installed on the D-ring nitrogen. Acyl analogues **6d**, **6e**, and **6f** were obtained by acylating amine **5** using their corresponding anhydrides in the presence of base (entries 5–7, Table 2). Acetamide **6d** has slightly lower RMA activity compared to Kf18; other amides, **6e** and **6f**, were devoid of the RMA activity. It is likely that the acetyl group of **6d** is similar but smaller to the methyl carbamate of Kf18. This fits with a “goldilock’s” trend in regard to the D-ring group size, where the relative sizes are:  $\text{MeCO} < \text{MeOCO} < \text{EtOCO} < \text{tBuOCO} < \text{BnOCO}$ , with the most active compound falling in the center.

The *para*-bromophenylsulfonamide motif has been an important component of other RMAs discovered in our lab (**1–3**, Figure 1). Hence, analogue **6g** was prepared. Surprisingly, this derivative displayed >4-fold loss in RMA activity compared to Kf18 (entry 8, Table 2). These results prompted our return to structural analogues with greater similarity to Kf18. In this light, urea is a similar functional group to carbamate in size, yet with higher polarity and metabolic stability. Based on this notion, several urea analogues, **6h–j**, were synthesized by

reacting **5** with commercially available isocyanates (entries 9–11, Table 2). Unsurprisingly, benzyl urea **6h** shows no detectable RMA activity, which is reminiscent of benzyl carbamate **6b**. However, the ethyl urea **6i** was also devoid of the RMA activity. The only urea tested that showed marginal activity was the unsubstituted analogue **6j** (entries 10 and 11, Table 2). This is likely a result of additional hydrogen bond donors on **6j**, which can substitute for favorable hydrophobic interactions of the ethyl carbamate in **6a**. The result observed for **6j**, prompted us to prepare an analogue with a guanidine group, **6k**. This functional group is similar to unsubstituted urea, but it has additional hydrogen bonding capabilities. Furthermore, this group has been crucial to activity in aza-tricyclic indoline RMAs (**3**, Figure 1). This compound showed clear improvement in RMA activity compared to **6j**, but it did not surpass that of Kf18.

To expand on this idea, two analogues were synthesized without the hydrogen bond accepting capabilities found in the methyl and ethyl carbamates. To accomplish this, lithium aluminum hydride was used to reduce compounds **6a** and **6d**, which gave analogues **6l** and **6m**, respectively (entries 14 and 15, Table 2). In fact, when compared to Kf18, these analogues demonstrate slightly improved RMA activity and similar mammalian toxicity. This initial entry into the SAR of Kf18 demonstrated that analogue **6a** with an ethyl carbamate group at the D-ring nitrogen position shows the most potent RMA activity with an 8-fold improvement in MRC activity and a 3-fold improvement in mammalian toxicity over the original screening hit Kf18. Clearly, the ethyl carbamate is ideal for this series of compounds, and it was therefore included along with the methyl carbamate in subsequent SAR studies.

### Additional Modifications of Kf18

In the next phase of the SAR study, the aim was to determine the optimal substitutions on the tetracyclic indoline core. Specifically, several series of analogues were prepared with variations in the aromatic region, the indoline nitrogen, as well as the size of the C ring. This was accomplished by using our previously developed synthetic strategy with minor modifications [33]. In brief, the aromatic substitution is altered by using commercially available phenyl hydrazines with various substitutions and different cyclic imines, **8a** or **8b**, to prepare their corresponding indoles, **9** or **10**, using a modified version of our one-pot three-component Fischer indole synthesis (Scheme 2). These indoles were then cyclized with a cationic gold catalyst to give the characteristic tetracyclic indoline core structure. The aniline nitrogen of cyclized products **11** and **12** could then be alkylated with individual alkyl triflates to afford the desired tetracyclic indoline analogues **13** and **14**, respectively.

In our previous report of the SAR of the tricyclic indoline RMA **1** (Figure 1), we found that alkylating the indoline nitrogen abolishes RMA activity and thus wondered whether this trend would be observed for Kf18 [38]. To explore this, the methyl group of Kf18 was replaced with a larger ethyl group to give compound **13a**. This change resulted in 4- to 8-fold improvement of the RMA activity compared to Kf18 (entry 2, Table 3). However, further increase of the size of the ethyl group to a propargyl group (i.e., **13b**, entry 3, Table 3) was prohibited. Interestingly, removing this alkyl group altogether and replacing it with a mere hydrogen to give compound **11** slightly improved RMA activity, albeit less than **13a**

(entry 4, Table 3). This suggests that the R<sup>3</sup> group is sensitive to the RMA activity, as both larger and smaller groups (ethyl and hydrogen) show improved RMA activity compared to the methyl group.

Next, changes to the aromatic substitution of Kf18 were explored. Analogue **13c** with no substitution on the phenyl ring has significantly reduced RMA activity. Replacing the 4,6-dimethyl group with 5-methyl or 5-chloro to deliver **13d** or **13e** respectively improves the RMA activity by at least 2-fold relative to Kf18 (entries 6 and 7, Table 3). Although the RMA activity was equivalent for these compounds, the 5-chloro derivative **13e** is less toxic to mammalian cells. Further exploration of the substitutions on the 5-position of the indoline shows the 5-fluoro and 5-methoxy substituted analogues (**13f**, **13g**, entries 9 and 10, Table 3) were devoid of RMA activity, despite having the more active ethyl carbamate on the D-ring nitrogen. These results suggest a prominent but unknown reliance on methyl or chloro groups in this class of RMA.

Kf18 has a fused seven membered ring that is not observed in other RMAs we have reported. In addition, this structural motif is a rarity in known indole alkaloid natural products. This information prompted us to reduce the C-ring size to a more common six-member ring **14a**. This analogue shows slightly improved RMA activity compared to Kf18 (entry 11, Table 3). Next, the ring size was decreased with the concomitant change in the aromatic substitution pattern by swapping the 4,6-dimethyl groups of **14a** with 5-methyl and 5-chloro to deliver **14b** and **14c**, respectively. Unexpectedly, these changes do not improve the RMA activity (entries 12 and 13, Table 3). Methyl and chloro groups have similar sizes, and it would be expected that their activity profiles should follow a similar trend; however, replacing the 5-methyl group with a chloro shows activity similar to the dimethyl analogue **14a** (entry 11, Table 3). A notable difference is that the mammalian toxicity for the 5-methyl analogue **14b** is comparable to its MRC in MRSA, while **14a** and **14c** have improved mammalian toxicity with the GI<sub>50</sub> values well above their MRCs. We then asked if changes to the aromatic region would meld with our previously discovered optimal ethyl carbamate on the D ring nitrogen, and synthesized analogues **14d** and **14e** (entry 14 and 15, Table 3). However, these combinatorial changes did not further improve the RMA activity. The ethyl carbamate analogue **6a** remains the best analogue in terms of its RMA activity and mammalian toxicity. It should also be noted that all tetracyclic indoline analogues showed no antibacterial activity at up to 64 µg/mL, the highest concentration tested.

### MRSA Strain Scope Studies

In addition to the two hospital-acquired (HA) MRSA strains, ATCC BAA-44 and NRS100, the best analogue, **6a**, was tested in several additional MRSA strains. MRSA NRS-45898 (a.k.a., NRS70 and N315) possesses the most prevalent U.S. hospital-acquired pulse-field type, USA100, and was endemic in many U.S. hospitals [41]. In recent years, community-acquired (CA) MRSA infections have consistently increased. Both NR-46070 (a.k.a., NRS384) [42] and NR-46231 (a.k.a., NRS702) are classified as USA300 isolates. USA300 isolates are among the most common types of CA-MRSA strains. The MICs of amox/clav in NRS-45898, NRS-46070, and NR-46231 are 16, 16, and 8 µg/mL, respectively, and the MIC of **6a** was >64 µg/mL in all three strains. In combination with 4 µg/mL amox/clav, the MRCs



of **6a** were found to be 2 µg/mL in all three strains, consistent with the MRCs in two previously tested MRSA strains. These results demonstrate that compound **6a** is a potent RMA for β-lactam antibiotics in both HA- and CA-MRSA strains.

In order to assess the synergistic action of **6a** with amox/clav and cefazolin, a checkerboard fractional inhibitory concentration indexes (FICI) evaluation was performed using strain ATCC BAA-44 [43]. The FICIs of **6a** with amox/clav and cefazolin were calculated as 0.127 and 0.078, respectively. Both of these are significantly less than 0.5, suggesting that **6a** has a strong synergistic effect with both antibiotics. In addition, **6a** was tested in a β-lactamase activity/nitrocefin assay using DMSO and clavulanic acid as negative and positive controls, respectively [44]. The results showed that **6a** has no effect on β-lactamase activity at up to 32 µg/mL (i.e., 16xMRC), suggesting that **6a** potentiates β-lactam antibiotics using a novel mechanism.

## Summary

Antibiotic-resistant bacterial infections have seen a marked increase in recent years, while antibiotic discovery has waned. Resistance-modifying agents offer an intriguing alternative strategy to fight against resistant bacteria, as they may further extend the clinic life span of β-lactam antibiotics, one of the best classes of antibiotics developed. Here we report our recent discovery, antibiotic profiling, and structure-activity relationships of a novel class of resistance-modifying agents, tetracyclic indolines. These selectively potentiate β-lactam antibiotics in methicillin-resistant *Staphylococcus aureus* (MRSA) without antibacterial or β-lactamase inhibitory activity on their own. Several series of structural analogues of the screening hit Kf18 have been synthesized and their antibacterial activity, resistance-modifying activity, and mammalian toxicity have been evaluated. The most potent analogue, **6a**, showed strong potentiation of amoxicillin/clavulanic acid in a variety of hospital-acquired and community-acquired MRSA strains with low mammalian toxicity. Although **6a** showed strong synergistic effect with amox/clav and cefazolin, it did not inhibit β-lactamase activity directly, suggesting that the tetracyclic indolines potentiate β-lactams with a novel mechanism. Further development of this novel class of RMA for in vivo studies and mechanistic investigations are ongoing and will be reported.

## Experimental Section

### Bacterial Strains

Strains ATCC BAA-44 (MRSA) was a gift from the laboratory of Daniel Feldheim. Strains NRS100 (MRSA), NRS-45898 (MRSA), NRS-46070 (MRSA), and NRS-702 (MRSA) were purchased from ATCC (<http://www.atcc.org>).

### Microdilution Tests for Minimal Inhibitory Concentration (MIC) Determination

MIC determination was performed as described previously.<sup>38</sup> The minimal inhibitory concentrations (MICs) of active Kf18 analogues were determined by the broth microdilution method detailed in the CLSI handbook. All antimicrobial compounds were purchased from Sigma-Aldrich. The growth media used for all MIC experiments was Mueller–Hinton broth (MHB) purchased from HIMEDIA through VWR (cat. 95039-356). The inoculum was

prepared by diluting a bacterial day culture (OD<sub>600</sub> 0.15–0.4) to OD<sub>600</sub> 0.002. This dilution was further diluted 2-fold when added to 96-well microplates (USA Scientific CytoOne 96-well TC plate, cat. CC7682-7596) for a final inoculum concentration of OD<sub>600</sub> 0.001. All plates were incubated at 37 °C with shaking for 18 h before results were interpreted.

### Minimal Re-sensitizing Concentration (MRC) Determination

MRC screens were performed as described previously.<sup>38</sup> Briefly, antibiotic MIC values where *S. aureus* is considered susceptible were determined from the CLSI handbook supplement. Kf18 analogues were diluted to 10 mg/mL in DMSO. Antibiotic was prepared at twice the intended final concentration in MHB. For amoxicillin/clavulanic acid, the initial concentration was 8/4 µg/mL and for cefazolin 16 µg/mL. A 50 µL portion of the antibiotic containing media was added to each well of 96-well plates, and 100 µL was added to the top row. A 6.4 µL portion of 10 mg/mL alkaloid solution was added to the top row of each plate to afford a concentration of 64 µg/mL in the top row of each plate, and 2-fold serial dilutions were performed down the columns. Once the plates were prepared, a day culture of MRSA was diluted to OD<sub>600</sub> 0.002, and 50 µL was added to each well. The final concentration of MRSA added was OD<sub>600</sub> 0.001, the final concentration of amoxicillin/clavulanic acid was 4/2 µg/mL and the final concentration of cefazolin was 8 µg/mL, and the highest concentration of Kf18 tested was 64 µg/mL. Plates were incubated overnight at 37 °C with shaking. The MRC value was determined as the concentration of Kf18 analogue in the presence of antibiotic at which there was no observable overnight growth.

