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Novel Terminal Bipheny-Based Diapophytoene Desaturases (CrtN) Inhibitors as Anti-MRSA/VISR/LRSA Agents with Reduced hERG Activity

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Abstract

CrtN has been identified as an attractive and druggable target for treating pigmented S. aureus infections. More than 100 new compounds were synthesized that target the overwhelming the defects of the CrtN inhibitor **1**. Analogs **23a-b** demonstrated significant activity against pigmented *S. aureus* Newman and thirteen MRSA strains (IC_{50} = 0.02~10.5 nM), along with lower hERG inhibition (IC_{50} > 30 μM, ~10-fold decrease in comparison with **1**). Furthermore, **23a-b** were confirmed to reduce the staphylococcal load in the kidney and heart in a mice model with normal treatment deeper than pretreatment ones, comparable even with vancomycin and linezolid. Remarkably, **23a** could strongly block the pigment biosynthesis of these nine multidrug-resistant MRSA strains, including excellent activity against LRSA strains and VISA strains *in vivo*, all which demonstrated that **23a** has huge potential against intractable MRSA, VISA and LRSA issues as a therapeutic drug.

Introduction

Staphylococcus aureus (*S. aureus*), a major human pathogen, causes serious skin and soft tissues infections,[1] respiratory disease and more serious illness like pneumonia, endocarditis and sepsis.[2] Infections caused by *S. aureus* has gained growing concern worldwide due to its capability for the rapid development of drug resistance induced by antibiotic misuse.[3] Resistance to antibiotics represents one of the most pressing challenges to the infectious disease community.[4-6] Increasing rates of infectious diseases caused by different methicillin-resistant *Staphylococcus aureus* (MRSA) strains have resulted in high infiltration of hospital and community settings.[7-11] Antibiotics that are approved for treatment of MRSA infections includevancomycin (VAN, glycopeptide antibiotic), linezolid (LZD, oxazolidinone antibiotic), daptomycin (lipopeptide antibiotic), dalbavancin (lipoglycopeptide antibiotic), oritavancin (glycopeptide antibiotic), ceftaroline (β-lactam antibiotic) and tedizolid (anoxazolidinone antibiotic). The appearance of VAN-intermediate resistance MRSA (VISA/MRSA)[12] and LZD-resistant MRSA (LRSA/MRSA) has especially left patients vulnerable. Recently, a report by the U.S. Centers for Disease Control and Prevention (CDC) stated that more than 2 million people have suffered MRSA infections, and 23,000 people have died directly due to these infections.[13] Great importance has been attached by governments and organizations worldwide, including the ND4BB project initiated by the European Union[14] and National Efforts by the United States.[15] On 27 February 2017, the World Health Organization (WHO)

released its first list of the world's deadliest superbugs, a catalog of 12 families of bacteria. The treatment of MRSA (VISA or LRSA) is urgent at high priority tiers.[16-21]

Anti-virulence strategies aiming at "disarming" the pathogen rather than inhibiting growth with weak selective pressure for the development of antibiotic resistance are now gaining interest.[22] Staphyloxanthin (STX) is an important virulence factor for pigmented *S. aureus.* Nonpigmented *S. aureus* is susceptible to be killed by reactive oxygen species. Hence, blocking STX biosynthesis is an underlying magnetically therapeutic target against all pigmented MRSA.[23] STX biosynthesis begins with the condensation of farnesyl diphosphate followed by a series of catalytic reactions of important enzymes (CrtM, CrtN, etc.). In 2008, Eric Oldfield and coworkers reported a CrtM inhibitor (BPH-652), which was introduced in our previous work,[24] and based on this work, several types of CrtM inhibitors have been identified by the same group, and BPH-652 was selected for these experiments because it had a good IC_{50} in pigment inhibition (110 nM).[25] The same group continued to develop a series of CrtM inhibitors (published in 2009) and the most active compounds are halogen-substituted phosphonosulfonates, with *K*i values as low as 5 nM against the enzyme and IC_{50} values for STX inhibition in *S. aureus* as low as 11nM.[26] Furthermore, in 2012, Fuyang Lin and coworkers reported X-ray crystallographic structures of three inhibitors bond to CrtM, and their results provided structural clues for the mechanism and inhibition of the head-to-head prenyl transferases.[27]

In our previous work, we demonstrated the enzyme CrtN to be an attractive and druggable target for fighting pigmented *S. aureus* infection[24] and a potent CrtN inhibitor **1** (5m[28], Figure 1), which could inhibit the STX biosynthesis of *S. aureus* Newman and three MRSA strains, sensitize four strains to immune clearance and effectively attenuate the virulence of three strains *in vivo*. However, prophylactic administration (24 h before infection) with high-dosage treatment (200 mg/kg) of **1**, along with the high hERG inhibition (IC_{50} = 3.71 μM), was impractical for clinical application.

Figure 1

In this study, we synthesized a series of CrtN inhibitors with new scaffolds, which not only demonstrated excellent activity against MRSA *in vitro* and *in vivo* at lower dosage, but also overcame the disadvantages of hERG inhibition. Linezolid and vancomycin, the last-resort antimicrobial agents, were introduced as positive control drugs into a murine model of *S. aureus* abscess formation to evaluate the effectiveness of our new analogues.

Design and Chemistry

In previous work, the varied scaffold and series of different substituents about benzofuran-derived CrtN inhibitors were not enough to investigate the relationship of structure and activity comprehensively. In this study, to further improve the affinity of the lead compound **1** and obtain novel structural scaffolds, chemical modifications were performed in four cycles. First, in region A (Figure 1), we first explored different

heteroaromatic rings and the related positions of substitutions (in region A) to generate novel scaffold compounds **2a-j**. In general, we observed that pigment inhibition varied greatly by the scaffold hopping, and compound **2b** revealed the strongest efficiency among these derivatives, which was enough for further modification study. Additionally, considering the structural diversity, compound **2j**, the second-best scaffold, was also identified as lead compound. Then, we replaced the *N*-methyl group of either **2b** or **2j** in region B (Figure 1) with various steric alkyl group (including hydrogen atom) and 6 analogues (**3a-f**) were designed (Table 1). Subsequently, we incorporated different substituted phenyls, furanyl, naphthalenyls, (cyclo)alkyls at the section C of either **2b** or **2j**, and seventy-four analogs (**4a-40a** and **4b-40b**) were further designed (Table 2-3). In addition, 10 analogs (**41a-45a** and **41b-45b**, Table 4) were prepared to evaluate whether the varies of linkers (allyl in region D) affected pigment inhibitory activity.

The synthesis routes of derivatives **2a-d** and **5a-40a** were outlined in Scheme 1. Intermediate **47** could be synthesized from commercial indole derivatives **46b** via reductive amination, and further coupled with *trans*-4-fluorocinnamaldehyde by the reductive amination to afford the target analog **3a.** Replacing the methyl with ethyl group or isopropyl group was to afford target analogs **3b-c**. In parallel, **46a-b** were suffered with methylamine under the reaction of reductive amination to yield intermediates **48a-b**. Various substituted acraldehydes were reduced by sodium borohydride, and accompanied with the bromination reaction for obtaining the intermediates **49a-z** and **50a-k**. Finally, the nucleophilic reactions of compounds

51a-z and **52a-k** with **48a-b** yielded target analogs **2a-d** and **5a-40a**. Meanwhile, derivatives **2e-j**, **3d-f** and **5b-40b** were prepared as described in scheme 2 and synthesis of these derivatives corresponded closely to scheme 1

Scheme 1-2

Scheme 3 outlines the synthesis strategy for the synthesis of derivatives **41a-b**. Coupling of commercially obtained 4-iodo-1,1'-biphenyl and tert-butyldimethyl(prop-2-yn-1-yloxy)silane gave **56**, which was reduced by TBAF to give **57**, and further brominated by PBr_3 to give intermediate **58**. The coupling of intermediate **58** with either **48b** or **55f** yielded analogs **41a-b**.

Scheme 3

Derivatives **42a-b** were prepared as described in scheme 4. **49t** was reduced by sodium borohydride, followed by bromination to give intermediate **60**. The nucleophilic substitution of intermediate **60** with **48b** or **55f** yielded analogs **42a-b**

Scheme 4

Scheme 5 outlines the synthesis strategy for the synthesis of derivatives **43a-b**. By the Wittig-Horner olefination, **61** was yielded from [1,1'-biphenyl]-4-carbaldehyde, then through reduction and bromination, intermediate **63** was generated**.** The nucleophilic substitution of intermediate **63** with **48b** or **55f** yielded analogs **43a-b**.

Scheme 5

Scheme 6 outlines the synthesis strategy used for the synthesis of derivatives **44a-b**. Through Wittig-Horner olefination, intermediate **64** was yielded from [1,1'-biphenyl]-4-carbaldehyde, then through reduction and bromination, intermediate **66** were generated. The nucleophilic substitution of intermediate **66** with **48b** or **55f** yielded analogs **44a-b**.

Scheme 6

As shown in scheme 7, by the Wittig-Horner olefination, intermediate **67** was yielded from (E)-3-([1,1'-biphenyl]-4-yl)acrylaldehyde, followed by reduction of the ethyl ester and bromination reaction to generate **69**. The nucleophilic substitution of compounds **69** with **48b** or **55f** yielded analogs **45a-b**.

Scheme 7

Results and Discussion

In total, 100 novel derivatives (**2a-j**, **3a-f**, **4a-45a** and **4b-45b**) were designed and synthesized. Their chemical structures are shown in Tables 1-4. The details of the synthesis procedures and structural characterization are described in the *Supporting Information*. All derivatives were confirmed to have ≥ 95% purity, and were identified with non-PAINS on the web at http://fafdrugs3.mti.univparis-diderot.fr/ recommended by editors from the ACS (American Chemical Society).

***In vitro* Pigment Inhibitory Activities against *S. aureus* Newman**

These synthesized compounds were evaluated for pigment inhibitory activities against *S. aureus* Newman and the results are shown in Table 1-4. We replaced the *N*-methyl group with various steric alkyl groups (including hydrogen), and 6 analogs (**3a-f**) were designed (Table 1). As shown in Table 1, in the respect of the substituents with various alkyl groups at *N* atom (including hydrogen atom, **2b**, **2j**, **3a-f**), compounds with *N*-methyl group exhibited the best pigment inhibitory activity (**2b** *vs* **3a-c**; **2j** *vs* **3d-f**), indicating that the *N*-methyl group is the optimal substituent for pigment inhibition.

Table 1

As shown in Table 2-3, substitution of phenyl with various types of groups (R^3) could significantly affect pigment inhibitory activity. Generally, (cyclo)alkyl or heteroaromatic or 1-naphthyl groups were detrimental to pigment inhibitory activity (**4a-9a** *vs* **2b**, **4b-9b** *vs* **2j**), while the introduction of 2-naphthyl group was favorable (**10a** *vs* **2b**), but inferior to analogue **2j**. Our previous studies found that the electron-withdrawing groups and electron-donating groups at the phenyl ring may have minor effects on activity.[28] To investigate the effect of substituted groups, more electron-withdrawing (fluoro, chloro, bromo, trifluoromethyl, difluoromethyl, nitro, phenyl, formate, cyan) and electron-donating groups (methyl, methoxyl, ethoxyl, *t*-butyl) were introduced at the phenyl ring. The results in Table 2-3 demonstrated that there was no relationship between activity and electronic effect. However, the substituted positions at the phenyl ring significantly affected the activity, and

substitution at the para position of the phenyl ring showed the best activity (**12a** *vs* **24a** *vs* **30a**, **12b** *vs* **24b** *vs* **30b**). Moreover, the substitution at the para-position with chloro, bromo, methyl, nitro, difluoromethyl, formate and phenyl (**12a**, **14a**, **15a**, **18a**, **19a**, **22a**, **23a** and **23b**) resulted in significant improvements in activity. Especially, analog **23a** (IC_{50} = 2.0 ± 0.1 nM) and **23b** (IC_{50} = 3.3 ± 0.4 nM) displayed better potency than other derivatives. Notably, the R^3 group of both **23a** and **23b** was 4-phenylphenyl (biphenyl).

Table 2-3

As shown in Table 4, compounds **41a-45a** and **41b-45b** were assessed to determine whether the allyl linker had influence on the pigment inhibition potency. The results indicated that the change of the allyl linker moiety was detrimental to improve pigment inhibitory activity. When the allyl linker was replaced by propargyl (**41b,** IC_{50} = 101.8 ± 5.2 nM) or vinyl (**45b**, IC_{50}=19.4 ± 0.2 nM), the pigment inhibitory activity decreased. Additionally, other linkers listed in Table 4 were detrimental to the pigment inhibitory activity.

Table 4

Structure-Activity Relationship

Based on the structural features and pigment inhibitory activities data, the SARs are summarized in detail. (1) *N*-substituent variation exerts great influence on pigment inhibitory activity (**2b** *vs* **3a-c, 2j** *vs* **3d-f)**, and the *N*-methyl is optimal; (2) The impact of the electronic characteristics of substituent in the phenyl ring on the potency is

weak, while the impact of the substituted position is critical. The substituent group on the para position can enhance the potency significantly(**12a** *vs* **24a** *vs* **30a, 12b** *vs* **24b** *vs* **30b**); (3) Replacement the phenyl ring with furanyl or thiophene or (cyclo)alkyl is not tolerable to the potency (**2b** *vs* **7a/8a, 2j** *vs* **7b/8b**); (4) the unsubstituted allyl linker is critical for high potency and the other linkers are on the contrary (**2b** *vs* **41a-45a, 2j** *vs* **41-45b**).

Cytotoxicity of human embryonic kidney cell (HEK-293) and human hepatocellular carcinoma cell (HepG2)

Based on the *in vitro* pigment inhibitory activities, four compounds (**12a**, **14a** and **23a-b**), whose IC_{50} values of pigment inhibitory activity of which are lower than 5nM, were selected to for cytotoxicity evaluation in HEK-293 and HepG2. As shown in Table 5, in comparison with amphotericin B, all compounds displayed far less cytotoxicity, especially, **23a** (CC_{50} = 48.1 μM by HEK-293, and CC_{50} = 105.8 μM by HepG2, respectively) were superior than amphotericin B (CC_{50} = 4.2 μM by HEK-293, and CC_{50} = 3.1 μM by HepG2, respectively).

Table 5

***In vitro* Pigment Inhibitory Activities against four MRSA strains**

USA400 MW2 and USA300 LAC,[29-30] two clones liable for the epidemic of community-acquired MRSA (CA-MRSA) infectious diseases in the United States; Mu50, a hospital-acquired MRSA (HA-MRSA) strain with VAN intermediate resistance MRSA (MRSA/VISA); NRS271, a linezolid resistance MRSA

(MRSA/LRSA);[31-32] these four MRSA strains (Table S4, *supporting information*) were used to investigate pigment inhibition activity of **23a-b**. The results are shown in Table 6. We were delighted to find that the color of all strains (USA400 MW2, USA300 LAC, Mu50 and NRS271) faded by the incubation with our compounds **23a-b**, and the IC_{50} value against MRSA were comparable with that against *S. aureus* Newman. Moreover, according to the results of the bacterial growth assay (Figure 2), different from conditional antibiotics, **23a-b** did not affect the growth of *S. aureus* strains and MRSAs, even given a high concentration (0.2 mM).

Table 6

Figure 2

***In vitro* Water Solubility, hERG Inhibition and CrtN Enzymatic Inhibitory Activities**

Compounds with high affinity for the hERG ion channel could induce QT interval prolongation, which is frequently related to potentially lethal arrhythmias (Table S2, *Supporting Information).* As shown in Table 7, we tested hERG inhibition activity of **23a-b**, and surprisingly found their IC_{50} values exceeded 30 μM, which achieved our top priority to decrease the heart cardiotoxicity and gave us much confidence for further development. We next evaluated their capacities of inhibiting the enzymatic activity of CrtN *in vitro*. Using our previous protocol,[28] both compounds were found to significantly inhibitenzymatic activity of CrtN at nanomolar concentrations (Table 7), However, although **23a-b** represented excellent

pigment inhibitory activity and cytotoxicity and hERG inhibition, water solubility of **23a-b** decreased a lot than **1** (from 10.0 mg/mL to about 0.2 mg/mL), due to the lipophilic biphenyl.

Table 7

***In vitro* Metabolic Stability of 23a-b in Human Liver Microsome**

Human liver microsome assay was utilized to preliminarily evaluate the effect of the stability of compounds in liver *in vitro*. As shown in Table 8, we took midazolam as control-compound as for its fast clearance rate in human liver microsome, and **23a-b** showed significant stability ($t_{1/2}$ = 50.7 mins of **23a** and $t_{1/2}$ = 93.7 mins of **23b**).

Table 8

***In vitro* Anti-fungal Activities of 23a-b.**

Because leading compound **1** originated from the anti-fungal agent Naftifine,[26] we would like to investigate whether our compound reserved the capacity of antifungal. As shown in Table 9, three fungus strains and three first-line drugs were chosen to proceed with the *in vitro* assay. Compared with the three positive control groups, **23a-b** exhibited weak activities against all three dermatophytes, which verified our compounds losing theirs antifungal activities.

Tables 9

Effects of 23a-b on Sensitizing *S. aureus* to Immune Clearance.

Since pigment could serve as a protective antioxidant to confer the resistance to immune clearance, we speculated that non-pigment *S. aureus* could be vulnerable to be killed by the block of STX with the treatment of our CrtN inhibition. Herein, two assays were introduced to investigate the effect of **23a-b** on sensitizing *S. aureus* to immune clearance *in vitro*, including hydrogen peroxide (H_2O_2) killing assay and human whole blood killing assay. To verify this argument experimentally, we first compared the susceptibility of mock-treatment with **23a**-treated (1 μM) *S. aureus* to H_2O_2 killing. As shown in Figure 3, non-pigmented *S. aureus* cells were more vulnerable to be killed by 1.5% H_2O_2 compared to the untreated *S. aureus* (mock) (survival, 3.0% *vs* 33.3%). In parallel, the survival of the known antioxidant nacetylcysteine (NAC)-treated *S. aureus* cells were far worse than the mock treatment as expected (51.3% *vs* 33.3%). Similarly, the survival percentage of the three MRSA strains greatly decreased (2.3% *vs* 28.7% in USA400 MW2; 2.3% *vs* 29.0% in USA300 LAC; 2.7% *vs* 24.3% in Mu50); correspondingly, the survival rates of the three NAC-treated MRSA strains worsened (54.3% *vs* 28.7% in USA400 MW2, 52.0% *vs* 29.0% in USA300 LAC, 53.0% *vs* 24.3% in Mu50). All results proved that the addition of H_2O_2 (with strong oxidation) exerted an impact on the MRSA strain survival, and the pigment definitely acted as the protective antioxidant. Subsequently, the other experiment was to compare the effect of analog-treated *S. aureus* with those of non-treated ones by human whole blood killing. The fresh human whole blood was added to **23a**-treated (1 μM) and untreated *S. aureus*, and the bacterial survival was measured. As shown in Figure 4, untreated *S. aureus* survived significantly better than

the **23a**-treated *S. aureus* (survival, 13.3% *vs* 1.3% in Newman, 20.0% *vs* 1.0% in USA400 MW2, 12.3% *vs* 0.7% in USA300 LAC, 9.6% *vs* 0.4% in Mu50. We then repeated the same experiment for **23b**, and the analysis was identical to that of **23a**. All collected results suggested that **23a-b** could render *S. aureus* more susceptible to immune clearance.

Figure 3-4

***In vivo* Effects of 23a-b on Attenuating the Virulence of *S. aureus* Newman and Two MRSA Strains.**

Since **23a-b** had promising activities *in vitro*, we next investigated *in vivo* efficacy in a systematic infection model. We subjected *S. aureus* Newman to a murine model of abscess formation via retro-orbital injection and measured the bacterial survival in the host organs. It was worth stressing that we first conducted the normal treatment procedure (giving the compounds 6 h after infection). As shown in Figure 5A-B, the mice were injected with 2.3×10^7 colony-forming units (CFU) of *S. aureus* Newman bacteria via retro-orbital injection. We provided the compounds with four different drug regiments—i.e., both 0.4 mg b.i.d. (giving the compounds twice a day)/4.5 d (180 mg/kg in total), and 0.1 mg b.i.d./4.5 d (45 mg/kg) in the pretreatment case (pretreatment with drugs or compounds 24 h in advance of the infection), along with both 0.4 mg b.i.d./3.5 d (140 mg/kg) and 0.1 mg b.i.d./3.5 d (35 mg/kg) in the normal treatment case (administered 6 h after the infection of strains), while LZD and VAN were set up as two positive control groups at the dosage of 0.4 mg b.i.d./4.5 d

(180 mg/kg) with pretreatment. The mice were sacrificed after 4.5 d, and we measured bacterial survival in kidneys and hearts. First, we analyzed **23a**-**b** in terms of attenuating the virulence of Newman (Figure 5A-B). Compared to the untreated group, the *staphylococcal* loads of all **23a** treated groups were significantly lower in kidneys and hearts ($p < 0.01$), while **23b**-treated groups were not as obvious. Surprisingly, both **23a**-treatment and **23b**-treatment with low dosage in the normal treatment group reduced bacterial load more than in the other three groups. For further investigation, we performed the same experiment on infection with Mu50 (VISA/MRSA) and NRS271 (LRSA/MRSA). The analysis of the data in Figure 5C-F revealed that compound-treatment groups had significantly decreased Mu50 and NRS271 *staphylococcal* loads in the kidneys and hearts, all of which corresponded to a greater than 95.0% decrease in surviving bacteria (significance $P < 0.001$), while all low-dosage compound-treatment groups were better than the high-dosage ones. Encouragingly, all low-dosage groups were not inferior to the positive-controlled ones; especially, **23a**-treatment with low dosage (0.1 mg b.i.d./3.5 d) in the normal treatment case displayed best activity again among the groups.

Figure 5

Along with the encouraging outcome *in vivo* described above, we concluded **23a**-treatment with low dosage in the normal treatment group to be the group with the greatest potential. To confirm the most appropriate treatment dosage, we lowered the dosage to 0.05 mg b.i.d./3.5 d (17.5 mg/kg in total) and 0.01 mg b.i.d./3.5 d (3.5

mg/kg). As shown in Figure 6A-B, **23a** (17.5 mg/kg) significantly decreased the Mu50 *staphylococcal* loads in kidneys by 1.09 $\log_{10}$ CFU (more than 91.8% decrease) and in hearts by 2.70 $\log_{10}$ CFU (more than 99.8% decrease); however, it was not comparable to the 0.1 mg b.i.d./3.5 d (35 mg/kg) group. Generally, we confirmed **23a**-treatment with 0.1 mg b.i.d./3.5 d (35 mg/kg) dosage in normal treatment still as the best treatment. To further evaluate the efficacy of **23a** at affecting the outcome of *S. aureus* sepsis, we challenged animals with 2×10^8 CFU Newman bacteria. The untreated mice nearly died out (90% animal) within 4 days, with **23a** resulting in 80% animal survival. By the eighth day, more than 70% of the **23a**-treated mice were alive, demonstrating a slight advantage over the **1**-treated group (Figure 7). This investigation clearly proved that the *in vivo* **23a**-treatment weakened the virulence of *S. aureus* Newman.

Figure 6-7

***In vitro* Pigment Inhibitory Activities against additional 9 MRSA Strains.**

In addition to four *S. aureus* strains above, 9 additional multidrug-resistant MRSA strains—NRS70, NRS100, NRS108, LRSA56, LRSA202,[33] LRSA205, HS663,[34] NF65Y and XN108[35] (Table S4, *supporting information*), were selected to further explore the effect of the lead compound **23a** against multiple resistant bacteria. First, the pigment inhibition of **23a** were conducted, and the results were shown in Table 10 indicated that **23a** could strongly block the pigment biosynthesis of these

nine MRSA strains (IC_{50}=0.02-10.5 nM), which meant the adaptability of our compound against MRSAs *in vitro*.

Table 10

***In vivo* Effects of 23a on Attenuating the Virulence of *S. aureus* LRSA102, LRSA56, NF65Y and XN108.**

Following, based on *in vitro* pigment inhibitory activities (Table 10) and MIC values of the nine MRSA strains (Table S4, *Supporting Information*), we chose four representative MRSA strains, LRSA56 (LRSA), LRSA202 (LRSA), NF65Y (VISA) and XN108 (VISA) to further investigate *in vivo* effects of **23a** *in vivo* (0.1 mg b.i.d./3.5 d, in normal treatment, Figure 8).