### Cytotoxicity of Kf18 Analogues in HeLa Cells

To evaluate the cytotoxicity of Kf18 analogues in mammalian cells, a cell viability assay was carried out using a CellTiter-Glo luminescent cell viability assay kit (Promega). Human cervical adenocarcinoma HeLa cells were seeded on white, cell-culture-treated, 96-well plates (Corning 3917) with Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal calf serum (FCS), 1% penicillin/streptomycin, at the densities of 20 000 cells/well. The medium volume for each well was 100 µL. Cells were incubated at 37 °C in 5% CO<sub>2</sub>/95% air for 16 h. The medium was removed from each well and replaced with 99 µL of warmed, fresh medium. To each well, 1 µL of Kf18 analogue was added in DMSO to final concentrations of 0.5–32 µg/mL. Each series was performed in triplicate. After incubation at 37 °C for another 24 h, the plates were equilibrated to room temperature for 30 min, and 100 µL of CellTiter-Glo reagent (Promega) was added to each well and mixed for 2 min on an orbital shaker. The plate was incubated at room temperature for another 10 min to stabilize the luminescent signal. The luminescence of each sample was recorded with an Envision Multilabel Plate Reader (PerkinElmer).

### β-Lactamase Activity Assays

β-lactamase Activity Assays were performed as described previously.<sup>43</sup> An overnight culture of MRSA was grown in MHB and sub-cultured 1:100. Cells were grown to OD<sub>600</sub> of ~0.5. Cells were divided into 5–6 10mL fractions in MHB and incubated 37 °C for 1 hour. Cells were placed on ice and media was separated from cells by centrifugation (3200xg, 4 °C, 30 min). In a UV-optical bottom 96-well plate 1 µl of DMSO; clavulanic acid at 2, 8, and 32



$\mu\text{g/mL}$ ; and **6a** at 2, 8, and 32  $\mu\text{g/mL}$  (1 $\times$ , 4 $\times$ , and 16 $\times$  MRC, respectively), was each added into separate wells, in triplicate. Then, 99  $\mu\text{L}$  of media was added and equilibrated to room temperature before addition of the colorigenic agent, nitrocefin. To each well 1  $\mu\text{L}$  of a 10 mM nitrocefin stock (in DMSO) was added (to afford a final, saturating, concentration of 100  $\mu\text{M}$ ). Nitrocefin hydrolysis was immediately monitored by tracking absorbance at 492 nm in real time using the Perkin Elmer EnVision plate reader. The initial rate of hydrolysis was obtained from the slope of the time course which was linear in the first several minutes of monitoring. This initial rate was used as a proxy from the relative concentration of  $\beta$ -lactamase in the media. DMSO was used as a negative control and clavulanic acid was used as a positive control.

### Fractional Inhibitory Concentration Index (FICI) determination

FICI was calculated as described previously,<sup>42</sup> with the formula  $\text{FICI} = \text{FICA} + \text{FICB}$  and where an FICI  $< 0.5$  indicates synergy. The FICI calculation for amox.clav with **6a** was as follows: FICA equaled the MRC of amox.clav (4  $\mu\text{g/mL}$ ) in combination with **6a** divided by the MIC of amox.clav alone (32  $\mu\text{g/mL}$ ); FICB equaled the MRC of **6a** (2  $\mu\text{g/mL}$ ) in combination with amox.clav divided by MIC of **6a** alone ( $>128$   $\mu\text{g/mL}$ ). The FICI calculation for cefazolin with **6a** was as follows: FICA equaled the MRC of cefazolin (8  $\mu\text{g/mL}$ ) in combination with **6a** divided by the MIC of cefazolin alone (128  $\mu\text{g/mL}$ ); FICB equaled the MRC of **6a** (2  $\mu\text{g/mL}$ ) in combination with cefazolin divided by MIC of **6a** alone ( $>128$   $\mu\text{g/mL}$ ).

### Chemistry

Unless otherwise noted, reagents were obtained commercially and used without further purification.  $\text{CH}_2\text{Cl}_2$  was distilled from  $\text{CaH}_2$  under a nitrogen atmosphere. THF was distilled from sodium–benzophenone under a nitrogen atmosphere. Toluene was distilled from sodium under a nitrogen atmosphere. All chemicals were purchased from Sigma-Aldrich, TCI America, or Alfa Aesar (United States) unless otherwise noted. Thin-layer chromatography (TLC) analysis of reaction mixtures was performed on Dynamic adsorbents silica gel F-254 TLC plates. Flash chromatography was carried out on Zeoprep 60 ECO silica gel.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded with Varian INOVA (400, 500 MHz) spectrometers. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 370 FT-IR spectrometer. Compound purity (>95%) was confirmed on the basis of the integration of the area under the UV absorption curve at  $\lambda = 254$  or 210 nm signals using an Agilent 1260 series HPLC system coupled with a 6120 Quadrupole mass spectrometer (column: ZORBAX Narrow Bore SB-C18 RRHT, 2.1  $\times$  50 mm, 1.8  $\mu\text{m}$ , PN 827700-902). The system was eluted at 0.5 mL/min with a gradient of water/acetonitrile with 0.1% formic acid: 0–5 min, 5–95% acetonitrile; 5–7 min, 95% acetonitrile; 7–7.25 min, 95–5% acetonitrile; 7.25–8.5 min, 5% acetonitrile.

### General Protocol for the One-Pot Three-Component Indole Synthesis (Method A)

The activating agent methyl chloroformate (1.2 equiv) was added to a solution of 4-dimethylaminopyridine (1.2 equiv) in anhydrous DMF at 0  $^\circ\text{C}$ . The reaction was stirred at 23  $^\circ\text{C}$  for 30 min. A solution of the alkynyl imine **8** (1.0 equiv) in anhydrous DMF was

added and the reaction was stirred at the same temperature for 0.5 h. Methanesulfonic acid (3.0 equiv) was next added to the above mixture at 0 °C. The reaction was then stirred at 23 °C for 2 h. Aryl hydrazine **7** (1.5 equiv) was added and the mixture stirred for an additional 1 h at 23 °C. The reaction was then heated to 60–120 °C (60 °C for electron-sufficient hydrazines and 120 °C for electron-deficient aryl hydrazines) for 20 h. The reaction was cooled down to room temperature. The residue was then dissolved in ethyl acetate and washed with brine and a saturated aqueous solution of sodium bicarbonate. The combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo to give a crude product, which was purified by column chromatography on silica gel to give the indole product **9** or **10**.

#### Methyl 2-(2-(hex-5-ynyl)-4,6-dimethyl-1*H*-indol-3-yl) ethyl carbamate (**9a**)

The title compound was synthesized from (3,5-dimethylphenyl)hydrazine hydrochloride (**7a**), compound **8a** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$  = 0.20; light yellow oil, 36%; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.77 (s, 1H), 6.95 (s, 1H), 6.69 (s, 1H), 4.78 (s, 1H), 3.68 (s, 3H), 3.39 (q,  $J$  = 6.8 Hz, 2H), 3.02 (t,  $J$  = 7.3 Hz, 2H), 2.74 (t,  $J$  = 7.7 Hz, 2H), 2.66 (s, 3H), 2.40 (s, 3H), 2.25 (td,  $J$  = 7.0, 2.7 Hz, 2H), 1.99 (t,  $J$  = 2.6 Hz, 1H), 1.82-1.76 (m, 2H), 1.61 (dt,  $J$  = 14.3, 7.1 Hz, 2H); ESI  $m/z$  calcd for C<sub>20</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 327.2, found 327.2; IR (thin film) 3387, 3350, 3309, 2947, 2865, 1700, 1525, 1454, 1376, 1253, 914, 836, 735, 635 cm<sup>-1</sup>.

#### Methyl (2-(2-(hex-5-yn-1-yl)-1*H*-indol-3-yl)ethyl) carbamate (**9c**)

The title compound was synthesized from phenyl hydrazine hydrochloride (**7c**), compound **8a** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$  = 0.20; light yellow oil, 35%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.97 (s, 1H), 7.51 (d,  $J$  = 7.6 Hz, 1H), 7.30-7.26 (m, 1H), 7.13 (td,  $J$  = 7.5, 1.4 Hz, 1H), 7.08 (td,  $J$  = 7.4, 1.3 Hz, 1H), 4.75 (s, 1H), 3.65 (s, 3H), 3.42 (q,  $J$  = 6.7 Hz, 2H), 2.91 (t,  $J$  = 6.9 Hz, 2H), 2.74 (t,  $J$  = 7.6 Hz, 2H), 2.21 (td,  $J$  = 7.0, 2.7 Hz, 2H), 1.96 (t,  $J$  = 2.7 Hz, 1H), 1.85-1.71 (m, 2H), 1.57 (p,  $J$  = 7.0 Hz, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 157.20, 136.14, 135.45, 128.43, 121.41, 119.47, 118.16, 110.54, 108.31, 84.20, 68.88, 52.14, 41.62, 28.97, 27.99, 25.61, 24.80, 18.33; ESI  $m/z$  calcd for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 299.1, found 299.1; IR (thin film) 3402, 3298, 2940, 2862, 1700, 1525, 1465, 1246, 1011, 747 cm<sup>-1</sup>.

#### Methyl (2-(2-(hex-5-yn-1-yl)-5-methyl-1*H*-indol-3-yl)ethyl)carbamate (**9d**)

The title compound was synthesized from *p*-tolylhydrazine hydrochloride (**7d**), compound **8a** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$  = 0.20; light yellow oil, 28%; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.76 (s, 1H), 7.29 (s, 1H), 7.18 (d,  $J$  = 8.2 Hz, 1H), 6.96 (dd,  $J$  = 8.2, 1.5 Hz, 1H), 4.72 (s, 1H), 3.66 (s, 3H), 3.43 (q,  $J$  = 6.7 Hz, 2H), 2.89 (t,  $J$  = 6.9 Hz, 2H), 2.74 (t,  $J$  = 7.6 Hz, 2H), 2.44 (s, 3H), 2.22 (td,  $J$  = 7.0, 2.7 Hz, 2H), 1.97 (t,  $J$  = 2.6 Hz, 1H), 1.86-1.70 (m, 2H), 1.61-1.55 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 157.21, 136.29, 133.75, 128.67, 122.86, 117.94, 110.21, 107.82, 84.22, 68.85, 52.11, 41.61, 28.97, 27.98, 25.64, 24.76, 21.64, 18.32; ESI  $m/z$  calcd for C<sub>19</sub>H<sub>24</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 313.18, found 313.2; IR (thin film) 3300, 2940, 2860, 1700, 1545, 1499, 1410, 1375, 1335, 1250, 1100, 1075, 1040, 945, 785, 630 cm<sup>-1</sup>.

**Methyl (2-(5-chloro-2-(hex-5-yn-1-yl)-1H-indol-3-yl)ethyl)carbamate (9e)**

The title compound was synthesized from 4-chlorophenylhydrazine hydrochloride (**7e**), compound **8a** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$ = 0.20; light yellow oil, 24%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.28 (s, 1H), 7.45 (d,  $J$ = 2.0 Hz, 1H), 7.16 (d,  $J$ = 8.5 Hz, 1H), 7.05 (dd,  $J$ = 8.5, 2.0 Hz, 1H), 4.83 (s, 1H), 3.67 (s, 3H), 3.39 (q,  $J$ = 6.8 Hz, 2H), 2.86 (t,  $J$ = 6.9 Hz, 2H), 2.71 (t,  $J$ = 7.6 Hz, 2H), 2.20 (td,  $J$ = 6.9, 2.7 Hz, 2H), 1.97 (s, 1H), 1.76 (p,  $J$ = 7.7 Hz, 2H), 1.55 (p,  $J$ = 7.1 Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.21, 137.82, 133.77, 129.60, 124.97, 121.38, 117.53, 111.51, 108.07, 84.12, 68.92, 52.17, 41.58, 28.78, 27.92, 25.59, 24.60, 18.24; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  333.1, found 333.1; IR (thin film) 3417, 3301, 2940, 2862, 1700, 1525, 1491, 1477, 1447, 1294, 1089, 829, 803, 780  $\text{cm}^{-1}$ .