As shown in Figure 8A , the mice were injected with 5.0×10^7 CFU of *S. aureus* LRSA56 bacteria via retro-orbital injection. Compared with untreated group, **23a**-treatment decreased the LRSA56 loads in kidneys by 0.77 $\log_{10}$ CFU (more than 83.0% decrease) and in hearts by 0.73 $\log_{10}$ CFU (more than 81.4% decrease). Compared with LZD-treated group, **23a**-treatment decreased the LRSA56 loads in kidneys by 0.34 $\log_{10}$ CFU (more than 54.3% decrease) and in hearts by 0.55 $\log_{10}$ CFU (more than 71.8% decrease), however, it showed no significant difference compared to the VAN-treatment group. As shown in Figure 7B, the analysis was just like Figure 7A, **23a** could be comparable to LZD, but worse than VAN.

As shown in Figure 7C-D, for VISA-resistance bacteria NF65Y and XN108, all the **23a**-treatment groups had significantly reduced *S. aureus* loads ($p < 0.001$), and

was comparable to the positive control groups, even though LAZ and VAN were given at higher doses. Especially, in Figure 7C, **23a**-treatment group showed extraordinary activity, exceeding VAN with significance $p < 0.01$. Consequently, we were quite confident that **23a** was the best candidate for further development.

Figure 8

***In vivo* Effects of 23a on Attenuating the Virulence of *S. aureus* Newman, Mu50 and NRS271 with Oral Administration.**

Because all *in vivo* investigations above were through intraperitoneal injection, oral administration was utilized for more investigations about curative effects of **23a** (0.4 mg b.i.d./3.5 d, 0.2 mg b.i.d./3.5 d and 0.1 mg b.i.d./3.5 d, in normal treatment, Figure 9). We kept VAN and LZD as positive control groups (0.4 mg b.i.d./4.5 d, in pretreatment).

As shown in Figure 9A-B, the mice were injected with 3.1×10^7 CFU of *S. aureus* Newman bacteria via retro-orbital injection. In the kidneys, compared with untreated group, **23a**-treatment decreased the Newman loads by 1.00 $\log_{10}$ CFU (90.0% decrease), but there was no significant difference in hearts. Compared with VAN-treated group, **23a**-treatment decreased the Newman loads in hearts by 0.38 $\log_{10}$ CFU (more than 55.3% decrease with significance $p < 0.1$.). However, all **23a**-treatment groups were not better than positive-controlled groups. As for Figure 9C-F, the analysis was just like that of Figure 9A, the best dosage of the three **23a**-treatment groups was still 0.2 mg b.i.d./ 3.5 d, and not better than VAN and

LZD-treatment groups. Consequently, the most appropriate dose of **23a** was 0.2 mg b.i.d./ 3.5 d with oral administration, which was not comparable to intraperitoneal injection.

Figure 9

***In vitro* Effects of 23a on CYP Enzymatic Inhibitory Activity.**

The study on CYP drug metabolizing enzymatic could be used to predict the side effect of compounds in liver *in vitro*. The data in Table 11 showed the CYP enzymatic inhibition of **23a**, and the results indicated that **23a** exhibited no significant inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4M and CYP3A4T (IC_{50} > 3 μM), which preliminarily proved that our compound had no side effect in liver.

Table 11

***In vivo* Rat and Mice Pharmacokinetics (PK) Profile of 23a.**

Because of its potency and attractive adaptability, compound **23a** was further evaluated by both rat (Table 12) and mice (Table 13) PK model. Initially, **23a** was characterized by low clearance (1750 mL/h/kg in rat and 1840 mL/h/kg in mice) and a terminal half-life after I.V. administration (2.46 h in rat and 2.05 h in mice), while the peak serum concentrations were observed at 2 h by P.O. administration. As shown in Table 12 and Table 13, the terminal half-life after P.O. administration was 1.29 h in rat and 3.35 h in mice. The oral bioavailability showed obvious difference between

species of **23a** which was 16.3% in rat and 83.3% in mice, which was high enough for a candidate drug. Furthermore, we supplemented PK study of intraperitoneal (I.P.) injection in rat as shown in Table12. Surprisingly, all the PK parameters were significantly higher than the two other methods of administrations, especially the terminal half-life reached 7.61 h, which made us confident that I.P. was the most appropriate method of administration for **23a**.

Table 12-13

Pharmacological Safety

The favorable PK profile of **23a** along with its highly desirable inhibitory potency against CrtN warranted its use in *in vitro* safety studies. The maximum tolerated dose of **23a** was determined for acute toxicity in rat. 30 rat were randomly divided into three groups and given single oral doses of 60 mg/kg, 250 mg/kg, or 1000 mg/kg of **23a** on the first day. The animals treated with **23a** did not exhibit any poisoning symptoms or mortality immediately or during the post-treatment period of 2 weeks. In addition, no abnormal behaviors or significant changes in the water/food consumption and body weight were observed during the period of the experiments. Therefore, **23a** was well tolerated up to a dose of 1000 mg/kg with no acute toxicity.

Resistance Development Study of 23a

As the drug resistance development was the central issue to design and evaluation of new antibiotics, we wondered whether these CrtN inhibitors could avoid the development of drug resistance under sequential H_2O_2 selection pressure.

Erythromycin, a macrolides antibiotics, was included as a positive control to compare with these CrtN inhibitors for their drug resistance development. In the initial susceptibility testing, we determined the MIC value of erythromycin and H_2O_2 were 0.125 μg/ml and 0.15‰ (*v*/*v*), respectively. Subsequent passaging for erythromycin was started with MIC/2 (0.0625μg/ml). And for H_2O_2 with CrtN inhibitors, we chose a concentration of 0.15‰ (*v*/*v*) H_2O_2, which imposed a selected pressure for bacteria growth and leading to a lagged time for bacteria to reach the exponential phase, and IC_{90} concentrations of **23a-b** for pigment production to initiate passaging. As it was shown in Figure.10, the MIC value of erythromycin against *S.aureus* Newman strain started to increase once beginning passaging, and the value had increased by a factor of over 16 after 12 passages. By contrast, the IC_{50} value of the CrtN inhibitors for pigment production of 12th passage of *S. aureus* Newman (under IC_{90} concentrations of **23a** or **23b**) was basically unchanged (1.8nM *vs* 2.0 nM for **23a**, 2.6 nM *vs* 3.3 nM for **23b**, Table 12). Meanwhile, if CrtN was mutated under the sequential H_2O_2 + CrtN inhibitors selection pressure, colored single colony would be appeared on the TSA plate containing these drugs. As shown in Fig. 11，when ~1000 CFUs of the 12th passage bacteria were spread onto TSA plate containing IC_{90} concentrations of **23a** or **23b**, all the colonies still remained non-pigmented. In contrast, pigmented bacteria were observed from TSA plate without CrtN inhibitors. In total, 100 TSA plates containing IC_{90} concentrations of **23a** or **23b** were included to determine the frequency of mutations. The frequencies of mutations at IC_{90} concentrations of CrtN

inhibitors for pigment production were less than ~ 1×10^{-5} for both **23a-b** after 12 sequential passaging.

Figure 10-11

Table 14

Finally, the MIC values of **23a** for the three other pathogens were investigated, including enterococcus faecium, *S. aureus* Newman, and pseudomonas aeruginosa, which all belong to the "ESKAPE" family. As shown in Table 15, the three values of MIC of **23a** were all above 500 μg/mL, which proved our inhibitor do not affect the growth of these pathogens.

Table 15

Conclusion

In summary, based on the results of scaffold hopping, 3-substituted benzofuran and 7-substituted indole were key skeletons. Subsequently, with the variation of the *N*-substituents, allyl linkers and phenyl moiety, 100 new analogs were synthesized. To investigate the pigment inhibition of *S. aureus* Newman, the unambiguous SARs were obtained. The most valid four pigment inhibitors **12a**, **14a** and **23a-b** (pigment inhibition IC_{50} < 5nM) were chosen among the analogs to test their cytotoxicity for HEK-293 and HepG2 cells, in order to keep the diversity of main structure, we maintained **23a-b** for further study. **23a-b** had the capacity to block the pigment

biosynthesis of USA400 MW2, USA300 LAC, Mu50 and NRS271 at a comparable level to the Newman strain. Notably, the hERG inhibition activity of **23a** (IC_{50} = 34.8 μM) and **23b** (IC_{50} > 40 μM) were largely improved compared to **1** (IC_{50} = 3.71 μM), ~ 10 fold decrease. We found that **23a-b** had submicromolar activity in CrtN enzymatic inhibition assay without any bactericidal impact on *S. aureus* bacteria (up to 200 μM) and proper human miarosome stability (50.7 mins of **23a** and 93.7mins of **23b** for half-life time). Furthermore, **23a-b** abandoned the antifungal activities (MIC > 8 μg/mL). According to the concept of antivirulence, **23a-b** (1 μM)-sensitized *S. aureus* strains were killed by H_2O_2 and human whole blood. In the *in vivo* assay, **23a-b** were proven efficacious in the *S. aureus* Newman and multidrug resistant MRSA (Mu50 and NRS271) model, and **23a** treatment with 0.1 mg b.i.d./3.5 d (35 mg/kg in total) in the normal treatment group was preferred. Next, all compound-treatment groups significantly decreased Mu50 (VISA/MRSA) loads in hearts and kidneys, which were compared with the efficacy of the positive groups, VAN and LZD. Regarding NRS271 (LRSA/MRSA), **23a-b** strongly decreased the NRS271 loads in kidneys and hearts (> 99% decrease), which were also comparable with the positive control groups. Considering **23a** had a slight advantage over **23b**, we preferred **23a** as the candidate drug and then proved it to be efficacious in *S. aureus* Newman sepsis model, with more than 70% survival after 8 d. Considering no better inhibitory activity under the lower dosage, the 0.1 mg b.i.d./3.5 d (35 mg/kg) case was guaranteed to be the most appropriate dosage. The pigment inhibitory activity of **23a** against another nine MRSA strains was at the same level to the Newman strain, which demonstrated that **23a** had a

broad spectrum bactericidal effect. Then two LRSA strains (LRSA56 and LRSA202) and two VISA strains (NF65Y and XN108) among the nine strains were tested *in vivo*, and **23a** showed extraordinary activity again, comparable to LZD and VAN. Moreover, **23a** showed no inhibitory activity on CYP enzymatic, and is characterized by an acceptable half-life, high volume of distribution and low clearance. **23a** was a potential antibiotic and had 16.3% orally bioavailable in rat and 83.8% orally bioavailable in mice. When we tried I.P. as method of administration in rat, **23a** showed extreme stability (7.61 h for half-life time). Lastly, we verified that **23a** was not easy to induce the resistance development, and used **23b** as contrast. We developed 12 passages of *S. aureus* Newman under pressure of **23a-b** and H_2O_2, and made sure that the frequencies of mutations at IC_{90} concentrations of CrtN inhibitors for pigment production were $< \sim 1\times10^{-5}$. In total, **23a** has the potential to be developed as therapeutic drugs, especially against intractable MRSA (VISA and LRSA) issues, by blocking virulence, and this class of antibiotics holds great promise in treatment of infections by difficult human pathogens.

Experimental Section

General Chemistry

Reagents and solvents were obtained from commercial suppliers at high quality and were used without further purification. TLC was performed on a HSGF 254 (150-200 μm thickness; Yantai Huiyou Co., China). UV light and I_2 were used to monitor synthetic progress. Column chromatography was performed on silica gel

(200-300 mesh), eluted with ethyl acetate and petroleum ether. NMR spectra data were obtained on a Bruker AMX-400 NMR using TMS as an internal standard. Chemical shifts were provided in parts per million. ^{1}H NMR data were reported from the aspect of multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant (Hz) and integrated value. Low- and high-resolution mass spectral (MS) data were acquired with electron spray ionization (ESI) produced by a Finnigan MAT-95 and LCQ-DECA spectrometer. The purity of each compound (> 95%) was determined by HPLC on an Agilent 1100 with a quaternary pump and diode-array detector (DAD). The melting points of each compound were determined on an SGW X-4 melting point apparatus.

Preparation of Salts.