**Ethyl (2-(5-fluoro-2-(hex-5-yn-1-yl)-1H-indol-3-yl) ethyl)carbamate (9f)**

The title compound was synthesized from 4-fluorophenylhydrazine hydrochloride hydrochloride (**7f**), compound **8a** and ethyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$ = 0.20; light yellow oil, 20%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.37 (s, 1H), 7.14 (ddd,  $J$ = 9.8, 5.9, 3.4 Hz, 2H), 6.83 (td,  $J$ = 9.1, 2.5 Hz, 1H), 4.84 (d,  $J$ = 6.1 Hz, 1H), 4.11 (tt,  $J$ = 7.1, 3.6 Hz, 2H), 3.37 (q,  $J$ = 6.7 Hz, 2H), 2.85 (t,  $J$ = 6.9 Hz, 2H), 2.70 (t,  $J$ = 7.6 Hz, 2H), 2.18 (td,  $J$ = 6.9, 2.7 Hz, 2H), 1.95 (t,  $J$ = 2.7 Hz, 1H), 1.75 (p,  $J$ = 7.6 Hz, 2H), 1.54 (p,  $J$ = 7.1 Hz, 2H), 1.29-1.22 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  171.41, 158.91, 156.83, 156.59, 138.21, 131.91, 128.90, 128.80, 111.07, 110.97, 109.27, 109.01, 108.44, 103.15, 102.91, 84.12, 68.85, 60.80, 41.44, 28.79, 27.91, 25.63, 24.72, 21.11, 18.20, 14.71, 14.21; ESI  $m/z$  calcd for  $\text{C}_{19}\text{H}_{23}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  331.2, found 331.2; IR (thin film) 3406, 3290, 3271, 2951, 2858, 1704, 1525, 1495, 1461, 1447, 1264, 1234, 1104, 1033, 866, 780, 650, 553  $\text{cm}^{-1}$ .

**Ethyl (2-(5-fluoro-2-(hex-5-yn-1-yl)-6-methoxy-1H-indol-3-yl)ethyl)carbamate (9g)**

The title compound was synthesized from 4-fluoro-3-methoxyphenylhydrazine hydrochloride (**7g**), compound **8a** and ethyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.0:1 v/v)  $R_f$ = 0.20; light yellow oil, 28%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (s, 1H), 7.16 (d,  $J$ = 11.7 Hz, 1H), 6.84 (d,  $J$ = 7.1 Hz, 1H), 4.87 (t,  $J$ = 6.0 Hz, 1H), 4.16-4.08 (m, 3H), 3.84 (s, 3H), 3.37 (q,  $J$ = 6.7 Hz, 2H), 2.82 (t,  $J$ = 6.9 Hz, 2H), 2.68 (t,  $J$ = 7.5 Hz, 2H), 2.18 (td,  $J$ = 6.9, 2.6 Hz, 2H), 1.95 (t,  $J$ = 2.6 Hz, 1H), 1.81-1.66 (m, 2H), 1.61-1.46 (m, 2H), 1.31-1.18 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  156.82, 150.35, 147.23, 144.18, 143.99, 135.93, 131.26, 121.28, 121.17, 108.17, 104.24, 103.97, 95.83, 95.81, 84.15, 68.80, 60.77, 56.81, 41.52, 28.94, 27.90, 25.58, 24.78, 18.20, 14.71; ESI  $m/z$  calcd for  $\text{C}_{20}\text{H}_{25}\text{FN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  361.2, found 361.2; IR (thin film) 3301, 2940, 2862, 1696, 1521, 1484, 1357, 1327, 1249, 1160, 1037, 1070, 858, 780, 631  $\text{cm}^{-1}$ .

**Methyl (2-(4,6-dimethyl-2-(pent-4-yn-1-yl)-1H-indol-3-yl)ethyl)carbamate (10a)**

The title compound was synthesized from (3,5-dimethylphenyl)-hydrazine hydrochloride (**7a**), compound **8b** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f$ = 0.20; yellow oil, 35%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (s, 1H), 6.92 (s, 1H), 6.67 (s, 1H), 4.78 (s, 1H), 3.66 (s, 3H), 3.37 (q,  $J$ = 6.8 Hz, 2H), 3.01 (t,  $J$ = 7.2

Hz, 2H), 2.83 (t,  $J = 7.4$  Hz, 2H), 2.64 (s, 3H), 2.38 (s, 3H), 2.22 (td,  $J = 6.9, 2.7$  Hz, 2H), 2.05 (t,  $J = 2.6$  Hz, 1H), 1.84 (p,  $J = 7.1$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.18, 136.24, 134.70, 131.25, 129.53, 124.42, 123.30, 109.01, 108.52, 83.94, 69.62, 52.17, 43.34, 28.57, 26.03, 24.51, 21.48, 20.18, 17.92; ESI  $m/z$  calcd for  $\text{C}_{19}\text{H}_{24}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  313.1, found 313.2; IR (thin film) 3379, 3301, 2955, 1681, 1599, 1511, 1451, 1372, 1212, 1078, 1045, 914, 780  $\text{cm}^{-1}$ .

#### Methyl (2-(5-methyl-2-(pent-4-yn-1-yl)-1H-indol-3-yl)ethyl)carbamate (10b)

The title compound was synthesized from *p*-tolylhydrazine hydrochloride (**7d**), compound **8b** and methyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.5:1 v/v)  $R_f = 0.20$ ; yellow oil, 29%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.29 (s, 1H), 7.44 (d,  $J = 2.0$  Hz, 1H), 7.16 (d,  $J = 8.5$  Hz, 1H), 7.04 (dd,  $J = 8.6, 2.0$  Hz, 1H), 4.81 (bs, 1H), 3.65 (s, 3H), 3.38 (q,  $J = 6.7$  Hz, 2H), 2.84 (dt,  $J = 16.5, 7.2$  Hz, 4H), 2.18 (td,  $J = 6.9, 2.7$  Hz, 2H), 2.09-2.00 (m, 1H), 1.83 (p,  $J = 7.1$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.21, 137.08, 133.82, 129.58, 125.04, 121.53, 117.62, 111.57, 108.53, 83.68, 69.72, 52.18, 41.60, 28.36, 24.66, 24.60, 17.87; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  299.2, found 299.2.

#### Methyl (2-(5-methyl-2-(pent-4-yn-1-yl)-1H-indol-3-yl)ethyl)carbamate (10c)

The title compound was synthesized from 4-chlorophenylhydrazine hydrochloride (**7e**), compound **8b** and methyl chloroformate through **Method A**. TLC hexanes:ethyl acetate, 2.0:1 v/v)  $R_f = 0.20$ ; yellow oil, 20%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.31 (s, 1H), 7.46 (d,  $J = 2.0$  Hz, 1H), 7.17 (d,  $J = 8.5$  Hz, 1H), 7.06 (dd,  $J = 8.6, 2.0$  Hz, 1H), 4.83 (s, 1H), 3.67 (s, 3H), 3.40 (q,  $J = 6.7$  Hz, 2H), 2.86 (dt,  $J = 16.5, 7.2$  Hz, 4H), 2.20 (td,  $J = 6.9, 2.7$  Hz, 2H), 2.11-1.99 (m, 1H), 1.85 (p,  $J = 7.1$  Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  157.21, 137.08, 133.82, 129.58, 125.04, 121.53, 117.62, 111.57, 108.53, 83.68, 69.72, 52.18, 41.60, 28.36, 24.66, 24.60, 17.87; ESI  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  319.1, found 319.2.

#### Ethyl (2-(5-chloro-2-(pent-4-yn-1-yl)-1H-indol-3-yl)ethyl)carbamate (10e)

The title compound was synthesized from 4-chlorophenylhydrazine hydrochloride (**7e**), compound **8b** and ethyl chloroformate through **Method A**. TLC (hexanes:ethyl acetate, 2.0:1 v/v)  $R_f = 0.20$ ; yellow oil, 23%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.61 (s, 1H), 7.45 (d,  $J = 2.0$  Hz, 1H), 7.14 (d,  $J = 8.5$  Hz, 1H), 7.03 (dd,  $J = 8.5, 2.0$  Hz, 1H), 4.90 (t,  $J = 6.1$  Hz, 1H), 4.11 (qd,  $J = 7.1, 2.8$  Hz, 2H), 3.38 (q,  $J = 6.7$  Hz, 2H), 2.86 (t,  $J = 6.9$  Hz, 2H), 2.80 (t,  $J = 7.5$  Hz, 2H), 2.16 (td,  $J = 6.9, 2.7$  Hz, 2H), 2.02 (t,  $J = 2.6$  Hz, 1H), 1.82 (p,  $J = 7.1$  Hz, 2H), 1.26-1.15 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.82, 137.10, 133.83, 129.52, 124.77, 121.28, 117.48, 111.54, 108.37, 83.65, 69.55, 60.82, 41.49, 28.30, 24.65, 24.55, 17.81, 14.66; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  333.1, found 333.1.

#### General Protocol for Gold(I)-Catalyzed Tandem Cyclization (Method B)

To a suspension of  $\text{Ph}_3\text{PAuNTf}_2$  (as the 2:1 toluene adduct) (0.05 equiv) in anhydrous toluene was added a solution of indole **9** or **10** (1.0 equiv) in anhydrous toluene. The suspension was heated to 50 °C until TLC showed that there was no starting material left (1–12 h) under argon atmosphere. The reaction mixture was then filtered through a short pad of

silica gel. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel to afford tetracyclic indoline product **11** or **12**.

**Methyl 1,3-dimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)-cyclohepta[b] indole-13-carboxylate (11a)**

The title compound was synthesized through Method B from compound **9a**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; white solid, 67%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.35 (s, 1H), 6.32 (s, 1H), 5.61 (s, 1H), 5.02 (s, 1H), 5.00 (s, 1H), 3.63 (s, 3H), 3.57 (dd,  $J$ = 10.2, 8.1 Hz, 1H), 3.06-3.01 (m, 1H), 2.60-2.54 (m, 2H), 2.31-2.26 (m, 1H), 2.24 (s, 3H), 2.19 (s, 3H), 2.09-2.06 (m, 1H), 1.98-1.89 (m, 1H), 1.84-1.81 (m, 1H), 1.73-1.68 (m, 1H), 1.61-1.53 (m, 2H), 1.29-1.20 (m, 1H); ESI  $m/z$  calcd for  $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  327.2, found 327.2; IR (thin film) 3383, 2944, 2918, 2877, 2858, 1681, 1451, 1376, 1287, 1212, 1197, 1045, 981, 836, 780, 747  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)-cyclohepta[b] indole-13-carboxylate (11c)**

The title compound was synthesized through Method B from compound **9c**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; colorless oil, 74%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (td,  $J$ = 7.6, 1.3 Hz, 1H), 6.94 (dd,  $J$ = 7.5, 1.3 Hz, 1H), 6.73 (td,  $J$ = 7.4, 1.0 Hz, 1H), 6.64 (d,  $J$ = 7.8 Hz, 1H), 5.68 (s, 1H), 4.99 (s, 1H), 4.82 (s, 1H), 3.62 (s, 3H), 3.56 (dt,  $J$ = 8.9, 5.3 Hz, 1H), 3.03-2.85 (m, 1H), 2.67-2.58 (m, 1H), 2.40-2.28 (m, 2H), 2.07 (ddd,  $J$ = 12.7, 5.7, 2.4 Hz, 1H), 2.01-1.86 (m, 1H), 1.81 (dd,  $J$ = 10.5, 5.4 Hz, 1H), 1.74-1.65 (m, 1H), 1.65-1.46 (m, 2H), 1.31-1.12 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.75, 154.15, 149.41, 131.44, 128.48, 123.57, 119.02, 110.94, 109.85, 90.14, 64.42, 51.95, 46.03, 33.40, 32.94, 32.71, 32.16, 24.45; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  299.1, found 299.2; IR (thin film) 3387, 3305, 2925, 2854, 1689, 1599, 1410, 1354, 1331, 1212, 1108, 1078, 702  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-2-methyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclo-hepta[b]indole-13-carboxylate (11d)**

The title compound was synthesized through Method B from **9d**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; white solid, 70%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.87 (dd,  $J$ = 7.9, 1.8 Hz, 1H), 6.74 (d,  $J$ = 1.8 Hz, 1H), 6.55 (d,  $J$ = 7.8 Hz, 1H), 5.57 (s, 1H), 4.98 (s, 1H), 4.82 (s, 1H), 3.61 (s, 3H), 3.55 (ddd,  $J$ = 10.2, 6.6, 2.3 Hz, 1H), 2.94 (td,  $J$ = 10.6, 7.4 Hz, 1H), 2.61 (dd,  $J$ = 14.6, 5.8 Hz, 1H), 2.39-2.29 (m, 3H), 2.15-2.00 (m, 1H), 1.92 (td,  $J$ = 14.9, 14.1, 3.4 Hz, 1H), 1.82 (d,  $J$ = 13.2 Hz, 1H), 1.77-1.66 (m, 1H), 1.64-1.46 (m, 2H), 1.31-1.10 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.71, 154.39, 147.13, 131.60, 128.97, 128.24, 124.13, 110.79, 109.70, 90.46, 64.41, 51.90, 46.00, 33.43, 32.97, 32.64, 32.23, 24.46, 21.02; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  313.2, found 313.2; IR (thin film) 3357, 2944, 2921, 2854, 1678, 1451, 1376, 1346, 1201, 1127, 981, 907, 858, 780  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-2-chloro-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epimino-ethano)cyclo-hepta[b]indole-13-carboxylate (11e)**

The title compound was synthesized through Method B from compound **9e**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; white solid, 71%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.01 (dd,  $J$ = 8.3, 2.2 Hz, 1H), 6.88 (d,  $J$ = 2.2 Hz, 1H), 6.55 (d,  $J$ = 8.3 Hz, 1H), 5.68 (s, 1H), 4.99 (s, 1H), 4.85 (s, 1H), 3.62 (s, 3H), 3.57 (ddd,  $J$ = 10.2, 6.5, 2.4 Hz, 1H), 2.95 (td,  $J$ = 10.4, 7.7 Hz, 1H), 2.69-2.54 (m, 1H), 2.40-2.27 (m, 2H), 2.16-2.01 (m, 1H), 1.98-1.74 (m, 2H), 1.73-1.47 (m, 3H), 1.31-1.13 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.74, 153.42, 147.98, 133.50, 128.41, 123.89, 123.47, 111.62, 110.77, 90.56, 64.50, 52.05, 45.99, 33.40, 32.92, 32.67, 32.07, 24.40; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  333.1, found 333.2; IR (thin film) 3383, 2929, 2884, 2854, 1685, 1447, 1369, 1197, 1164, 978, 899, 814, 780  $\text{cm}^{-1}$ .

**Ethyl (5aR,10aS)-2-fluoro-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epimino-ethano)cyclo-hepta[b]indole-13-carboxylate (11f)**

The title compound was synthesized through Method B from compound **9f**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; white solid, 78%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.75 (td,  $J$ = 8.8, 2.7 Hz, 1H), 6.65 (dd,  $J$ = 8.3, 2.6 Hz, 1H), 6.53 (dd,  $J$ = 8.5, 4.2 Hz, 1H), 5.60 (s, 1H), 4.98 (d,  $J$ = 1.2 Hz, 1H), 4.84 (d,  $J$ = 1.1 Hz, 1H), 4.28-3.91 (m, 2H), 3.59 (ddd,  $J$ = 10.3, 7.1, 1.9 Hz, 1H), 3.08-2.85 (m, 1H), 2.61 (ddt,  $J$ = 14.7, 6.1, 1.6 Hz, 1H), 2.39-2.22 (m, 2H), 2.08 (ddd,  $J$ = 12.7, 5.7, 2.5 Hz, 1H), 1.99-1.76 (m, 2H), 1.75-1.65 (m, 1H), 1.65-1.45 (m, 2H), 1.20 (t,  $J$ = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.31, 155.97, 154.38, 153.65, 145.45, 133.20, 133.13, 114.88, 114.65, 111.42, 110.90, 110.66, 110.11, 110.03, 90.76, 64.65, 60.75, 45.91, 33.35, 33.04, 32.64, 32.11, 24.38, 14.69; ESI  $m/z$  calcd for  $\text{C}_{19}\text{H}_{23}\text{FN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  331.1, found 331.1; IR (thin film) 3383, 2930, 2877, 2854, 1677, 1491, 1413, 1380, 1350, 1290, 1182, 1111, 1007, 959, 862, 813, 784, 657, 571, 530.

**Ethyl (5aR,10aS)-2-fluoro-3-methoxy-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epimino-ethano)cyclohepta[b]indole-13-carboxylate (11g)**

The title compound was synthesized through Method B from **9g**. TLC (hexanes:ethyl acetate, 8:1 v/v)  $R_f$ = 0.20; white solid, 71%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.65 (d,  $J$ = 10.6 Hz, 1H), 6.29 (d,  $J$ = 7.0 Hz, 1H), 5.61 (s, 1H), 4.94 (t,  $J$ = 1.1 Hz, 1H), 4.80 (d,  $J$ = 1.1 Hz, 1H), 4.16-3.95 (m, 2H), 3.82 (s, 3H), 3.64-3.50 (m, 1H), 3.05-2.87 (m, 1H), 2.65-2.52 (m, 1H), 2.36-2.17 (m, 2H), 2.13-2.03 (m, 1H), 1.97-1.76 (m, 2H), 1.73-1.42 (m, 3H), 1.21 (t,  $J$ = 7.1 Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.46, 153.87, 148.35, 147.89 (d,  $J$ = 12.1 Hz), 145.44 (d,  $J$ = 1.8 Hz), 122.27 (d,  $J$ = 6.0 Hz), 145.23, 111.30, 111.09, 111.03, 96.02, 90.76, 64.35, 60.74, 56.35, 45.96, 33.31, 33.04, 32.49, 32.07, 24.42, 14.70; ESI  $m/z$  calcd for  $\text{C}_{20}\text{H}_{25}\text{FN}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  361.2, found 361.2.

**Methyl (4bS,8aR)-2,4-dimethyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epimino-ethano)carbazole-10-carboxylate (12a)**

The title compound was synthesized through Method B from compound **10a**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$ = 0.20; white solid, 90%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.35 (d,  $J$ = 0.8 Hz, 1H), 6.32 (s, 1H), 5.42 (s, 2H), 4.91 (d,  $J$ = 1.4 Hz, 2H), 4.73 (s, 2H),



3.74-3.54 (m, 4H), 3.21-3.08 (m, 1H), 2.64-2.56 (m, 1H), 2.53-2.44 (m, 1H), 2.34-2.28 (m, 1H), 2.26 (s, 3H), 2.20 (s, 3H), 2.17-2.11 (m, 2H), 1.69-1.62 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  154.79, 149.73, 147.90, 138.18, 135.17, 125.11, 122.57, 112.00, 109.11, 89.08, 61.21, 51.85, 46.38, 30.61, 30.16, 30.09, 22.83, 21.42, 18.53; ESI  $m/z$  calcd for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  313.2, found 313.0.

#### Methyl (4bS,8aR)-3-methyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)-carbazole-10-carboxylate (12b)

The title compound was synthesized through **Method B** from compound **10b**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$  = 0.20; white solid, 64%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.88 (dd,  $J$  = 7.7, 1.7 Hz, 1H), 6.57 (d,  $J$  = 7.8 Hz, 1H), 6.95 (d,  $J$  = 5.46 (s, 1H), 4.87 (s, 1H), 4.80 (s, 1H), 3.73-3.51 (m, 4H), 3.17-3.03 (m, 1H), 2.74-2.53 (m, 1H), 2.35-2.12 (m, 7H), 1.72-1.54 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.73, 148.74, 146.56, 131.99, 128.66, 128.03, 125.28, 125.24, 112.07, 112.00, 110.60, 89.11, 59.75, 51.84, 46.41, 32.02, 31.67, 31.07, 23.09, 21.09; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  299.2, found 299.1.

#### Methyl (4bS,8aR)-3-chloro-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)-carbazole-10-carboxylate (12c)

The title compound was synthesized through **Method B** from compound **10c**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$  = 0.20; white solid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.10 (d,  $J$  = 2.1 Hz, 1H), 7.03 (dd,  $J$  = 8.3, 2.1 Hz, 1H), 6.58 (d,  $J$  = 8.3 Hz, 1H), 5.56 (s, 1H), 4.90 (s, 1H), 4.79 (s, 1H), 3.76-3.49 (m, 4H), 3.22-3.01 (m, 1H), 2.77-2.50 (m, 1H), 2.41-2.10 (m, 3H), 1.78-1.47 (m, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.74, 147.93, 147.56, 133.85, 128.18, 124.84, 123.46, 112.44, 111.66, 89.23, 59.87, 52.00, 46.39, 31.98, 31.53, 30.93, 22.90; ESI  $m/z$  calcd for  $\text{C}_{17}\text{H}_{19}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  319.1, found 319.1.

#### Ethyl (4bS,8aR)-3-chloro-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)carbazole-10-carboxylate (12e)

The title compound was synthesized through **Method B** from compound **10e**. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$  = 0.20; white solid, 74%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.07 (s, 1H), 7.00 (d,  $J$  = 8.3 Hz, 1H), 6.55 (d,  $J$  = 8.3 Hz, 1H), 5.56 (s, 2H), 4.87 (s, 1H), 4.77 (s, 2H), 4.22-3.93 (m, 2H), 3.64-3.52 (m, 1H), 3.15-3.02 (m, 1H), 2.72-2.52 (m, 1H), 2.33-2.09 (m, 4H), 1.70-1.52 (m, 3H), 1.16 (t,  $J$  = 7.1 Hz, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.35, 147.96, 147.59, 133.85, 128.09, 124.76, 123.32, 112.28, 111.54, 89.08, 60.67, 59.84, 46.31, 31.92, 31.48, 30.87, 22.82, 14.60; ESI  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  333.1, found 333.1.

#### General protocol for alkylation reaction of indoline (Method C)

To a solution of tetracyclic indoline (**11** or **12**) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.050 M) was added ROTf (MeOTf or EtOTf, 10 equiv) at  $0^\circ\text{C}$ . The resulting mixture was stirred at  $0-23^\circ\text{C}$  for 2-12 h under argon. Then, the mixture is quenched by aqueous  $\text{NaHCO}_3$ , diluted by ethyl acetate, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, concentration in vacuo. The residue is purified by column chromatography on silica gel to give product **13** or **14**.

**Methyl (5aR,10aS)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (4)**

The title compound was synthesized through Method C from compound **11a** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f = 0.20$ ; white solid, 86%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (s, 1H), 6.10 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 3.72-3.41 (m, 5H), 3.05-3.00 (m, 4H), 2.41 (dd,  $J = 12.3, 5.0$  Hz, 1H), 2.28 (s, 3H), 2.26-2.19 (m, 1H), 2.16 (s, 3H), 2.13-2.10 (m, 1H), 1.76-1.69 (m, 3H), 1.57-1.45 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  155.30, 151.86, 151.14, 138.38, 133.88, 123.55, 121.36, 112.73, 104.17, 93.88, 65.48, 51.96, 47.10, 33.39, 32.46, 32.08, 31.49, 31.09, 24.29, 22.85, 21.73, 17.22, 14.30; ESI  $m/z$  calcd for  $\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  341.2, found 341.2; IR (thin film) 2925, 2854, 1704, 1596, 1443, 1361, 1190, 1104, 963, 903, 817, 776  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-5-ethyl-1,3-dimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (13a)**

The title compound was synthesized through Method C from **11a** and EtOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f = 0.20$ ; colorless oil, 25%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.20 (s, 1H), 6.08 (s, 3H), 5.01 (s, 2H), 4.96 (s, 4H), 3.71-3.46 (m, 7H), 3.08-3.01 (m, 1H), 2.32-2.19 (m, 5H), 2.17-2.12 (m, 1H), 2.10 (s, 3H), 1.71-1.60 (m, 4H), 1.48-1.41 (m, 1H), 1.32-1.27 (m, 1H), 1.14 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.00, 150.73, 150.45, 138.06, 133.86, 124.59, 120.53, 113.36, 104.48, 94.34, 65.72, 51.94, 46.78, 38.16, 33.76, 32.03, 31.81, 23.81, 21.81, 17.54, 12.88; ESI  $m/z$  calcd for  $\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  355.2, found 355.0; IR (thin film) 2925, 2858, 1704, 1596, 1443, 1361, 1186, 1104, 1045, 981, 896, 821, 806, 776  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-5-methyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (13c)**

The title compound was synthesized through Method C from compound **11c** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f = 0.20$ ; white solid, 50%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.19-7.09 (m, 1H), 6.92-6.83 (m, 1H), 6.68 (t,  $J = 7.3$  Hz, 1H), 6.41 (d,  $J = 7.8$  Hz, 1H), 5.02 (s, 1H), 4.85 (s, 1H), 3.72-3.46 (m, 5H), 3.02-2.92 (m, 4H), 2.37-2.19 (m, 2H), 2.19-2.13 (m, 1H), 1.79-1.61 (m, 2H), 1.64-1.51 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.26, 153.65, 151.25, 130.86, 128.70, 122.79, 117.56, 111.09, 105.42, 93.60, 65.35, 52.02, 46.88, 33.63, 33.26, 32.14, 31.45, 29.87, 24.44; ESI  $m/z$  calcd for  $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  313.2, found 313.2; IR (thin film) 2925, 2892, 2858, 1700, 1611, 1436, 1366, 1346, 1197, 1108, 959, 892, 776, 736  $\text{cm}^{-1}$ .

**Methyl (5aR,10aS)-2,5-dimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (13d)**

The title compound was synthesized through Method C from compound **11d** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f = 0.20$ ; white solid, 83%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.97-6.86 (m, 1H), 6.67 (d,  $J = 1.8$  Hz, 1H), 6.30 (d,  $J = 7.8$  Hz, 1H), 5.00 (s, 1H), 4.83 (s, 1H), 3.76-3.63 (m, 2H), 3.58 (s, 3H), 2.98 (s, 3H), 2.91 (dt,  $J = 11.4, 5.4$  Hz, 1H), 2.39-2.15 (m, 5H), 2.14-2.06 (m, 1H), 1.82-1.47 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.27, 153.91, 149.20, 130.95, 128.95, 126.72, 123.56, 110.89, 105.25, 93.86, 65.32,

51.99, 46.91, 33.64, 33.20, 32.21, 31.56, 29.88, 24.46, 20.94; ESI  $m/z$  calcd for  $C_{20}H_{26}N_2O_2$   $[M + H]^+$  327.2, found 327.2; IR (thin film) 2929, 2880, 2858, 1707, 1503, 1443, 1357, 1339, 1283, 1104, 963, 858, 810,  $776\text{ cm}^{-1}$ .