Taking **4a** as an example, to a solution of oily derivative **4a** (100 mg) in ethyl ether (10 mL) stirred at room temperature bubbled with hydrogen chloride gas for 1 min. After stirring for 15 min, the solvent was removed by rotary evaporation and the residue was suspended in ethyl acetate/petroleum ether (1:100, v/v, 10 mL) for an additional hour of agitation. The precipitate was filtrated and washed with ethyl acetate to obtain the final compound in the form of hydrochloride. All other final derivatives underwent through this process to yield an amorphous, solid form or oil. Spectroscopic data reported below are in their hydrochloride form.

(E)-N-(benzofuran-2-ylmethyl)-N-methyl-3-(4-(trifluoromethyl))phenyl)prop-2-en-1-amine hydrochloride (2a).

A solution of intermediate **48a** (X=O, 163.0 mg, 1 mmol), **51a** (290.0 mg, 1.1 mmol) and K_2CO_3 (280.0 mg, 2 mmol) in DMF (10 mL) was stirred at room temperature overnight. The mixture was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed. The residue was then purified via flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1/5, v/v) to give the free base of **2a** as white solid. Yield: 44%. **2a** was prepared by the general procedure given above as white solid, m.p. 161-162 ^{o}C. 1H NMR (400 MHz, MeOD) δ 7.72 – 7.63 (m, 5H), 7.60 – 7.54 (m, 1H), 7.45 – 7.36 (m, 1H), 7.35 – 7.27 (m, 1H), 7.20 (s, 1H), 7.02 (d, J = 15.8 Hz, 1H), 6.56 – 6.46 (m, 1H), 4.66 (s, 2H), 4.10 (dd, J = 14.3, 7.1 Hz, 2H), 2.95 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.67, 146.49, 139.13, 138.76, 127.49, 127.22, 127.22, 125.67, 125.50, 125.33, 125.29, 124.59, 123.34, 121.54, 119.72, 111.05, 110.86, 57.44, 51.29, 39.09. HRMS (ESI) m/z calcd for $C_{20}H_{19}F_3NO$ $(M+H)^+$ 346.1419, found 346.1418.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(4-(trifluoromethyl))phenyl)prop-2-en-1-amine hydrochloride (2b).

Yield: 57%. **2b** was synthesized by the general procedure given above as white solid, m.p. 165-166 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.73–7.64 (m, 5H), 7.60 (d, J = 7.8 Hz, 1H), 7.41 (dtd, J = 17.8, 7.3, 1.2 Hz, 2H), 7.01 (d, J = 15.9 Hz, 1H), 6.59–6.47 (m, 1H), 4.61 (d, J = 37.0 Hz, 2H), 4.24–4.07 (m, 1H), 4.00 (s, 1H), 2.92 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 157.89,

155.54, 147.94, 139.07, 138.78, 130.18, 127.26, 127.26, 126.49, 125.30, 124.15, 123.48, 120.12, 119.50, 119.27, 111.52, 109.86, 57.26, 47.87, 38.56. HRMS (ESI) m/z calcd for $C_{20}H_{19}F_3NO$ $(M+H)^+$ 346.1419, found 346.1418.

(E)-N-(benzo[b]thiophen-2-ylmethyl)-N-methyl-3-(4-(trifluoromethyl))phenyl)prop-2-en-1-amine hydrochloride (2c).

Yield: 42%. **2c** was synthesized by the general procedure given above as white solid. m.p. 223-224 ^oC. ^1H-NMR (400 MHz, MeOD) δ 7.99 – 7.85 (m, 2H), 7.75 – 7.63 (m, 5H), 7.49 – 7.37 (m, 2H), 7.02 (d, J = 15.8 Hz, 1H), 6.53 (dt, J = 15.2, 7.4 Hz, 1H), 4.73 (s, 2H), 4.02 (s, 2H), 2.94 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 141.02, 139.18, 139.11, 138.93, 130.89, 129.50, 127.30, 127.30, 125.57, 125.51, 125.33, 125.30, 124.80, 124.12, 122.81, 122.08, 119.48, 57.18, 53.43, 38.51.HRMS (ESI) m/z calcd for $C_{20}H_{19}F_3NS$ $(M+H)^+$ 362.1190, found 360.1193.

(E)-N-(benzo[b]thiophen-3-ylmethyl)-N-methyl-3-(4-(trifluoromethyl))phenyl)prop-2-en-1-amine hydrochloride (2d).

Yield: 50%. **2d** was synthesized by the general procedure given above as white solid. m.p. 198-200 ^oC. 1H NMR (400 MHz, MeOD) δ 8.02 (s, 3H), 7.68 (s, 3H), 7.50 (d, J = 19.3 Hz, 2H), 6.99 (d, J = 16.0 Hz, 1H), 6.53 (s, 1H), 4.71 (d, J = 53.3 Hz, 2H), 4.09 (d, J = 40.8 Hz, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 140.38, 139.08, 138.87, 137.86, 131.76, 127.27, 127.27, 125.50, 125.35, 125.31, 125.27, 124.98, 124.78, 124.48, 122.81, 121.27, 119.55, 57.55, 51.26, 38.81. HRMS (ESI) m/z calcd for $C_{20}H_{18}F_3NS$ $[M+H]^+$ 361.1112, found 361.1114.

(E)-N-((1H-indol-2-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2e).

Yield: 25%. **2e** was synthesized by the general procedure given above as white oil. ^{1}H NMR (400 MHz, Acetone) δ 7.98 (s, 1H), 7.71 – 7.64 (m, 4H), 7.59 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 15.8 Hz, 1H), 6.55 – 6.45 (m, 1H), 4.62 (t, J = 11.2 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 4.11 (dd, J = 13.1, 7.0 Hz, 1H), 3.94 (dd, J = 13.4, 7.7 Hz, 1H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.12, 138.76, 137.21, 127.90, 127.25, 127.25, 125.78, 125.50, 125.32, 125.28, 124.51, 122.84, 120.46, 119.80, 119.63, 111.21, 106.12, 57.05, 52.11, 38.49. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1496.

(E)-N-((1H-indol-3-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2f).

Yield: 78%. **2f** was synthesized by the general procedure given above as white solid. m.p. 165-168 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.64 (d, J = 7.9 Hz, 1H), 7.62 – 7.54 (m, 4H), 7.35 (t, J = 7.5 Hz, 1H), 7.26 (s, 1H), 7.12 (dd, J = 11.0, 4.0 Hz, 1H), 7.05 (dd, J = 11.0, 3.9 Hz, 1H), 6.66 (d, J = 15.9 Hz, 1H), 6.48 (dt, J = 15.9, 6.8 Hz, 1H), 3.86 (s, 2H), 3.33 (d, J = 6.9 Hz, 2H); ^{13}C NMR (101 MHz, MeOD) δ 139.09，138.51, 136.68, 128.08, 127.19, 127.05, 127.05, 126.00, 125.37, 125.33, 124.57, 122.18, 120.09, 119.94, 117.59, 111.65, 102.64, 95.65, 56.57, 50.82, 38.09. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1499.

(E)-N-((1H-indol-4-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2g).

Yield: 79%. **2g** was synthesized by the general procedure given above as white solid. m.p. 155-157 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.54 (t, J = 8.8 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 7.9 Hz, 1H), 7.24 – 7.08 (m, 3H), 6.72 (s, 1H), 6.59 (d, J = 16.0 Hz, 1H), 6.50 – 6.37 (m, 1H), 3.85 (s, 2H), 3.28 (d, J = 6.4 Hz, 2H), 2.29 (d, J = 12.3 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.11，138.48, 135.18, 128.02, 127.11, 126.85, 126.85, 126.12, 125.39, 125.31, 124.67, 123.12, 122.56, 120.01, 119.84, 117.19, 111.25, 102.59, 95.59, 56.47, 50.72, 38.01. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1499.

(E)-N-((1H-indol-5-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2h).

Yield: 88%. **2h** was synthesized by the general procedure given above as white solid. m.p. 129-131 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.63 – 7.51 (m, 3H), 7.46 (d, J = 8.1 Hz, 2H), 7.36 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 6.61 – 6.50 (m, 2H), 6.49 – 6.38 (m, 1H), 3.67 (s, 2H), 3.24 (d, J = 6.4 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 138.95, 138.45, 137.11, 127.47, 127.15, 126.85, 125.78, 125.50, 125.33, 125.21, 124.89, 122.68, 120.35, 119.14, 119.53, 111.45, 106.52, 57.55, 53.45, 38.36. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1501.

(E)-N-((1H-indol-6-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2i).

Yield: 65%. **2i** was synthesized by the general procedure given above as white solid. m.p. 134-137 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.1 Hz, 3H), 7.46 (d, J = 8.1 Hz, 2H), 7.39 (s, 1H), 7.20 (s, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.63 – 6.52 (m, 2H), 6.48 – 6.37 (m, 1H), 3.72 – 3.64 (m, 2H), 3.24 (d, J = 6.4 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.04，138.11, 136.98, 129.03, 127.09, 126.65, 126.65, 126.01, 125.58, 125.47, 124.87, 121.88, 120.02, 118.97, 117.81, 111.94, 101.54, 95.95, 56.67, 50.98, 38.31. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1498.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (2j).

Yield: 74%. **2j** was synthesized by the general procedure given above as white solid. m.p. 146-148 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.98 (s, 1H), 7.71 – 7.64 (m, 4H), 7.59 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.20 (t, J = 7.4 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 12.8 Hz, 1H), 6.55 – 6.45 (m, 1H), 4.62 (t, J = 11.2 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 4.11 (dd, J = 13.1, 7.0 Hz, 1H), 3.94 (dd, J = 13.4, 7.7 Hz, 1H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.12, 138.76, 137.21, 127.90, 126.45, 126.45, 125.81, 125.47, 125.39, 125.11, 124.35, 122.74, 121.08, 119.81, 119.13, 111.23, 105.89, 57.01, 52.21, 38.39. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1501.

(E)-N-((3a,7a-dihydrobenzofuran-3-yl)methyl)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (3a).

To a solution of **47** (895.0 mg, 5 mmol) in methanol, **49a** (1320.0 mg, 5 mmol) and K_2CO_3 (140.0 mg, 10 mmol) were added in batches at room temperature. Thereafter the reaction mixture was stirred for 4 h and concentrated. The residue was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed. The residue was then purified via flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1/1, v/v) to give free base of **3a** as colorless oil. **3a** was prepared using general procedure of salification as colorless oil. Yield: 65%. ^{1}H-NMR (400 MHz, MeOD) δ 8.15 (s, 1H), 7.88 – 7.78 (m, 1H), 7.61 (s, 1H), 7.36 – 7.33 (m, 2H), 6.94 (dd, J = 7.5, 1.0 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.82 (d, J = 23.9 Hz, 2H), 5.65 (s, 1H), 4.62 (d, J = 37.6 Hz, 2H), 4.03 (d, J = 7.2 Hz, 2H); ^{13}C NMR (101 MHz, MeOD) δ 160.71, 155.73, 148.11, 147.99, 130.40, 128.24, 128.17, 127.69, 126.32, 126.22, 124.29, 124.25, 123.04, 121.89, 113.19, 112.78, 110.78, 76.08, 51.45. HRMS (ESI) m/z calcd for $C_{19}H_{17}F_3NO$ $(M+H)^+$ 332.1262, found 332.1263.

(E)-N-((3a,7a-dihydrobenzofuran-3-yl)methyl)-N-ethyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine (3b).

To a solution of the free base of **3a** (360.0 mg, 1.4 mmol) in DMF (10 mL) was added sodium hydride (52 mg, 1.4 mmol) in batches at 0 ^{o}C under N_2 atmosphere. The reaction mixture was stirred for 15 min and iodoethane (219.0 μL, 2.7 mmol) was

added into the solution. The mixture was stirred at room temperature overnight, poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed. The residue was then purified via flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1/5, v/v) to give the free base of **11b** as colorless oil. Yield: 50%..^{1}H-NMR (400 MHz, MeOD) δ 8.15 (s, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 6.4 Hz, 2H), 7.44 (ddd, J = 9.5, 5.9, 2.2 Hz, 3H), 7.41 – 7.33 (m, 2H), 6.98 (d, J = 15.8 Hz, 1H), 6.51 – 6.33 (m, 1H), 4.63 (s, 2H), 4.06 (dd, J = 7.0, 3.4 Hz, 2H), 3.37 (q, J = 7.3 Hz, 2H), 1.47 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.48 , 147.91, 140.15, 134.28, 128.57, 128.57, 127.29, 126.93, 126.46, 126.46, 125.28, 123.44, 123.11, 119.34, 119.31, 111.51, 109.83, 54.28, 48.31, 45.28, 8.22. HRMS (ESI) m/z calcd for $C_{21}H_{21}NO$ $(M+H)^+$ 360.1575, found 360. 1576.

(E)-N-((3a,7a-dihydrobenzofuran-3-yl)methyl)-N-isopropyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-amine (3c).

Yield: 50%. **3c** was synthesized using general procedure of salification as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.03 (d, J = 5.7 Hz, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.58 (dd, J = 7.9, 2.4 Hz, 1H), 7.37 (dddd, J = 33.9, 26.7, 12.6, 5.2 Hz, 4H), 7.20 (t, J = 7.9 Hz, 1H), 6.92 (td, J = 7.1, 4.0 Hz, 1H), 6.81 (d, J = 8.1 Hz, 1H), 4.71 – 4.58 (m, 1H), 4.57 – 4.44 (m, 3H), 3.95 – 3.79 (m, 1H), 3.31 (d, J = 1.6 Hz, 6H); ^{13}C NMR (101 MHz, MeOD) δ 155.57, 147.96, 139.62, 127.04, 127.04, 126.41, 125.86, 125.80, 125.74, 125.30, 123.47, 123.47, 123.08, 119.31,

114.63, 111.51, 109.86, 57.39, 47.54, 37.50, 37.50. HRMS (ESI) m/z calcd for $C_{22}H_{23}F_3NO$ $(M+H)^+$ 374.1732, found 374.1733.

(E)-N-(benzofuran-3-ylmethyl)-N-methy-2-en-1-amine hydrochloride (4a).

(E)-1-bromobut-2-ene was bought from the chemical reagent companies Yield: 45%. **4a** was synthesized by the general procedure given above as white solid. m.p. 171-173 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.15 (s, 1H), 7.87 – 7.81 (m, 1H), 7.60 (dt, J = 10.1, 4.9 Hz, 1H), 7.46 – 7.37 (m, 2H), 6.96 – 6.83 (m, 1H), 6.19 – 6.08 (m, 1H), 4.60 (dd, J = 17.9, 9.2 Hz, 1H), 4.49 – 4.42 (m, 1H), 3.91 (dt, J = 23.7, 11.8 Hz, 1H), 3.74 (dd, J = 13.1, 7.9 Hz, 1H), 2.84 (s, 3H), 1.85 (dt, J = 5.1, 2.5 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.47, 147.93, 138.69, 126.46, 125.22, 123.42, 119.40, 119.00, 111.45, 109.90, 57.37, 48.17, 38.10, 16.87. HRMS (ESI) m/z calcd for $C_{14}H_{18}NO$ $(M+H)^+$ 284.2014, found 284.2008.

(E)-N-((1H-indol-7-yl)methyl)-N-methylbut-2-en-1-amine hydrochloride (4b).

Yield: 62%. **16a** was synthesized by the procedure of **4b** as white solid. m.p. 154-156 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.67 (s, 1H), 7.36 (s, 1H), 7.19 (s, 1H), 7.11 (s, 1H), 6.56 (s, 1H), 6.02 (s, 1H), 5.62 (s, 1H), 4.43 (s, 2H), 3.71 – 6.38 (m, 2H), 2.65 (s, 3H), 1.71 – 1.61 (m, 3H); ^{13}C NMR (126 MHz, MeOD) δ 138.25, 135.47, 129.26, 125.33, 124.17, 122.18, 119.07, 118.91, 112.20, 102.02, 57.51, 55.37, 37.78, 16.73. HRMS (EI) m/z calcd for $C_{14}H_{18}N_2$ $(M)^+$ 214.1470, found 214.1471.

(E)-N-(benzofuran-3-ylmethyl)-3-cyclopentyl-N-methyprop-2-en-1-amine hydrochloride (5a).

Yield: 54%. **5a** was synthesized by the general procedure given above as white solid. m.p. 154-156 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.47 – 7.34 (m, 2H), 6.07 (dd, J = 15.4, 7.7 Hz, 1H), 5.62 (dt, J = 14.8, 7.3 Hz, 1H), 4.59 (d, J = 14.0 Hz, 1H), 4.42 (d, J = 13.9 Hz, 1H), 3.99 – 3.84 (m, 1H), 3.77 – 3.62 (m, 1H), 2.82 (s, 3H), 2.59 (dd, J = 15.9, 8.3 Hz, 1H), 1.85 (s, 2H), 1.77 – 1.58 (m, 4H), 1.39 (s, 2H); ^{13}C NMR (101 MHz, MeOD) δ 155.44, 148.27, 147.84, 126.39, 125.28, 123.43, 119.27, 115.81, 111.50, 109.94, 57.47, 43.10, 38.13, 32.26, 32.26, 24.71, 24.71. HRMS (ESI) m/z calcd for $C_{18}H_{24}NO$ $(M+H)^{+}$ 270.1858, found 270.1857.

(E)-N-((1H-indol-7-yl)methyl)-3-cyclopentyl-N-methylprop-2-en-1-amine hydrochloride (5b).

Yield: 74%. **5b** was synthesized by the general procedure given above as white solid. m.p. 159-161 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 2.4 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 6.55 (d, J = 3.1 Hz, 1H), 5.95 (dd, J = 12.8, 7.7 Hz, 1H), 5.59 (dt, J = 8.4, 1.8 Hz, 1H), 4.40 (d, J = 12.1 Hz, 2H), 3.65 (d, J = 7.2 Hz, 2H), 2.64 (s, 3H), 2.53 – 2.49 (m, 1H), 1.84 (d, J = 8.4 Hz, 2H), 1.75 – 1.56 (m, 4H), 1.40 – 1.31 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 147.78, 135.48, 129.27, 125.35, 124.21, 122.21, 119.02, 115.83, 112.14, 102.03,

57.58, 55.45, 42.95, 37.79, 32.15, 32.15, 24.59, 24.59. HRMS (EI) m/z calcd for $C_{18}H_{26}N_2$ $(M)^+$ 268.1939, found 268.1940.

(E)-N-(benzofuran-3-ylmethyl)-3-cyclohexyl-N-methyprop-2-en-1-amine hydrochloride (6a).

Yield: 57%. **6a** was synthesized by the general procedure given above as yellow soil. ^{1}H-NMR (400 MHz, MeOD) δ 8.10 (s, 1H), 7.80 (d, J = 7.3 Hz, 1H), 7.58 (t, J = 9.1 Hz, 1H), 7.47 – 7.30 (m, 2H), 6.19 – 5.97 (m, 1H), 5.71 – 5.53 (m, 1H), 4.52 (d, J = 46.0 Hz, 2H), 3.81 (d, J = 66.3 Hz, 2H), 2.80 (d, J = 14.3 Hz, 3H), 2.65 – 2.51 (m, 1H), 1.85 (dt, J = 11.2, 6.8 Hz, 2H), 1.75 – 1.50 (m, 5H), 1.44 – 1.23 (m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.49, 149.31, 141.84, 125.28, 123.43, 119.27, 115.81, 112.54， 111.50, 109.94, 57.78, 55.55, 40.68, 37.86, 32.01, 32.01, 25.68, 25.50, 25.50. HRMS (ESI) m/z calcd for $C_{19}H_{26}NO$ $(M+H)^+$ 284.2014, found 284.2008.

(E)-N-((1H-indol-7-yl)methyl)-3-cyclohexyl-N-methylprop-2-en-1-amine hydrochloride (6b).

Yield: 72%. **6b** was synthesized by the general procedure given above as white solid. m.p. 165-167 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 3.1 Hz, 1H), 7.23 (d, J = 7.1 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.56 (d, J = 3.1 Hz, 1H), 5.99 (d, J = 2.4 Hz, 1H), 5.62 – 5.49 (m, 1H), 4.55 (s, 2H), 3.78 (s, 2H), 2.73 (s, 3H), 2.09 (d, J = 6.8 Hz, 1H), 1.85 – 1.45 (m, 5H), 1.35 – 1.25 (m, 2H), 1.24 – 1.05 (m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 148.94, 135.59, 129.37, 125.46, 124.35, 122.33, 119.12, 115.51, 112.20, 102.13, 57.78, 55.55, 40.68, 37.86, 32.01, 32.01,

25.68, 25.50, 25.50. HRMS (EI) m/z calcd for $C_{19}H_{26}N_2$ $(M)^+$ 282.2096, found 282.2095.

(E)-N-(benzofuran-3-ylmethyl)-3-(furan-2-yl)-N-methylprop-2-en-1-amine hydrochloride (7a).

Yield: 35%. **7a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 8.14 (d, J = 20.9 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.40 (ddd, J = 15.0, 13.9, 6.8 Hz, 2H), 6.76 (dd, J = 25.9, 15.6 Hz, 1H), 6.60 – 6.44 (m, 2H), 6.28 – 6.12 (m, 1H), 4.66 (d, J = 13.9 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 4.10 (dt, J = 14.4, 7.2 Hz, 1H), 3.91 (dd, J = 13.1, 8.3 Hz, 1H), 2.93 – 2.76 (m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.53, 150.91, 147.94, 143.54, 128.41, 125.28, 125.18, 123.46, 119.29, 111.50, 111.41, 111.07, 110.98, 109.81, 57.37, 48.14, 38.26. HRMS (ESI) m/z calcd for $C_{17}H_{18}NO_2$ $(M+H)^+$ 268.1338, found 268.1334.

(E)-N-((1H-indol-7-yl)methyl)-3-(furan-2-yl)-N-methylprop-2-en-1-amine hydrochloride (7b).

Yield: 66%. **7b** was synthesized by the general procedure given above as white solid. m.p. 147-149 ^{o}C. ^{1}H NMR (500 MHz, MeOD) δ 7.71 (d, J = 7.8 Hz, 1H), 7.53 (s, 1H), 7.36 – 7.21 (m, 1H), 7.28 (t, J = 12.2 Hz, 1H), 7.19 – 7.11 (m, 1H), 6.75 – 6.66 (m, 1H), 6.58 (d, J = 3.1 Hz, 1H), 6.53 – 6.45 (m, 2H), 6.24 – 6.14 (m, 1H), 4.63 (s, 2H), 4.09 – 3.87 (m, 2H), 2.77 – 2.57 (m, 1H); ^{13}C NMR (126 MHz, MeOD) δ 150.89, 143.33, 135.50, 129.31, 128.14, 125.39, 124.26, 122.30, 119.06, 113.94,

112.00, 111.27, 110.71, 102.06, 57.47, 55.55, 37.86. HRMS (EI) m/z calcd for $C_{17}H_{18}N_2O$ $(M)^+$ 266.1419, found 266.1418.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(thiophen-2-yl)prop-2-en-1-amine hydrochloride (8a).

Yield: 40%. **8a** was synthesized by the general procedure given above as yellow soil. ^{1}H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.80 (d, J = 1.2 Hz, 1H), 7.61 – 7.58 (m, 1H), 7.44 (dd, J = 7.2, 1.2 Hz, 1H), 7.39 – 7.35 (m, 1H), 7.2 5 (t, J = 7.6 Hz, 2H), 7.16 (d, J = 7.5 Hz, 1H), 6.91 (d, J = 15.8 Hz, 1H), 6.41 – 6.31 (m, 1H), 4.66 (t, J = 9.5 Hz, 1H), 4.54 – 4.46 (m, 1H), 4.11 (dt, J = 7.0, 5.7 Hz, 1H), 3.94 (dd, J = 13.1, 8.2 Hz, 1H), 2.90 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 155.42, 147.85, 140.92, 138.17 , 135.09, 129.40, 128.26, 127.21, 125.16, 123.81, 123.35, 119.24, 115.81, 111.39, 57.55, 48.12, 38.27. HRMS (ESI) m/z calcd for $C_{17}H_{18}NOS$ $(M+H)^+$ 360.1422, found 360.1421.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(thiophen-2-yl)prop-2-en-1-amine hydrochloride (8b).