**Methyl (5aR,10aS)-2-chloro-5-methyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (13e)**

The title compound was synthesized through Method C from compound **11e** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$ = 0.20; white solid, 50%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.04 (dd,  $J$ = 8.3, 2.2 Hz, 1H), 6.79 (d,  $J$ = 2.2 Hz, 1H), 6.27 (d,  $J$ = 8.3 Hz, 1H), 4.99 (s, 1H), 4.85 (s, 1H); 3.71-3.39 (m, 5H), 2.97-2.88 (m, 4H), 2.29-2.21 (m, 1H), 2.16-2.08 (m, 2H), 1.76-1.67 (m, 2H), 1.53-1.42 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.22, 152.91, 149.86, 132.82, 128.46, 123.19, 111.79, 106.20, 93.82, 65.35, 52.11, 46.84, 33.66, 33.21, 32.04, 31.54, 29.86, 24.39; ESI  $m/z$  calcd for  $C_{19}H_{23}ClN_2O_2$   $[M+H]^+$  347.1, found 347.2; IR (thin film) 2948, 2925, 2884, 2858, 1693, 1491, 1443, 1365, 1343, 1275, 1197, 1115, 974, 903, 810,  $791\text{ cm}^{-1}$ .

**Ethyl (5aR,10aS)-2-fluoro-5-methyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epimino-ethano)cyclohepta[b]indole-13-carboxylate (13f)**

The title compound was synthesized through Method C from compound **11f** and EtOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$ = 0.20; colorless oil, 89%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.80 (td,  $J$ = 8.9, 2.6 Hz, 1H), 6.61 (dd,  $J$ = 8.2, 2.6 Hz, 1H), 6.26 (dd,  $J$ = 8.6, 4.0 Hz, 1H), 5.00 (d,  $J$ = 1.1 Hz, 1H), 4.86 (s, 1H), 4.02 (s, 0H), 3.72 (t,  $J$ = 9.2 Hz, 1H), 3.45 (s, 1H), 3.09-2.83 (m, 4H), 2.26 (td,  $J$ = 12.2, 7.7 Hz, 1H), 2.17-2.08 (m, 2H), 1.73 (dddd,  $J$ = 30.1, 16.0, 7.1, 3.2 Hz, 1H), 1.56-1.48 (m, 2H), 1.35-1.17 (m, 5H); ESI  $m/z$  calcd for  $C_{20}H_{25}FN_2O_2$   $[M+H]^+$  345.2, found 345.2.

**Ethyl (5aR,10aS)-2-fluoro-3-methoxy-5-methyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (13g)**

The title compound was synthesized through Method C from compound **11g** and EtOTf. TLC (hexanes:ethyl acetate, 8:1 v/v)  $R_f$ = 0.20; white solid, 93%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.61 (d,  $J$ = 10.5 Hz, 1H), 6.02 (d,  $J$ = 6.8 Hz, 1H), 4.96 (s, 1H), 4.83 (s, 1H), 4.07-4.01 (m, 2H), 3.89 (s, 3H), 3.71 (t,  $J$ = 9.2 Hz, 1H), 3.42 (s, 1H), 3.06-2.86 (m, 5H), 2.24 (td,  $J$ = 12.2, 7.7 Hz, 1H), 2.10 (dt,  $J$ = 11.9, 4.9 Hz, 2H), 1.84-1.66 (m, 2H), 1.59-1.45 (m, 3H), 1.35-1.17 (m, 5H); ESI  $m/z$  calcd for  $C_{21}H_{27}FN_2O_3$   $[M+H]^+$  375.2, found 375.2.

**Methyl (4bS,8aR)-2,4,9-trimethyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epimino-ethano)carbazole-10-carboxylate (14a)**

The title compound was synthesized through Method C from compound **12a** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$ = 0.20; colorless oil, 64%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.21 (s, 1H), 6.03 (s, 1H), 4.95 (s, 1H), 4.89 (s, 1H), 3.75-3.55 (m, 4H), 3.15 (td,  $J$ = 10.3, 6.2 Hz, 1H), 2.99-2.77 (m, 4H), 2.42-2.32 (m, 1H), 2.23 (s, 4H), 2.18 (s, 4H), 1.97 (dt,  $J$ = 14.4, 8.2 Hz, 1H), 1.87 (td,  $J$ = 14.7, 12.8, 5.6 Hz, 1H), 1.54-1.45 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  155.39, 151.41, 147.76, 138.36, 134.21, 124.07, 120.77, 111.33, 104.36, 92.53, 61.97, 52.06, 46.61, 31.34, 30.45, 29.57, 26.79, 21.74, 20.71, 17.89; ESI  $m/z$

calcd for  $C_{19}H_{24}N_2O_2$   $[M+H]^+$  327.2, found 327.2; IR (thin film) 2948, 2869, 1704, 1596, 1443, 1369, 1201, 1123, 896, 821, 736  $cm^{-1}$ .

**Methyl (4bS,8aR)-3,9-dimethyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)-carbazole-10-carboxylate (14b)**

The title compound was synthesized through Method C from compound **12b** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$  = 0.20; colorless oil, 50%;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.91 (d,  $J$  = 7.8 Hz, 1H), 6.79 (s, 1H), 6.28 (d,  $J$  = 7.9 Hz, 1H), 4.92 (d,  $J$  = 13.0 Hz, 2H), 3.70-3.61 (m, 4H), 3.22-3.15 (m, 1H), 2.94 (s, 3H), 2.29-2.14 (m, 7H), 2.08-2.00 (m, 1H), 1.61-1.49 (m, 2H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  155.46, 148.53, 148.21, 131.24, 128.85, 126.37, 123.80, 110.66, 106.07, 92.80, 61.03, 52.04, 47.15, 33.14, 30.69, 30.61, 27.06, 21.22, 20.95; ESI  $m/z$  calcd for  $C_{19}H_{24}N_2O_2$   $[M+H]^+$  313.2, found 313.2; IR (thin film) 2947, 2921, 2892, 1711, 1502, 1450, 1368, 1216, 1178, 1108, 992, 955, 776  $cm^{-1}$ .

**Methyl (4bS,8aR)-3-chloro-9-methyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)carbazole-10-carboxylate (14c)**

The title compound was synthesized through Method C from compound **12c** and MeOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$  = 0.20; colorless oil, 65%;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.03 (dd,  $J$  = 8.3, 2.2 Hz, 1H), 6.90 (d,  $J$  = 2.2 Hz, 1H), 6.25 (d,  $J$  = 8.2 Hz, 1H), 4.92 (d,  $J$  = 13.0 Hz, 2H), 3.70-3.61 (m, 4H), 3.22-3.15 (m, 1H), 2.94 (s, 3H), 2.29-2.14 (m, 4H), 2.08-2.00 (m, 1H), 1.61-1.49 (m, 2H); ESI  $m/z$  calcd for  $C_{18}H_{21}ClN_2O_2$   $[M+H]^+$  333.1, found 333.1.

**Ethyl (4bS,8aR)-3,9-dimethyl-5-methylene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)-carbazole-10-carboxylate (14d)**

The title compound was prepared through deprotecting methyl carbamate of compound **14b**, ethyl carbonylation reaction with  $ClCOOEt$ . TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$  = 0.20; colorless oil;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.91 (d,  $J$  = 7.8 Hz, 1H), 6.79 (s, 1H), 6.28 (d,  $J$  = 7.9 Hz, 1H), 4.94 (s, 1H), 4.90 (s, 1H), 4.22-4.01 (m, 2H), 3.74-3.58 (m, 1H), 3.22-3.10 (m, 1H), 2.93 (s, 3H), 2.29-2.13 (m, 7H), 2.07-2.00 (m, 1H), 1.53-1.47 (m, 2H), 1.20 (t,  $J$  = 7.1 Hz, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  155.12, 148.60, 148.26, 131.35, 128.85, 126.38, 123.81, 110.62, 106.08, 92.79, 61.09, 60.69, 47.19, 33.17, 30.76, 30.68, 27.10, 21.24, 20.98, 14.80; ESI  $m/z$  calcd for  $C_{20}H_{26}N_2O_2$   $[M+H]^+$  327.2, found 327.2; IR (thin film) 2933, 2865, 1704, 1502, 1406, 1380, 1335, 1212, 1115, 1070, 951, 802, 771  $cm^{-1}$ .

**Ethyl (4bS,8aR)-3-chloro-9-methyl-5-methyl-ene-5,6,7,8-tetrahydro-9H-8a,4b-(epiminoethano)-carbazole-10-carboxylate (14e)**

The title compound was synthesized through Method C from compound **12e** and EtOTf. TLC (hexanes:ethyl acetate, 12:1 v/v)  $R_f$  = 0.20; colorless oil, 68%;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  7.03 (dd,  $J$  = 8.3, 2.2 Hz, 1H), 6.90 (d,  $J$  = 2.2 Hz, 1H), 6.25 (d,  $J$  = 8.2 Hz, 1H), 4.92 (d,  $J$  = 3.8 Hz, 2H), 4.17-4.01 (m, 2H), 3.72-3.60 (m, 1H), 3.20-3.14 (m, 1H), 2.93 (s, 3H), 2.67-2.64 (m, 1H), 2.29-2.09 (m, 4H), 2.05-1.98 (m, 1H), 1.57-1.41 (m, 2H), 1.23-1.18 (m, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  154.97, 148.96, 147.77, 132.99, 128.35,

123.31, 121.61, 111.17, 106.83, 92.64, 60.81, 46.99, 33.07, 30.51, 30.42, 27.13, 20.88, 14.74; ESI m/z calcd for C<sub>19</sub>H<sub>23</sub>ClN<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 347.1, found 347.1; IR (thin film) 2981, 2940, 2873, 1700, 1607, 1481, 1406, 1380, 1335, 1212, 1115, 1085, 944, 806, 776, 735 cm<sup>-1</sup>.

**(5a*S*,10a*S*)-1,3,5-Trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indole (5)**

A solution of Kf18 in toluene (0.10 M) was added Me<sub>3</sub>SiI (2.0 equiv) at room temperature. Then mixture was heated to 70 °C for 5 h, until Kf18 disappeared. The mixture was cooled to 0 °C in ice bath, followed by addition of aqueous NaHCO<sub>3</sub>. The mixture was diluted with ethyl acetate, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated. The residue was purified by column chromatography on silica gel to give product. TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 16:1 v/v) *R<sub>f</sub>* = 0.20; colorless oil, 96%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.20 (s, 1H), 6.05 (s, 1H), 5.16 (s, 1H), 5.06 (s, 1H), 3.27 (s, 1H), 3.08 (dd, *J* = 11.2, 6.1 Hz, 1H), 2.80 (s, 3H), 2.58 (ddd, *J* = 12.3, 11.2, 4.4 Hz, 1H), 2.37 (td, *J* = 12.3, 6.3 Hz, 1H), 2.25 (s, 3H), 2.24-2.18 (m, 1H), 2.15 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.09 (s, 3H), 2.07-2.03 (m, 1H), 1.73-1.55 (m, 1H), 1.52-1.43 (m, 1H), 1.37-1.18 (m, 2H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 152.22, 151.07, 138.16, 133.89, 125.48, 120.34, 112.36, 102.82, 94.75, 64.51, 45.47, 37.17, 34.72, 34.64, 31.79, 28.30, 24.06, 21.74, 17.28; ESI m/z calcd for C<sub>19</sub>H<sub>26</sub>O<sub>2</sub> [M+H]<sup>+</sup> 283.2, found 283.2; IR (thin film) 3312, 3085, 2925, 2854, 1596, 1480, 1443, 1365, 1305, 1227, 1074, 1030, 892, 817 cm<sup>-1</sup>.

**General procedure for the preparation of compound 6a, 6b and 6g (Method D)**

To a solution of compound **5** (1.0 equiv), *N,N*-diisopropylethylamine (DIPEA, 6.0 equiv), and 4-dimethylaminopyridine (DMAP, 0.2 equiv) in DMF (0.030 M) at 0 °C was added the alkyl chloroformate or 4-chlorobenzenesulfonyl chloride (3.0 equiv). Then the mixture was stirred at room temperature overnight. The mixture was then quenched by aqueous NaHCO<sub>3</sub>, diluted by ethyl acetate, washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product.

**Ethyl (5a*R*,10a*S*)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indole-13-carboxylate (6a)**

The title compound was prepared through Method D from compound **5** and ethyl chloroformate. TLC (hexanes:ethyl acetate, 10:1 v/v) *R<sub>f</sub>* = 0.20; yellow oil, 90%; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.23 (s, 1H), 6.06 (s, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.01 (s, 2H), 3.69 (t, *J* = 9.1 Hz, 1H), 3.38 (s, 1H); 3.03-2.96 (m, 4H), 2.37 (dd, *J* = 12.3, 4.8 Hz, 1H), 2.24 (s, 3H), 2.21-2.15 (m, 1H), 2.12-2.06 (m, 4H), 1.73-1.64 (m, 2H), 1.58-1.40 (m, 4H), 1.19 (bs, 3H); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 154.90, 151.90, 151.16, 138.35, 133.90, 123.58, 121.29, 112.69, 104.12, 93.79, 65.46, 60.61, 47.07, 33.39, 32.47, 31.57, 31.03, 24.30, 21.75, 17.24, 14.77; ESI m/z calcd for C<sub>22</sub>H<sub>30</sub>N<sub>2</sub>O<sub>2</sub> [M+H]<sup>+</sup> 355.2, found 355.2; IR (thin film) 2925, 2858, 1704, 1596, 1380, 1335, 1190, 1104, 1130, 959, 896, 862, 826 cm<sup>-1</sup>.

**Benzyl (5aR,10aS)-1,3,5-Trimethyl-10-methyl-ene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (6b)**

The title compound was prepared through Method D from compound **5** and benzyl chloroformate. TLC (hexanes:ethyl acetate, 10:1 v/v)  $R_f$  = 0.20; yellow oil, 54%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.44-7.28 (m, 5H), 6.25 (s, 1H), 6.09 (s, 1H), 5.20-4.95 (m, 5H), 3.77 (dd,  $J$  = 10.6, 7.3 Hz, 1H), 3.41 (s, 1H), 3.07 (ddd,  $J$  = 12.3, 10.5, 5.2 Hz, 1H), 2.99 (s, 3H), 2.40 (dd,  $J$  = 12.3, 5.1 Hz, 1H), 2.31-2.20 (m, 4H), 2.14 (s, 4H), 1.80-1.45 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.55, 151.87, 151.09, 138.41, 137.12, 135.28, 133.91, 128.72, 128.68, 128.56, 128.48, 127.93, 127.77, 123.51, 121.37, 112.74, 104.20, 94.06, 69.88, 66.38, 65.44, 47.15, 33.37, 32.44, 31.56, 31.07, 29.74, 24.27, 21.75, 17.22; ESI  $m/z$  calcd for  $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2$   $[\text{M}+\text{H}]^+$  417.2, found 417.2; IR (thin film) 2929, 2858, 1704, 1598, 1458, 1477, 1443, 1395, 1354, 1339, 1272, 1190, 959, 896, 736, 702  $\text{cm}^{-1}$ .

**(5aR,10aS)-13-((4-Chlorophenyl)sulfonyl)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole (6g)**

The title compound was prepared through Method D from compound **5** and 4-chlorobenzenesulfonyl chloride. TLC (hexanes:ethyl acetate, 8:1 v/v)  $R_f$  = 0.20; yellow oil, 40%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d,  $J$  = 8.6 Hz, 1H), 7.42 (d,  $J$  = 8.6 Hz, 2H), 6.26 (s, 1H), 6.11 (s, 1H), 5.01 (s, 1H), 4.95 (s, 1H), 3.31 (dd,  $J$  = 10.0, 6.7 Hz, 1H), 3.23 (s, 1H), 3.07-2.93 (m, 4H), 2.26 (s, 4H), 2.17-2.10 (m, 1H), 2.08 (s, 3H), 1.80-1.63 (m, 4H), 1.45 (p,  $J$  = 12.4 Hz, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  151.52, 150.09, 140.06, 138.71, 138.58, 133.66, 129.31, 129.23, 129.09, 128.58, 123.34, 121.85, 113.52, 104.44, 99.31, 66.84, 48.50, 33.52, 32.05, 31.98, 30.74, 24.27, 21.72, 17.24; ESI  $m/z$  calcd for  $\text{C}_{25}\text{H}_{29}\text{ClN}_2\text{O}_2\text{S}$   $[\text{M}+\text{H}]^+$  457.2, found 457.1; IR (thin film) 2925, 2858, 1598, 1480, 1335, 1160, 1093, 884, 825, 736  $\text{cm}^{-1}$ .

**Tert-butyl (5aR,10aS)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxylate (6c)**

To a solution of triphosgene (9.5 mg, 1.0 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.8 mL) at  $-78^\circ\text{C}$  was added pyridine (21  $\mu\text{L}$ ). The mixture was stirred for 10 min at  $-78^\circ\text{C}$ . A solution of substrate **5** (9.0 mg, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.4 mL) was added to the above solution slowly. The resulting solution was stirred at  $-78^\circ\text{C}$  for 30 min before warmed to  $0^\circ\text{C}$  over 1 h and stirred for another 30 min at  $0^\circ\text{C}$ . A solution of  $^t\text{BuOH}$  (22 mg, 10 equiv) and  $\text{Et}_3\text{N}$  (44  $\mu\text{L}$ , 10 equiv) in anhydrous  $\text{CH}_2\text{Cl}_2$  (0.8 mL) was added to the above solution at  $0^\circ\text{C}$  and stirred for 2 h before quenched by aqueous  $\text{NaHCO}_3$ , diluted by ethyl acetate, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **6c**. TLC (hexanes:ethyl acetate, 3:1 v/v)  $R_f$  = 0.20; yellow oil, 46%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.17 (s, 1H), 6.05 (s, 1H), 5.19 (s, 1H), 5.07 (s, 1H), 3.01 (dd,  $J$  = 11.3, 6.2 Hz, 1H), 2.85 (s, 3H), 2.59-2.52 (m, 1H), 2.46 (td,  $J$  = 11.6, 4.3 Hz, 1H), 2.28-2.15 (m, 5H), 2.06 (s, 3H), 1.98 (dd,  $J$  = 11.8, 4.2 Hz, 1H), 1.81-1.72 (m, 2H), 1.68-1.62 (m, 1H), 1.59-1.53 (m, 1H), 1.47 (s, 9H), 1.32-1.27 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  174.67, 153.57, 151.09, 137.92, 133.45, 125.92, 120.16, 112.84, 103.59, 93.96, 81.09, 67.37, 53.13, 46.17, 37.54, 34.60, 30.34, 28.24, 27.93,



21.78, 17.38; ESI  $m/z$  calcd for  $C_{24}H_{34}N_2O_2$   $[M+H]^+$  383.2, found 383.2; IR (thin film) 2929, 2858, 1730, 1596, 1458, 1369, 1141, 896, 821, 736  $cm^{-1}$ .

#### Acetylation of **5** using anhydrides to afford analogues **6d** and **6e** (Method E)

To a solution of **5** (1.0 equiv),  $Et_3N$  (6.0 equiv) and DMAP (0.2 equiv) in  $CH_2Cl_2$  (0.03 M) at 0 °C was added anhydride ( $Ac_2O$  or  $(CF_3CO)_2O$ , 3.0 equiv). The resulting mixture was slowly warmed to room temperature and stirred overnight before quenched by aqueous  $NaHCO_3$ , diluted by ethyl acetate, washed with brine, dried over  $Na_2SO_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **6d** or **6e**.

#### 1-((5a*R*,10a*S*)-1,3,5-Trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indol-13-yl)ethan-1-one (**6d**)

The title compound was prepared through Method E. TLC (hexanes:ethyl acetate, 5:1 v/v)  $R_f$  = 0.20; colorless oil, 90%;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.25 (s, 1H), 6.10 (s, 1H), 5.01 (s, 1H), 5.00 (s, 1H), 3.53 (dd,  $J$  = 10.0, 7.3 Hz, 2H), 3.17 (ddd,  $J$  = 12.4, 9.8, 5.2 Hz, 1H), 3.02 (s, 3H), 2.48 (dd,  $J$  = 12.4, 5.1 Hz, 1H), 2.29-2.27 (m, 4H), 2.15 (s, 3H), 2.12-2.04 (m, 1H), 1.98 (s, 3H), 1.82-1.64 (m, 3H), 1.63-1.43 (m, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  170.15, 152.08, 151.11, 138.60, 133.94, 123.06, 121.29, 112.66, 104.22, 95.09, 65.22, 48.95, 33.26, 32.48, 32.41, 31.24, 29.46, 25.79, 24.32, 21.77, 17.20; ESI  $m/z$  calcd for  $C_{21}H_{28}N_2O$   $[M+H]^+$  325.2, found 325.2; IR (thin film) 2925, 2858, 1655, 1598, 1395, 1275, 1194, 1032, 896, 825  $cm^{-1}$ .

#### 2,2,2-Trifluoro-1-((5a*R*,10a*S*)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indol-13-yl)ethan-1-one (**6e**)

The title compound was prepared through Method E. TLC (hexanes:ethyl acetate, 6:1 v/v)  $R_f$  = 0.20; colorless oil, 78%;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  6.80 (s, 1H), 6.75 (s, 2H), 5.03 (s, 1H), 4.71 (s, 1H), 3.13 (s, 3H), 2.99 (dq,  $J$  = 13.7, 6.9 Hz, 1H), 2.93-2.78 (m, 3H), 2.68 (dq,  $J$  = 18.8, 7.1 Hz, 2H), 2.61-2.48 (m, 3H), 2.38 (s, 3H), 2.32 (s, 5H), 2.10-2.01 (m, 1H), 1.81-1.54 (m, 3H);  $^{13}C$  NMR (101 MHz,  $CDCl_3$ )  $\delta$  175.32, 146.58, 143.95, 139.52, 135.49, 128.71, 128.04, 114.21, 109.42, 99.84, 62.89, 37.98, 36.33, 34.98, 31.68, 31.38, 24.32, 21.58, 18.88; ESI  $m/z$  calcd for  $C_{21}H_{22}F_3N_2O$   $[M+H]^+$  379.2, found 379.1; IR (thin film) 3257, 3093, 2929, 2858, 1707, 1491, 1383, 1175, 1160, 1130, 1056, 1037, 914, 840, 732  $cm^{-1}$ .

#### 4-Oxo-4-((5a*R*,10a*S*)-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indol-13-yl)butanoic acid (**6f**)

To a solution of compound **5** (1.0 equiv), *N,N*-diiso-propylethylamine (DIPEA, 8.0 equiv) and 4-dimethyl-aminopyridine (DMAP, 0.2 equiv) in anhydrous  $CH_2Cl_2$  (0.03M) at 0 °C was added succinic anhydride (5.0 equiv). The mixture was stirred at room temperature overnight before quenched by aqueous HCl (1.0 M), diluted by ethyl acetate, washed with brine, dried over  $Na_2SO_4$ , filtered, concentrated to afford compound **6f**.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  6.26 (s, 1H), 6.09 (s, 1H), 5.00 (s, 2H), 3.54 (dd,  $J$  = 9.8, 7.4 Hz, 1H), 3.46 (dd,  $J$  = 14.0, 6.5 Hz, 1H), 3.12 (ddd,  $J$  = 12.5, 9.9, 5.3 Hz, 1H), 2.98 (s, 3H), 2.67-2.41 (m, 6H),

2.25 (s, 3H), 2.13 (s, 3H), 2.10-2.02 (m, 1H), 1.78-1.64 (m, 2H), 1.63-1.43 (m, 4H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  175.10, 172.07, 151.72, 150.69, 138.82, 134.02, 122.63, 121.73, 112.98, 104.55, 96.31, 64.97, 47.97, 33.09, 32.47, 32.40, 31.75, 31.21, 30.50, 29.34, 24.22, 21.76, 17.18; ESI  $m/z$  calcd for  $\text{C}_{23}\text{H}_{30}\text{N}_2\text{O}_3$   $[\text{M}+\text{H}]^+$  383.2, found 383.2.