Yield: 43%. **8b** was synthesized by the general procedure given above as white solid. m.p. 144-147 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, J = 7.7 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.16 (d, J = 7.1 Hz, 1H), 7.08 (d, J = 7.0 Hz, 2H), 7.02 – 6.92 (m, 1H), 6.91 (d, J = 4.2 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.19 – 6.07 (m, 1H), 4.29 (s, 2H), 3.66 (d, J = 7.2 Hz, 2H), 2.58 (d, J = 8.1 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 140.66, 135.49, 130.70, 129.00, 127.20, 126.95, 125.20, 124.98, 123.32, 121.17,

119.38, 118.96, 115.56, 101.76, 58.18, 56.84, 39.11. HRMS (EI) m/z calcd for $C_{17}H_{18}N_2S$ $(M)^+$ 282.1191, found 282.1189.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(naphthalen-1-yl)prop-2-en-1-amine hydrochloride (9a).

Yield: 46%. **9a** was synthesized by the general procedure given above as white solid. m.p. 149-151 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.16 (d, J = 8.7 Hz, 2H), 7.94 – 7.87 (m, 2H), 7.86 – 7.73 (m, 3H), 7.61 (d, J = 7.8 Hz, 1H), 7.59 – 7.34 (m, 5H), 6.49 – 6.34 (m, 1H), 4.67 (d, J = 36.8 Hz, 2H), 4.18 (d, J = 49.8 Hz, 2H), 2.97 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.54, 148.00, 138.05, 133.77, 132.67, 131.01, 129.06, 128.32, 126.456, 126.27, 125.76, 125.26, 124.07, 123.48, 122.98, 122.05, 119.37, 111.51, 109.89, 57.67, 48.18, 38.48. HRMS (ESI) m/z calcd for $C_{23}H_{22}NO$ $(M+H)^+$ 328.1701, found 328.1700.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(naphthalen-1-yl)prop-2-en-1-amine hydrochloride (9b).

Yield: 39%. **9b** was synthesized by the general procedure given above as white solid. m.p. 137-139 ^oC. ^1H NMR (400 MHz, MeOD) δ 8.15 (d, J = 8.1 Hz, 1H), 7.88 (dd, J = 8.2, 7.8 Hz, 2H), 7.72 – 7.63 (m, 3H), 7.60 – 7.46 (m, 4H), 7.36 (d, J = 3.1 Hz, 1H), 7.24 (d, J = 7.1 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 6.47 – 6.36 (m, 1H), 4.43 (s, 2H), 3.88 (d, J = 7.1 Hz, 2H), 2.71 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 136.87, 135.43, 134.87, 133.62, 133.29, 130.90, 128.88, 128.30, 128.12, 125.92, 125.49, 125.12, 124.83, 123.73, 123.34, 123.12, 123.02, 121.14,

118.88, 115.30, 58.32, 56.80, 39.18. HRMS (EI) m/z calcd for $C_{23}H_{22}N_2$ $(M)^+$ 326.1783, found 326.1784.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(naphthalen-2-yl)prop-2-en-1-amine hydrochloride (10a).

Yield: 51%. **10a** was synthesized by the general procedure given above as white solid. m.p. 148-150 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.14 (s, 1H), 7.91 – 7.81 (m, 5H), 7.73 (dd, J = 8.7, 1.7 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.53 – 7.48 (m, 2H), 7.41 (dtd, J = 18.2, 7.3, 1.3 Hz, 2H), 7.12 (d, J = 15.7 Hz, 1H), 6.60 – 6.44 (m, 1H); ^{13}C NMR (126 MHz, MeOD) δ 155.43, 147.86, 140.73, 133.63, 133.40, 132.61, 128.09, 127.78, 127.44, 127.24, 126.35, 126.27, 126.17, 125.16, 123.36, 122.87, 119.27, 116.48, 111.39, 109.81, 57.58, 47.94, 38.34. HRMS (ESI) m/z calcd for $C_{23}H_{22}NO$ $(M+H)^+$ 328.1701, found 328.1700.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(naphthalen-2-yl)prop-2-en-1-amine hydrochloride (10b).

Yield: 55%. **10b** was synthesized by the general procedure given above as white solid. m.p. 173-174 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.85 – 7.62 (m, 4H), 7.71 (t, J = 6.7 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.39 (d, J = 3.2 Hz, 1H), 7.30 (d, J = 7.1 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 6.4 Hz, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.53 – 6.42 (m, 1H), 4.80 – 4.56 (m, 2H), 4.21 – 3.97 (m, 2H), 2.86 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 140.82, 135.62, 133.73, 133.49, 132.73, 129.46, 128.16, 127.87, 127.53, 127.34, 126.36, 126.27, 125.54, 124.42, 122.99, 122.48, 119.20, 116.39, 112.07,

102.22, 57.91, 55.69, 38.15. HRMS (EI) m/z calcd for $C_{23}H_{22}N_2$ $(M)^+$ 326.1783, found 326.1786.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-phenylprop-2-en-1-amine hydrochloride (11a).

Yield: 60%. **11a** was synthesized by the general procedure given above as white solid. m.p. 167-169 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.80 (m, 1H), 7.60 (m, 1H), 7.48 (d, J = 23.1 Hz, 2H), 7.39 (m, 5H), 6.95 (d, J = 16.0 Hz, 1H), 6.40 (m, 1H), 4.68 (d, J = 13.7 Hz, 1H), 4.52 (d, J = 13.5 Hz, 1H), 4.12 (s, 1H), 3.95 (s, 1H), 2.88 (d, J = 17.6 Hz 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.52, 147.92, 140.80, 135.26, 128.78, 128.48, 128.48, 126.73, 126.73, 126.43, 125.26, 123.45, 119.33, 116.27, 111.49, 109.93, 57.61, 47.35, 38.39. HRMS (ESI) m/z calcd for $C_{19}H_{20}NO$ $(M+H)^+$ 278.1545, found 278.1545.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-phenylprop-2-en-1-amine hydrochloride (11b).

Yield: 76%. **11b** was synthesized by the general procedure given above as white solid. m.p. 180-181 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.76 – 7.67 (m, 1H), 7.51 (d, J = 7.0 Hz, 2H), 7.40 – 7.25 (m, 5H), 7.16 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 4.8 Hz, 1H), 6.57 (t, J = 6.4 Hz, 1H), 6.37 – 6.25 (m, 1H), 4.79 – 4.75 (m, 1H), 4.60 – 4.50 (m, 1H), 4.19 – 4.07 (m, 1H), 3.90 – 3.65 (m, 1H), 2.83 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 138.29, 135.42, 134.24, 134.12, 129.18, 128.39, 128.39, 128.05, 128.05, 125.19,

125.18, 123.87, 121.85, 119.11, 118.25, 101.97, 57.75, 55.98, 38.40. HRMS (EI) m/z calcd for $C_{19}H_{20}N_2$ $(M)^+$ 276.1626, found 276.1625.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (12a).

Yield: 51%. **12a** was synthesized by the general procedure given above as white solid. m.p. 147-148 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.80 (d, J = 7.4 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.46 – 7.34 (m, 4H), 6.92 (d, J = 16.3 Hz, 1H), 6.39 (dd, J = 15.2, 7.9 Hz, 1H), 4.59 (d, J = 36.9 Hz, 2H), 4.02 (d, J = 52.6 Hz, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.48, 147.94, 139.33, 134.47, 128.61, 128.61, 128.22, 128.22, 126.41, 125.33 125.29, 123.47, 119.31, 117.20, 111.51, 109.81, 57.43, 47.21, 38.43. HRMS (ESI) m/z calcd for $C_{19}H_{19}ClNO$ $(M+H)^+$ 312.1155, found 312.1154.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (12b).

Yield: 64%. **12b** was synthesized by the general procedure given above as white solid. m.p. 159-163 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.66 (d, J = 7.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.22 (d, J = 7.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.79 (d, J = 2.8 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.44 – 6.33 (m, 1H), 4.41 (s, 2H), 3.79 (d, J = 6.7 Hz, 2H), 2.67 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 138.21, 135.45, 134.16, 134.09, 129.21, 128.42, 128.42, 128.01, 128.01, 125.24, 125.16,

123.96, 121.97, 119.00, 118.28, 101.96, 57.74, 55.99, 38.42. HRMS (EI) m/z calcd for $C_{19}H_{19}FN_2$ $(M)^+$ 310.1237, found 310.1236.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (13a).

Yield: 56%. **13a** was synthesized by the general procedure given above as white solid. m.p. 162-164 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.64 – 7.51 (m, 3H), 7.40 (ddd, J = 15.1, 13.9, 6.8 Hz, 2H), 7.12 (t, J = 8.7 Hz, 2H), 6.92 (d, J = 15.8 Hz, 1H), 6.41 – 6.24 (m, 1H), 4.54 (s, 2H), 4.02 (d, J = 51.4 Hz, 2H), 2.90 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 155.53, 147.97, 139.51, 128.77, 128.77, 128.69, 128.69, 126.37, 125.27, 123.46, 119.29, 116.17, 115.38, 115.17, 111.49, 109.88, 57.51, 47.88, 38.37. HRMS (ESI) m/z calcd for $C_{19}H_{19}FNO$ $(M+H)^+$ 296.1451, found 296.1450.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (13b).

Yield: 54%. **13b** was synthesized by the general procedure given above as white solid. m.p. 161-163 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.68 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 8.5Hz, 2H), 7.37 (d, J = 2.4 Hz, 1H), 7.23 (d, J = 4.6 Hz, 1H), 7.16 – 7.07 (m, 3H), 6.81 (d, J = 12.8 Hz, 1H), 6.57 (d, J = 3.1 Hz, 1H), 6.37 – 6.27 (m, 1H), 4.46 (s, 2H), 3.83 (d, J = 7.0 Hz, 2H), 2.70 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 138.96, 135.48, 131.73, 129.28, 128.61, 128.58, 125.35, 124.20, 122.20, 119.05, 118.15,

116.45, 115.19, 115.02, 112.35, 102.03, 57.69, 55.70, 38.13. HRMS (EI) m/z calcd for $C_{19}H_{19}FN_2$ $(M)^+$ 294.1532, found 294.1531.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-bromophenyl)-N-methylprop-2-en-1-amine hydrochloride (14a).

Yield: 43%. **14a** was synthesized by the general procedure given above as white solid. m.p. 164-165 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.81 (d, J = 7.4 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 8.4 Hz, 2H), 7.47 – 7.35 (m, 4H), 6.90 (d, J = 15.8 Hz, 1H), 6.51 – 6.31 (m, 1H), 4.58 (s, 2H), 4.01 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.50, 147.75, 139.49, 134.24, 131.64, 131.64, 128.45, 128.45, 126.39, 125.11, 123.47, 122.58, 119.29, 117.11, 111.30, 109.92, 57.43, 48.09, 38.39. HRMS (ESI) m/z calcd for $C_{19}H_{19}BrNO$ $(M+H)^+$ 356.0650, found 358.0636.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-bromophenyl)-N-methylprop-2-en-1-amine hydrochloride (14b).

Yield: 51%. **14b** was synthesized by the general procedure given above as white solid. m.p. 131-134 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.63 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 3.1 Hz, 1H), 7.18 (d, J = 7.0 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 6.8 Hz, 1H), 6.54 (d, J = 3.1 Hz, 1H), 6.46 – 6.35 (m, 1H), 4.29 (s, 2H), 3.67 (d, J = 6.9 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 135.84, 135.38, 135.10, 131.33, 131.33, 128.79, 128.25, 128.04, 128.04, 124.73, 121.69, 121.56, 120.94, 118.83, 115.77, 58.22, 56.94, 39.31. HRMS (EI) m/z calcd for $C_{19}H_{19}BrN_2$ $(M)^+$ 354.0732, found 354.0734.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(p-tolyl)prop-2-en-1-amine hydrochloride (15a).

Yield: 46%. **15a** was synthesized by the general procedure given above as white solid. m.p. 164-165 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.62 (dd, J = 15.1, 7.8 Hz, 2H), 7.40 (qd, J = 14.2, 6.8 Hz, 3H), 7.23 – 7.11 (m, 2H), 7.08 (d, J = 16.0 Hz, 1H), 6.59 – 6.38 (m, 1H), 4.61 (s, 2H), 4.09 (s, 2H), 2.91 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.53, 147.88, 140.78, 139.05, 132.50, 129.09, 129.09, 126.70, 126.70, 126.42, 125.26, 123.44, 119.33, 115.11, 111.49, 109.96, 57.75, 47.88, 38.38, 19.88. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO$ $(M+H)^{+}$ 292.1701, found 292.1702.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(p-tolyl)prop-2-en-1-amine hydrochloride (15b).

Yield: 76%. **15b** was synthesized by the general procedure given above as white solid. m.p. 122-124 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.69 (d, J = 7.8 Hz, 1H), 7.46 – 7.35 (m, 3H), 7.25 (d, J = 7.2 Hz, 1H), 7.19 (d, J = 7.9 Hz, 2H), 7.13 – 7.00 (m, 2H), 6.81 (d, J = 15.8 Hz, 1H), 6.57 (t, J = 5.5 Hz, 1H), 6.37 – 6.26 (m, 1H), 4.52 (s, 2H), 3.88 (d, J = 7.3 Hz, 2H), 2.73 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 140.50, 138.87, 135.50, 132.46, 129.30, 128.95, 128.95, 126.59, 126.59, 125.38, 124.25, 122.26, 119.06, 115.04, 112.15, 102.06, 57.85, 55.57, 37.97, 19.78. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2$ $(M)^{+}$ 290.1783, found 290.1784.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-bromophenyl)-N-methylprop-2-en-1-amine hydrochloride (16a).

Yield: 43%. **16a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.85 – 7.74 (m, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.42 – 7.35 (m, 2H), 6.98 – 6.91 (m, 2H), 6.88 (d, J = 15.7 Hz, 1H), 6.22 (dt, J = 15.5, 7.5 Hz, 1H), 4.66 (d, J = 13.9 Hz, 1H), 4.50 (d, J = 13.9 Hz, 1H), 4.10 (dd, J = 12.7, 7.2 Hz, 1H), 3.91 (dd, J = 13.0, 7.8 Hz, 1H), 3.81 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 160.61, 155.51, 147.93, 140.59, 128.18, 128.18, 127.87, 126.43, 125.25, 123.45, 119.36, 113.81, 113.81, 113.47, 111.48, 109.91, 57.84, 54.40, 48.13, 38.26. HRMS (ESI) m/z calcd for $C_{20}H_{21}NO_2$ $(M+H)^+$ 307.1572, found 307.1575.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (16b).

Yield: 61%. **16b** was synthesized by the general procedure given above as white solid. m.p. 152-154 ^{o}C. ^{1}H NMR (500 MHz, MeOD) δ 7.68 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 3.1 Hz, 1H), 7.29 – 7.20 (m, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.91 (d, J = 4.6 Hz, 2H), 6.80 (d, J = 2.4 Hz, 1H), 6.56 (d, J = 6.4 Hz, 1H), 6.25 – 6.14 (m, 1H), 4.51 (s, 2H), 3.87 (d, J = 5.5 Hz, 2H), 3.80 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 160.42, 140.13, 135.50, 129.27, 128.04, 128.04, 127.88, 125.36, 124.26, 122.21, 119.06, 113.67, 113.67, 113.41, 112.25, 102.02, 57.94, 55.49, 54.28, 37.89. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2O$ $(M)^+$ 306.1732, found 306.1731.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-ethoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (17a).

Yield: 41%. **17a** was synthesized by the general procedure given above as white solid. m.p. 153-154 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.12 (d, J = 5.9 Hz, 1H), 7.81 (d, J = 6.0 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.47 – 7.34 (m, 4H), 6.96 – 6.79 (m, 3H), 6.30 – 6.14 (m, 1H), 4.66 (d, J = 14.0 Hz, 1H), 4.50 (d, J = 13.8 Hz, 1H), 4.07 (ddd, J = 20.8, 13.6, 7.2 Hz, 3H), 3.91 (dd, J = 13.0, 8.0 Hz, 1H), 2.88 (s, 3H), 1.39 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 159.90, 155.50, 147.96, 140.60, 128.18, 128.18, 127.76, 126.45, 125.25, 123.45, 119.40, 114.33, 114.33, 113.82, 111.48, 109.91, 63.19, 57.85, 47.95, 38.25, 13.70. HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_2$ $(M+H)^+$ 322.1807, found 322.1808.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-ethoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (17b).

Yield: 67%. **17b** was synthesized by the general procedure given above as white solid. m.p. 148-149 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.70 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.36 (t, J = 6.6 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.90 (t, J = 7.5 Hz, 2H), 6.83 – 6.81 (m, 1H), 6.57 (d, J = 3.2 Hz, 1H), 6.19 – 6.04 (m, 2H), 4.61 (s, 2H), 4.09 – 4.00 (m, 2H), 3.97 (d, J = 7.4 Hz, 2H), 2.81 (d, J = 27.0 Hz, 3H), 1.41 – 1.33 (m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 159.83, 140.27, 135.59, 129.38, 128.13, 128.13, 127.85, 125.46, 124.31, 122.30, 119.15, 114.29,

114.29, 113.64, 112.41, 102.13, 63.17, 58.09, 55.61, 38.02, 13.70. HRMS (EI) m/z calcd for $C_{21}H_{24}N_2O$ $(M)^+$ 320.1889, found 320.1890.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(4-nitrophenyl)prop-2-en-1-amine hydrochloride (18a).

Yield: 45%. **18a** was synthesized by the general procedure given above as yellow oil ^oC. ^1H NMR (400 MHz, MeOD) δ 8.25 (d, J = 8.5 Hz, 2H), 8.14 (s, 1H), 7.81 (t, J = 13.0 Hz, 1H), 7.75 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.41 (dq, J = 14.6, 7.2 Hz, 2H), 7.05 (d, J = 15.8 Hz, 1H), 6.63 (dd, J = 15.5, 7.8 Hz, 1H), 4.70 (d, J = 13.6 Hz, 1H), 4.57 (d, J = 14.0 Hz, 1H), 4.19 (dd, J = 13.2, 6.9 Hz, 1H), 4.06 – 3.94 (m, 1H), 2.92 (d, J = 7.7 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.51, 148.08, 147.82, 141.60, 138.11, 127.68, 127.68, 126.43, 125.28, 123.59, 123.59, 123.48, 121.35, 119.39, 111.50, 109.79, 57.12, 47.89, 38.62. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_3$ $(M+H)^+$ 323.1396, found 323.1393.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(4-nitrophenyl)prop-2-en-1-amine hydrochloride (18b).

Yield: 73%. **18b** was synthesized by the general procedure given above as white solid. m.p. 133-136 ^oC. ^1H NMR (400 MHz, MeOD) δ 8.25 (d, J = 8.7 Hz, 2H), 7.75 – 7.65 (m, 3H), 7.39 (d, J = 2.4 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 15.7 Hz, 1H), 6.65 – 6.54 (m, 2H), 4.53 (s, 2H), 3.94 (d, J = 5.5 Hz, 2H), 2.77 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 147.23, 142.30, 135.37, 134.98, 128.85, 127.40, 127.17, 127.17, 125.47, 124.82, 123.39, 123.39, 123.28, 121.15,

118.87, 115.33, 57.93, 56.99, 39.42. HRMS (EI) m/z calcd for $C_{19}H_{19}N_3O_2(M)^+$ 321.1477, found 321.1478.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-(difluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (19a).

Yield: 55%. **19a** was synthesized by the general procedure given above as white solid. m.p. 145-146 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.67 – 7.53 (m, 5H), 7.47 – 7.35 (m, 2H), 6.98 (d, J = 16.1 Hz, 1H), 6.84 (d, J = 56.0 Hz, 1H), 6.47 (dt, J = 15.1, 7.5 Hz, 1H), 4.55 (s, 2H), 3.99 (s, 2H), 2.91 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.57, 147.96, 139.62, 137.66, 127.04, 127.04, 126.41, 125.86, 125.80, 125.74, 125.30, 123.47, 119.31, 118.26, 114.63, 111.51, 109.86, 57.39, 48.14, 38.50. HRMS (ESI) m/z calcd for $C_{20}H_{20}F_2NO$ $(M+H)^+$ 328.1513, found 328.1512.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-(difluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (19b).

Yield: 64%. **19b** was synthesized by the general procedure given above as yellow oil. ^1H NMR (400 MHz, MeOD) δ 7.48 – 7.30 (m, 5H), 7.25 (d, J = 3.1 Hz, 1H), 7.03 (d, J = 6.9 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.86 (s, 1H), 6.72 (s, 1H), 6.60 (d, J = 16.1 Hz, 1H), 6.58 – 6.55 (m, 1H), 6.52 – 6.41 (m, 2H), 3.87 (s, 2H), 3.27 (d, J = 6.6 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 139.53, 135.34, 131.99, 128.55, 128.42, 126.21, 126.21, 125.51, 125.45, 124.13, 121.62, 120.82, 119.28, 118.60,

117.24, 114.89, 101.15, 59.29, 58.82, 41.06. HRMS (EI) m/z calcd for $C_{20}H_{20}F_2N_2$ $(M)^+$ 326.1595, found 326.1596.

(E)-4-(3-((benzofuran-3-ylmethyl)(methyl)amino)prop-1-en-1-yl)benzonitril e hydrochloride (20a).

Yield: 51%. **20a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.13 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 7.1 Hz, 1H), 7.74 (d, J = 8.2 Hz, 3H), 7.69 (d, J = 8.3 Hz, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.47 – 7.35 (m, 3H), 6.99 (d, J = 15.7 Hz, 1H), 6.64 – 6.52 (m, 1H), 4.69 (d, J = 13.9 Hz, 1H), 4.56 (d, J = 14.0 Hz, 1H), 4.18 (dd, J = 13.3, 6.7 Hz, 1H), 4.00 (dd, J = 13.1, 8.1 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 155.43, 147.86, 139.73, 138.46, 132.24, 132.24, 127.38, 127.38, 126.30, 125.19, 123.37, 120.51, 119.21, 117.95, 111.79, 111.41, 109.77, 57.08, 48.18, 38.54. HRMS (ESI) m/z calcd for $C_{20}H_{19}NO$ $(M+H)^+$ 303.1497, found 303.1496.

(E)-4-(3-(((1H-indol-7-yl)methyl)(methyl)amino)prop-1-en-1-yl)benzonitrile hydrochloride (20b).

Yield: 52%. **20b** was synthesized by the general procedure given above as white solid. m.p. 138-139 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.67 (d, J = 8.4 Hz, 2H), 7.60 (s, 3H), 7.31 (s, 1H), 7.12 (s, 1H), 7.04 (s, 1H), 6.75 (d, J = 8.6 Hz, 1H), 6.53 (d, J = 4.6 Hz, 2H), 4.19 (s, 2H), 3.54 (d, J = 2.4 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 140.07, 137.69, 135.55, 132.28, 132.28, 129.34, 127.41, 127.41, 125.38,

124.13, 122.17, 121.62, 119.13, 118.11, 112.96, 111.66, 102.10, 57.59, 56.21, 38.69. HRMS (EI) m/z calcd for $C_{20}H_{19}N_3$ $(M)^+$ 301.1579, found 301.1581.

(E)-N-(benzofuran-3-ylmethyl)-3-(4-(tert-butyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (21a).

Yield: 55%. **21a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.16 (s, 1H), 7.85 (dd, J = 7.1, 1.4 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.47 – 7.39 (m, 6H), 6.97 – 6.91 (m, 1H), 6.43 – 6.31 (m, 1H), 4.70 (d, J = 13.9 Hz, 1H), 4.54 (d, J = 13.9 Hz, 1H), 4.19 – 4.10 (m, 1H), 3.99 – 3.89 (m, 1H), 2.92 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 157.29, 155.43, 147.80, 136.07, 130.02, 127.32, 126.67, 126.67, 125.35, 125.35, 123.69, 123.35, 120.29, 119.18, 116.55, 111.40, 110.76, 109.78, 58.12, 54.50, 38.29, 38.29, 38.29. ^{13}C NMR (101 MHz, MeOD) δ 155.47, 152.12, 147.97, 140.54, 132.54, 129.90, 129.85, 126.57, 126.57, 126.51, 125.35, 125.35, 125.21, 123.44, 119.49, 115.54, 111.45, 110.00, 57.73, 47.93, 38.32, 34.16, 30.26, 30.26, 30.26. HRMS (ESI) m/z calcd for $C_{23}H_{28}NO$ $(M+H)^+$ 334.2171, found 334.2172.

(E)-N-((1H-indol-7-yl)methyl)-3-(4-(tert-butyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (21b).