**Amino((5a *R*,10a*S*)-1,3-dimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indol-13-yl)methaniminium 2,2,2-tri-fluoroacetate (6k)**

To a solution of **5** (1.0 equiv),  $\text{Et}_3\text{N}$  (4.0 equiv) in  $\text{ClCH}_2\text{CH}_2\text{Cl}$  (0.070 M), at 0 °C was added *N,N'*-di-Boc-*N''*-trifluoromethanesulfonylguanidine (6.0 equiv) under argon. The mixture was stirred at room temperature for 3 days before diluted with ethyl acetate, washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **Boc-6k**. TLC (hexanes:ethyl acetate, 2:1 v/v)  $R_f$ = 0.20; yellow oil, 38%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.44 (s, 1H), 6.36 (s, 1H), 5.21 (d,  $J$ = 11.4 Hz, 1H), 5.05 (d,  $J$ = 8.8 Hz, 2H), 4.95 (d,  $J$ = 11.4 Hz, 1H), 3.72 (dd,  $J$ = 11.6, 8.3 Hz, 1H), 3.02 (td,  $J$ = 11.8, 6.5 Hz, 1H), 2.69 (dd,  $J$ = 13.0, 6.5 Hz, 1H), 2.40-2.34 (m, 1H), 2.33-2.27 (m, 1H), 2.23 (s, 3H), 2.18 (s, 3H), 2.07 (d,  $J$ = 6.3 Hz, 1H), 2.05-2.02 (m, 1H), 1.84 (d,  $J$ = 13.6 Hz, 1H), 1.78-1.68 (m, 2H), 1.48 (s, 12H), 1.41 (s, 9H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  151.57, 150.23, 148.76, 139.16, 135.85, 125.33, 123.85, 120.96, 117.77, 114.31, 108.77, 90.12, 64.26, 58.55, 47.50, 32.87, 32.65, 32.20, 30.09, 28.45, 28.29, 28.10, 27.95, 21.59, 17.20; IR (thin film) 3301, 2985, 2933, 1789, 1737, 1559, 1328, 1257, 1190, 1130, 1104, 821, 788, 728  $\text{cm}^{-1}$ . To a solution of the **Boc-6k** (16 mg) in  $\text{CH}_2\text{Cl}_2$  (1.2 mL) at 0 °C was added trifluoroacetic acid (1.2 mL). The mixture was stirred for 12 h before concentrated in vacuo to afford **6k**: white solid, 95%.  $^1\text{H}$  NMR (500 MHz, Methanol- $d_4$ )  $\delta$  6.64 (s, 1H), 6.57 (s, 1H), 5.24-5.17 (m, 2H), 5.14 (s, 1H), 4.70 (d,  $J$ = 13.4 Hz, 1H), 3.73 (t,  $J$ = 9.3 Hz, 1H), 3.07-2.96 (m, 1H), 2.90 (ddd,  $J$ = 11.7, 9.7, 7.2 Hz, 1H), 2.57 (ddd,  $J$ = 13.3, 11.6, 8.9 Hz, 1H), 2.29 (s, 3H), 2.27 (s, 4H), 2.20-2.09 (m, 3H), 1.95-1.87 (m, 2H), 1.82-1.73 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz, Methanol- $d_4$ )  $\delta$  159.85, 153.15, 150.13, 147.58, 139.09, 136.06, 125.62, 113.99, 108.70, 90.20, 62.76, 50.91, 46.48, 32.29, 32.07, 31.18, 29.74, 21.89, 20.04, 15.85.

**(5a*R*,10a*S*)-*N*-Benzyl-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indole-13-carboxamide (6h)**

To a solution of compound **5** (1.0 equiv),  $\text{Et}_3\text{N}$  (4.0 equiv) in  $\text{CH}_3\text{CN}$  (0.030 M) at 0 °C was added benzyl isocyanate (6.0 equiv). The mixture was stirred at room temperature for 2 h before diluted with ethyl acetate, washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give **6h**. TLC (hexanes:ethyl acetate, 5:1 v/v)  $R_f$ = 0.20; yellow oil, 91%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58-7.03 (m, 5H), 6.21 (s, 1H), 6.08 (s, 1H), 4.98 (s, 1H), 4.42 (t,  $J$ = 5.5 Hz, 1H), 4.38-4.20 (m, 2H), 3.79-3.55 (m, 1H), 3.35 (td,  $J$ = 7.8, 1.2 Hz, 1H), 3.07-3.00 (m, 4H), 2.51-2.40 (m, 1H), 2.36-2.27 (m, 1H), 2.25 (s, 3H), 2.13 (s, 3H), 2.10-2.04 (m, 1H), 1.70 (d,  $J$ = 6.3 Hz, 2H), 1.57-1.45 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  156.78, 152.07, 151.22, 139.70, 138.50, 133.92, 128.70, 127.81, 127.33, 123.37, 121.08, 112.62, 104.18, 94.92, 65.19, 46.51, 44.66, 33.36, 32.52, 32.07, 31.10, 31.05, 24.38, 21.77, 17.24; ESI  $m/z$  calcd for  $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$  416.2, found 416.2; IR (thin film) 3376, 2948, 2918, 2858, 1640, 1536, 1477, 1343, 1238, 1201, 1030, 974, 903, 821, 732  $\text{cm}^{-1}$ .

**(5aR,10aS)-N-Ethyl-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxamide (6i)**

TLC (hexanes:ethyl acetate, 5:1 v/v)  $R_f$ = 0.20; yellow oil, 50%;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.23 (s, 1H), 6.08 (s, 1H), 4.99 (d,  $J$ = 1.3 Hz, 2H), 4.08 (t,  $J$ = 5.4 Hz, 1H), 3.63 (dd,  $J$ = 15.2, 6.9 Hz, 1H), 3.33 (td,  $J$ = 7.7, 1.3 Hz, 1H), 3.17 (qd,  $J$ = 7.2, 5.4 Hz, 2H), 3.08-2.97 (m, 4H), 2.47 (ddd,  $J$ = 12.2, 5.3, 1.2 Hz, 1H), 2.32 (dd,  $J$ = 12.0, 7.7 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 3H), 2.12-2.03 (m, 1H), 1.77-1.45 (m, 6H), 1.08 (t,  $J$ = 7.2 Hz, 3H); ESI  $m/z$  calcd for  $\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$  354.2, found 354.2.

**(5aR,10aS)-1,3,5-Trimethyl-10-methylene-7,8,9, 10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole-13-carboxamide (6j)**

To a solution of compound **5** (1.0 equiv), *N,N*-diisopropylethylamine (DIPEA, 6.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (0.030 M) at  $-78^\circ\text{C}$  was added trichloroacetyl isocyanate (6.0 equiv). The mixture was warmed slowly to room temperature over 1 h, and stirred at room temperature for another 1.5 h before diluted with  $\text{CH}_2\text{Cl}_2$ , washed with  $\text{H}_2\text{O}$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated. The residue was purified by column chromatography on silica gel to give **6j**. TLC (hexanes:ethyl acetate, 2:3 v/v)  $R_f$ = 0.20; yellow oil, 40%;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.26 (s, 1H), 6.11 (s, 1H), 5.01 (s, 1H), 4.26 (s, 2H), 3.58 (d,  $J$ = 14.5 Hz, 1H), 3.39 (t,  $J$ = 7.9 Hz, 1H), 3.11 (ddd,  $J$ = 11.8, 8.2, 5.3 Hz, 1H), 3.04 (s, 3H), 2.51 (dd,  $J$ = 12.3, 5.2 Hz, 1H), 2.34 (td,  $J$ = 11.4, 10.7, 6.9 Hz, 1H), 2.28 (s, 3H), 2.17 (s, 3H), 2.10 (d,  $J$ = 13.7 Hz, 2H), 1.79-1.61 (m, 2H), 1.58-1.48 (m, 2H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  154.03, 152.02, 151.13, 138.57, 133.95, 123.20, 121.21, 112.68, 104.29, 94.81, 68.05, 65.24, 47.48, 33.29, 32.52, 31.99, 31.06, 30.60, 24.35, 21.76, 17.23; ESI  $m/z$  calcd for  $\text{C}_{20}\text{H}_{27}\text{N}_3\text{O}$   $[\text{M}+\text{H}]^+$  326.2, found 326.2; IR (thin film) 3413, 3339, 2925, 2858, 1722, 1652, 1592, 1417, 1361, 1235, 1201, 1022, 959, 896, 825  $\text{cm}^{-1}$ .

**Reduction of 6a or 6d to afford compound 6l and 6m (Method F)**

To a solution of substrate (**6a** or **6d**) in THF (0.025 M), at  $0^\circ\text{C}$  was added  $\text{LiAlH}_4$  (1.0 M in THF, 5.0 equiv). The mixture was stirred at  $65^\circ\text{C}$  for 1.0 h before cooled to  $0^\circ\text{C}$  and quenched with ethyl acetate followed by aqueous  $\text{NaHCO}_3$ . The mixture was then diluted with ethyl acetate, washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to give product **6l** or **6m**.

**(5aS,10aS)-1,3,5,13-Tetramethyl-10-methylene-7,8,9,10-tetrahydro-5H,6H-5a,10a-(epiminoethano)cyclohepta[b]indole (6l)**

The title compound was prepared through Method F from **6a**. TLC ( $\text{CH}_2\text{Cl}_2$ : MeOH, 9:1 v/v)  $R_f$ = 0.20; yellow oil, 98%;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.24 (s, 1H), 6.03 (s, 1H), 5.20 (s, 1H), 5.10 (s, 1H), 3.10 (s, 1H), 2.93 (s, 3H), 2.61 (td,  $J$ = 12.1, 5.6 Hz, 1H), 2.54-2.47 (m, 1H), 2.43 (s, 3H), 2.38-2.30 (m, 1H), 2.25 (s, 3H), 2.20 (dt,  $J$ = 12.4, 1.9 Hz, 1H), 2.07 (s, 4H), 1.83-1.50 (m, 6H);  $^{13}\text{C}$  NMR (101 MHz,  $\text{CDCl}_3$ )  $\delta$  152.28, 149.74, 138.41, 133.80, 125.74, 121.15, 113.82, 107.73, 102.64, 65.48, 53.42, 35.67, 34.75, 32.60, 32.12, 31.78, 23.60, 21.72, 17.24, 14.28; ESI  $m/z$  calcd for  $\text{C}_{20}\text{H}_{28}\text{N}_2$   $[\text{M}+\text{H}]^+$  297.2, found 297.2; IR (thin film) 2925, 2854, 1596, 1462, 1443, 1235, 1030, 896, 817  $\text{cm}^{-1}$ .

**(5a*S*,10a*S*)-13-Ethyl-1,3,5-trimethyl-10-methylene-7,8,9,10-tetrahydro-5*H*,6*H*-5a,10a-(epiminoethano)cyclohepta[*b*]indole (6*m*)**

The title compound was prepared through Method F from compound **6d**. TLC (CH<sub>2</sub>Cl<sub>2</sub>:MeOH, 9:1 v/v) *R<sub>f</sub>*= 0.20; yellow oil, 87%; <sup>1</sup>H NMR (500 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 6.15 (s, 1H), 5.94 (s, 1H), 5.16 (s, 1H), 5.08 (s, 1H), 3.03 (dd, *J*= 8.4, 6.2 Hz, 1H), 2.90 (dd, *J*= 11.6, 7.4 Hz, 1H), 2.86 (s, 3H), 2.39 (td, *J*= 11.7, 6.2 Hz, 1H), 2.33-2.25 (m, 2H), 2.24 (s, 4H), 2.22-2.15 (m, 2H), 2.07 (s, 3H), 1.96 (dd, *J*= 11.6, 4.3 Hz, 1H), 1.70-1.61 (m, 2H), 1.51-1.41 (m, 3H), 1.07 (t, *J*= 7.1 Hz, 3H); <sup>13</sup>C NMR (101 MHz, CD<sub>2</sub>Cl<sub>2</sub>) δ 153.01, 151.66, 137.39, 133.09, 126.50, 119.26, 112.02, 101.26, 65.20, 48.82, 42.73, 34.85, 32.66, 32.36, 32.02, 31.63, 29.65, 23.52, 21.21, 16.95, 14.54; ESI *m/z* calcd for C<sub>21</sub>H<sub>30</sub>N<sub>2</sub> [M+H]<sup>+</sup> 311.2, found 311.2; IR (thin film) 2925, 2854, 1596, 1484, 1458, 1227, 1160, 963, 896, 817 cm<sup>-1</sup>.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

We are grateful to Dr. Ann Eakin (Concept Acceleration Program, National Institute of Allergy and Infectious Diseases) for helpful discussions. The following reagents were provided by the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) for distribution by BEI Resources, NIAID, NIH: *Staphylococcus aureus* strains NR-45898, NR-46231, and NR-46070. Funding for this project was provided by Colorado Bioscience Discovery Evaluation Grant Program and National Institute of Health under grant number R21-AI121581.

**ABBREVIATIONS**

<b>RMA</b>	resistance-modifying agent
<b>CLSI</b>	Clinical Laboratory Standards Institutes
<b>MRSA</b>	methicillin-resistant <i>Staphylococcus aureus</i>
<b>MIC</b>	minimum inhibitory concentration
<b>MRC</b>	minimum re-sensitizing concentration
<b>GI<sub>50</sub></b>	half-growth inhibitory concentration
<b>HA-MRSA</b>	hospital-acquired MRSA
<b>CA-MRSA</b>	community-acquired MRSA

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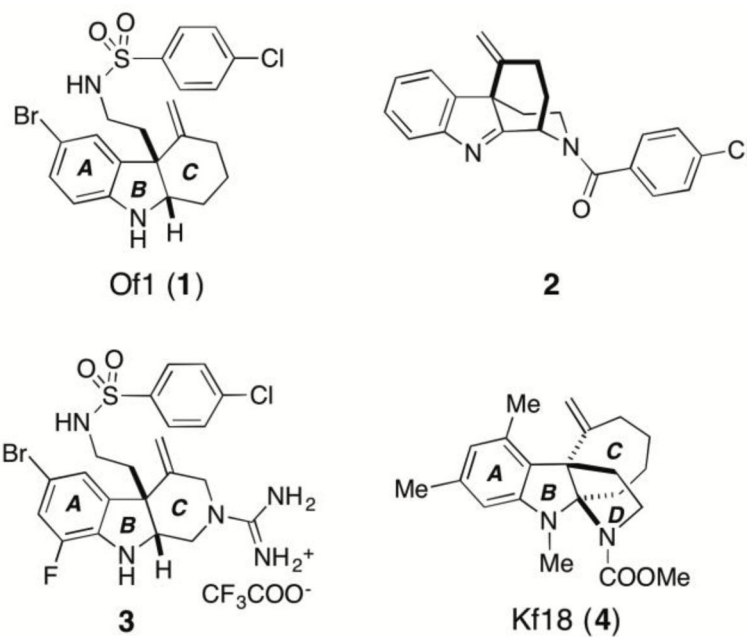
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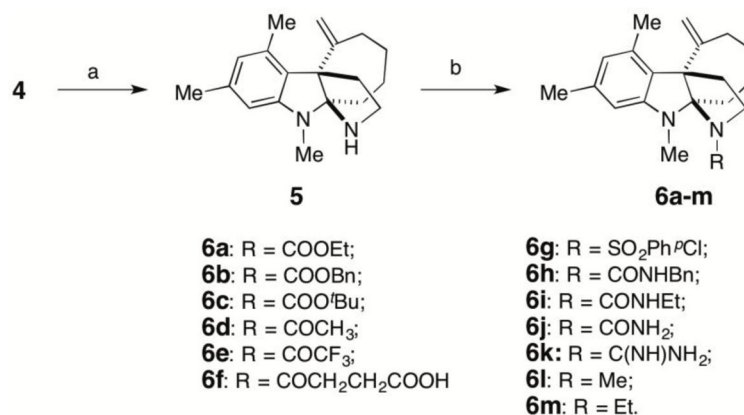
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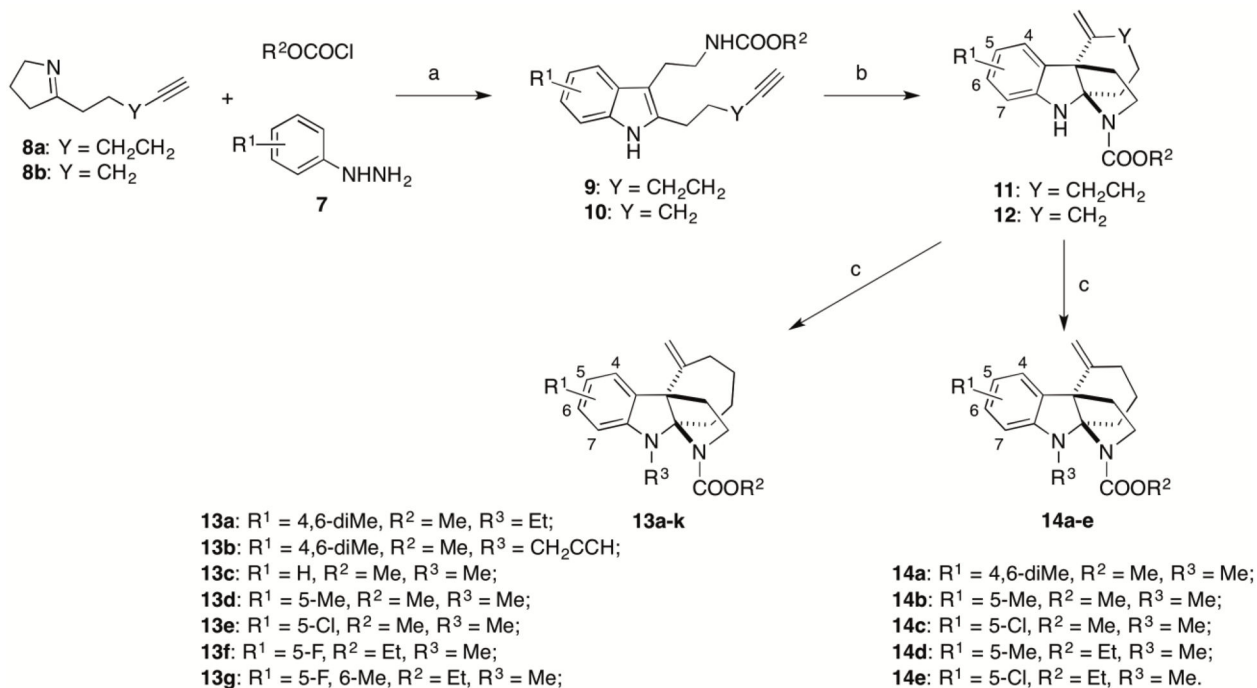
- A novel class of tetracyclic indolines was discovered in a  $\beta$ -lactam potentiator screen in MRSA
- The compound selectively potentiates  $\beta$ -lactams but not any other classes of antibiotics
- This novel class of compounds does not have antibacterial activity on its own, nor do they inhibit the  $\beta$ -lactamase activity directly
- Structure-activity relationship (SAR) study identified a more potent analogue with reduced mammalian cell toxicity



**Figure 1.** Structures of a series of polycyclic indole derivatives that potentiate  $\beta$ -lactams in MRSA.

**Scheme 1. Modifications of Kf18 (4)**

Reagents and conditions: a) Me<sub>3</sub>SiI, toluene, 70 °C, 4 h; (b) for **6a**, **6b**, **6g**, ClCOOEt, ClCOOBn, or ClSO<sub>2</sub>Ph<sup>p</sup>Cl, DIPEA, DMAP, DMF; for **6c**, triphosgene, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, <sup>t</sup>BuOH, Et<sub>3</sub>N; for **6d-f**, Ac<sub>2</sub>O, (CF<sub>3</sub>CO)<sub>2</sub>O or succinic anhydride, DMAP, DIPEA, DMF, rt; for **6k**, 1) *N,N*-di Boc-*N*-(trifluoromethane-sulfonyl)guani-dine, Et<sub>3</sub>N, ClCH<sub>2</sub>CH<sub>2</sub>Cl, 2) CH<sub>2</sub>Cl<sub>2</sub>, TFA; for **6h**, benzyl isocyanate, Et<sub>3</sub>N, CH<sub>3</sub>CN; for **6i**, ethyl isocyanate, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>; for **6j**, trichloroacetyl isocyanate, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>.



**Scheme 2. Synthesis of additional analogs of 4**

Reagents and conditions: (a) R<sup>2</sup>OCOC1, DMAP, DMF, 23 °C, 0.5 h; **8**, 0.5 h; MsOH, then **7**, 60–120 °C, 24 h; (b) 5 mol% Ph<sub>3</sub>PAuNTf<sub>2</sub>, 50 °C, toluene; (c) R<sup>3</sup>OTf, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C, 7 h.

**Table 1**Tetracyclic indoline Kf18 (4) selectively potentiates  $\beta$ -lactam antibiotics in MRSA

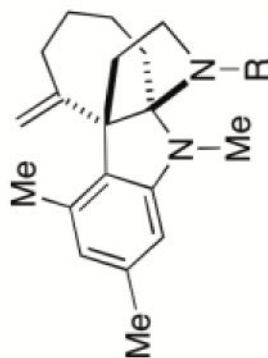
Entry	Antibiotic	MIC <sup>a</sup>	MIC (+Kf18) <sup>a,b</sup>	Fold of potentiation
1	methicillin	128	8	16
2	amox/clav	32	4	8
3	cefazolin	128	8	16
4	meropenem	32	2	16
5	oxacillin	64	8	8
6	tetracycline	32	16	2
7	ciprofloxacin	8	4	2
8	clindamycin	256	256	1
9	erythromycin	128	128	1
10	gentamycin	256	256	1
11	streptomycin	256	256	1
12	daptomycin	256	256	1

<sup>a</sup>Minimum inhibitory concentration in  $\mu\text{g/mL}$  in MRSA strain ATCC BAA-44.<sup>b</sup>MIC value in the presence of 20  $\mu\text{M}$  of Kf18.



Table 2

Biological Activities of Tetracyclic Indolines Kf18 (4), 5, and 6a-m



Entry	Compd	R	MRC (cefazolin) <sup>a,b</sup>	MRC (amox/clav) <sup>a,c</sup>	MIC <sup>a,b</sup>	GI <sub>50</sub> <sup>a,d</sup>
1	Kf18	COOMe	16	16	>64	20
2	<b>6a</b>	COOEt	2	2	>64	61
3	<b>6b</b>	COOBn	>64	64	>64	>64
4	<b>6c</b>	COO <sup>t</sup> Bu	8	4	>64	47
5	<b>6d</b>	COCH <sub>3</sub>	32	32	>64	15
6	<b>6e</b>	COCF <sub>3</sub>	>64	>64	>64	>64
7	<b>6f</b>	COCH <sub>2</sub> CH <sub>2</sub> COOH	>64	>64	>64	>64
8	<b>6g</b>	SO <sub>2</sub> PhCl	>64	>64	>64	>64
9	<b>6h</b>	CONHBn	>64	>64	>64	>64
10	<b>6i</b>	CONHEt	>64	>64	>64	51
11	<b>6j</b>	CONH <sub>2</sub>	64	64	>64	19
12	<b>5</b>	H	32	64	>64	26
13	<b>6k</b>	C(NH)NH <sub>2</sub>	16	32	>64	19
14	<b>6l</b>	Me	8	16	>64	20
15	<b>6m</b>	Et	8	32	>64	18

<sup>a</sup>Numbers are in µg/mL.<sup>b</sup>MRSA NRS-100.<sup>c</sup>MRSA ATCC BAA-44.

*d* HeLa cells.

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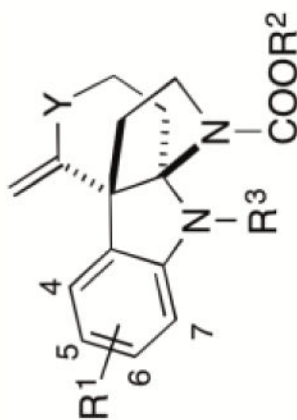
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Table 3

Biological Activities of Additional Analogues of Tetracyclic Indolines



Entry	Cmpd	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Y	MRC (cefazolin) <sup>a,b</sup>	MRC (amox/clav) <sup>a,c</sup>	MIC <sup>a,b</sup>	GI <sub>50</sub> <sup>a,d</sup>
1	Kf18	4,6-diMe	Me	Me	CH <sub>2</sub> CH <sub>2</sub>	16	16	>64	20
2	13a	4,6-diMe	Me	Et	CH <sub>2</sub> CH <sub>2</sub>	2	4	>64	30
3	13b	4,6-diMe	Me	CH <sub>2</sub> CCH	CH <sub>2</sub> CH <sub>2</sub>	64	64	>64	17
4	11	4,6-diMe	Me	H	CH <sub>2</sub> CH <sub>2</sub>	4	8	>64	28
5	13c	H	Me	Me	CH <sub>2</sub> CH <sub>2</sub>	>64	>64	>64	30
6	13d	5-Me	Me	Me	CH <sub>2</sub> CH <sub>2</sub>	8	4	>64	27
7	13e	5-Cl	Me	Me	CH <sub>2</sub> CH <sub>2</sub>	8	4	>64	53
8	6a	4,6-diMe	Et	Me	CH <sub>2</sub> CH <sub>2</sub>	2	2	>64	61
9	13f	5-F	Et	Me	CH <sub>2</sub> CH <sub>2</sub>	>64	>64	>64	>64
10	13g	5-F-6-MeO	Et	Me	CH <sub>2</sub> CH <sub>2</sub>	>64	>64	>64	>64
11	14a	4,6-diMe	Me	Me	CH <sub>2</sub>	16	8	>64	40
12	14b	5-Me	Me	Me	CH <sub>2</sub>	16	16	>64	15
13	14c	5-Cl	Me	Me	CH <sub>2</sub>	16	8	>64	41
14	14d	5-Me	Et	Me	CH <sub>2</sub>	64	32	>64	43
15	14e	5-Cl	Et	Me	CH <sub>2</sub>	16	8	>64	41

<sup>a</sup>Numbers are in µg/mL.

MRSA NRS-100,  
MRSA ATCC BAA-44,  
HeLa cells.

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