Yield: 80%. **21b** was synthesized by the general procedure given above as white solid. m.p. 119-122 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.59 (d, J = 7.8, 1H), 7.37 (d, J = 3.2 Hz, 4H), 7.32 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.09 – 7.03 (m, 1H), 6.69 (d, J = 12.8 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 6.31 (d, J = 7.2 Hz, 1H), 4.25 (d, J

= 6.4 Hz, 2H), 3.82 – 3.62 (m, 2H), 2.58 – 2.54 (m, 2H), 1.32 – 1.09 (m, 9H); ^{13}C NMR (101 MHz, MeOD) δ 151.13, 136.49, 135.48, 133.42, 128.78, 126.12, 126.12, 125.39, 125.17, 125.17, 124.94, 124.68, 122.93, 120.68, 118.86, 116.83, 58.76, 57.24, 39.59, 34.05, 30.29, 30.29, 30.29. HRMS (EI) m/z calcd for $C_{23}H_{28}N_2$ $(M)^+$ 332.2252, found 332.2253.

Methyl(E)-4-(3-((benzofuran-3-ylmethyl)(methyl)amino)prop-1-en-1-yl)benzoate hydrochloride (22a).

Yield: 55%. **22a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.5 Hz, 1H), 7.62 (t, J = 8.8 Hz, 3H), 7.48 – 7.30 (m, 2H), 7.00 (d, J = 15.8 Hz, 1H), 6.60 – 6.43 (m, 1H), 4.69 (d, J = 13.9 Hz, 1H), 4.54 (d, J = 13.7 Hz, 1H), 4.15 (d, J = 7.1 Hz, 1H), 4.04 – 3.94 (m, 1H), 3.91 (s, 3H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 166.60, 155.52, 148.02, 139.81, 139.38, 130.15, 129.60, 129.60, 126.82, 126.82, 126.42, 125.28, 123.47, 119.33, 111.50, 109.82, 57.32, 51.31, 48.16, 38.52. HRMS (ESI) m/z calcd for $C_{21}H_{22}NO_3$ $(M+H)^+$ 336.1600, found 336.1599.

methyl(E)-4-(3-(((1H-indol-7-yl)methyl)(methyl)amino)prop-1-en-1-yl)benzoate hydrochloride (22b).

Yield: 73%. **22b** was synthesized by the general procedure given above as white oil. ^{1}H NMR (400 MHz, MeOD) δ 7.97 (s, 2H), 7.54 – 7.45 (m, 3H), 7.29 (s, 1H), 7.09 (s, 1H), 7.02 (s, 1H), 6.72 (d, J = 6.4 Hz, 1H), 6.49 (s, 2H), 4.10 (s, 2H), 3.89 (s, 3H), 3.50 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 135.59, 133.26, 132.91,

129.46, 129.46, 127.14, 126.58, 126.58, 125.24, 124.18, 123.18, 122.35, 121.98, 119.02, 105.24, 102.01, 57.73, 56.16, 51.18, 38.62. HRMS (EI) m/z calcd for $C_{21}H_{22}N_2O_2$ $(M)^+$ 334.1681, found 334.1682.

(E)-3-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N-methylprop-2-en-1-amine hydrochloride (23a).

Yield: 61%. **23a** was synthesized by the general procedure given above as white solid. m.p. 157-158 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.86 – 7.77 (m, 1H), 7.67 – 7.58 (m, 7H), 7.41 (dddd, J = 23.2, 15.9, 9.3, 4.8 Hz, 5H), 6.99 (d, J = 15.7 Hz, 1H), 6.50 – 6.34 (m, 1H), 4.68 – 4.44 (m, 2H), 4.06 (d, J = 55.9 Hz, 2H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, DMSO) δ 155.03, 148.79, 140.67, 139.90, 138.50, 135.09, 129.47, 129.47, 128.16, 127.91, 127.91, 127.43, 127.43, 127.40, 127.04, 127.04, 125.58, 123.79, 121.03, 118.87, 112.12, 110.51, 56.77, 47.37, 38.73. HRMS (ESI) m/z calcd for $C_{25}H_{24}NO$ $(M+H)^+$ 354.1858, found 354.1857.

(E)-N-((1H-indol-7-yl)methyl)-3-([1,1'-biphenyl]-4-yl)-N-methylprop-2-en-1-amine hydrochloride (23b).

Yield: 69%. **23b** was synthesized by the general procedure given above as white solid. m.p. 199-200 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.72 (d, J = 7.7 Hz, 1H), 7.67 – 7.57 (m, 6H), 7.44 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 3.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 15.7 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 6.46 – 6.34 (m, 1H), 4.67 (s, 2H), 4.05 (d, J = 6.2 Hz, 2H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 140.23, 140.15, 135.61, 134.28, 129.45, 128.57,

128.57, 127.38, 127.28, 127.28, 126.92, 126.92, 126.44, 126.44, 125.52, 124.35, 122.44, 119.20, 116.16, 115.62, 112.18, 102.23, 57.92, 55.74, 38.16. HRMS (EI) m/z calcd for $C_{25}H_{24}N_2$ $(M)^+$ 352.1939, found 352.1937.

(E)-N-(benzofuran-3-ylmethyl)-3-(2-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (24a).

Yield: 43%. **24a** was synthesized by the general procedure given above as white solid. m.p. 145-146 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.42 (dd, J = 17.3, 7.5 Hz, 3H), 7.37 – 7.29 (m, 3H), 6.40 (dt, J = 15.4, 7.6 Hz, 1H), 4.58 (s, 2H), 4.04 (s, 2H), 2.91 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.53, 148.02, 136.42, 133.33, 133.09, 130.03, 129.52, 127.27, 127.11, 126.41, 125.29, 123.49, 119.77, 119.34, 111.51, 109.81, 57.35, 48.16, 38.48. HRMS (ESI) m/z calcd for $C_{19}H_{19}ClNO$ $(M+H)^+$ 312.1155, found 312.1156.

(E)-N-((1H-indol-7-yl)methyl)-3-(2-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (24b).

Yield: 80%. **24b** was synthesized by the general procedure given above as white solid. m.p. 185-188 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.66 (d, J = 7.9 Hz, 2H), 7.43 (d, J = 6.4 Hz, 1H), 7.37 (d, J = 2.4 Hz, 1H), 7.32 (d, J = 7.8 Hz, 2H), 7.21 (t, J = 6.4 Hz, 2H), 7.12 (t, J = 4.8 Hz, 1H), 6.56 (d, J = 2.4 Hz, 1H), 6.45 – 6.34 (m, 1H), 4.40 (s, 2H), 3.82 (d, J = 6.9 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 135.65, 135.47, 133.36, 132.91, 129.76, 129.36, 129.28, 127.14, 126.94, 125.33, 124.18,

122.18, 120.29, 119.04, 112.49, 102.04, 57.64, 55.95, 38.34. HRMS (EI) m/z calcd for $C_{19}H_{19}ClN_2$ $(M)^+$ 310.1237, found 310.1233.

(E)-N-(benzofuran-3-ylmethyl)-3-(2-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (25a).

Yield: 47%. **25a** was synthesized by the general procedure given above as white solid. m.p. 140-141 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.85 – 7.76 (m, 1H), 7.68 – 7.54 (m, 2H), 7.49 – 7.29 (m, 3H), 7.27 – 6.99 (m, 3H), 6.56 – 6.40 (m, 1H), 4.61 (d, J = 45.6 Hz, 2H), 4.08 (d, J = 69.5 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.56, 148.07, 136.47, 134.12, 133.08, 130.23, 129.49, 127.25, 127.15, 126.44, 125.21, 123.39, 119.69, 119.29, 111.48, 109.77, 57.32, 48.14, 38.51. HRMS (ESI) m/z calcd for $C_{19}H_{19}FNO$ $(M+H)^+$ 296.1451, found 296.1452.

(E)-N-((1H-indol-7-yl)methyl)-3-(2-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (25b).

Yield: 54%. **25b** was synthesized by the general procedure given above as white solid. m.p. 167-168 ^oC ^1H NMR (500 MHz, MeOD) δ 7.72 (d, J = 7.8 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.36 (d, J = 12.4 Hz, 1H), 7.29 (d, J = 7.2 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.05 (s, 1H), 6.59 (d, J = 3.1 Hz, 1H), 6.50 – 6.42 (m, 1H), 4.66 (s, 2H), 4.15 – 3.96 (m, 2H), 2.83 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 135.49, 132.57, 130.34, 130.27, 129.31, 127.84, 125.39, 124.29, 124.17, 122.31, 119.39, 119.06, 115.41, 115.23, 112.08, 102.06, 57.89 , 55.78, 38.12. HRMS (EI) m/z calcd for $C_{19}H_{19}FN_2$ $(M)^+$ 294.1532, found 294.1532.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(o-tolyl)prop-2-en-1-amine hydrochloride (26a).

Yield: 32%. **26a** was synthesized by the general procedure given above as white solid. m.p. 164-165 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, J = 15.7, 7.5 Hz, 1H), 7.56 (d, J = 8.7 Hz, 1H), 7.47 (t, J = 7.1 Hz, 2H), 7.32 – 7.27 (m, 1H), 7.26 – 7.22 (m, 1H), 7.18 – 7.11 (m, 3H), 6.77 (d, J = 15.7 Hz, 1H), 6.20 (dt, J = 15.7, 6.6 Hz, 1H), 3.71 (s, 2H), 3.27 (d, J = 6.6 Hz, 2H), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.50, 147.99, 138.61, 135.96, 134.24, 130.13, 128.59, 126.49, 125.98, 125.66, 125.24, 123.45, 119.37, 117.66, 111.48, 109.88, 57.71, 47.88, 38.34, 18.38. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO$ $(M+H)^+$ 292.1701, found 292.1702.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(o-tolyl)prop-2-en-1-amine hydrochloride (26b).

Yield: 73%. **26b** was synthesized by the general procedure given above as white solid. m.p. 167-169 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.67 (d, J = 7.5 Hz, 1H), 7.54 – 7.48 (m, 1H), 7.36 (d, J = 3.2 Hz, 1H), 7.23 (d, J = 7.2 Hz, 1H), 7.20 – 7.15 (m, 3H), 7.10 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 3.2 Hz, 1H), 6.27 – 6.16 (m, 1H), 4.48 (s, 2H), 3.87 (d, J = 6.6 Hz, 2H), 2.72 (d, J = 6.8 Hz, 3H), 2.35 (d, J = 3.4 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 136.99, 135.71, 135.56, 134.63, 130.03, 129.13, 128.25, 125.91, 125.60, 125.48, 125.13, 123.85, 121.74, 119.65, 119.04, 113.93, 58.26, 56.33, 38.69, 18.40. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2$ $(M)^+$ 290.1783, found 290.1784.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(2-nitrophenyl)prop-2-en-1-amine hydrochloride (27a).

Yield: 32%. **27a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.14 (s, 1H), 8.07 – 8.02 (m, 1H), 7.85 – 7.80 (m, 1H), 7.76 – 7.71 (m, 2H), 7.63 – 7.56 (m, 2H), 7.46 – 7.34 (m, 3H), 6.38 – 6.27 (m, 1H), 4.70 (d, J = 13.9 Hz, 1H), 4.56 (d, J = 13.2 Hz, 1H), 4.17 (d, J = 7.3 Hz, 1H), 4.04 (d, J = 8.0 Hz, 1H), 2.95 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.50, 148.11, 147.96, 136.34, 133.44, 130.93, 129.47, 129.06, 126.44, 125.26, 124.26, 123.48, 121.62, 119.43, 111.48, 109.77, 57.01, 48.14, 38.57. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_3$ $(M+H)^+$ 323.1396, found 323.1397.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(2-nitrophenyl)prop-2-en-1-amine hydrochloride (27b).

Yield: 69%. **27b** was synthesized by the general procedure given above as white solid. m.p. 179-181 ^{o}C. ^{1}H NMR (500 MHz, MeOD) δ 7.99 (d, J = 8.0 Hz, 1H), 7.68 (dd, J = 14.9, 7.2 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.36 (d, J = 3.1 Hz, 1H), 7.30 – 7.20 (m, 2H), 7.10 (d, J = 6.8 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.38 – 6.27 (m, 1H), 4.53 (d, J = 7.2 Hz, 2H), 3.90 (d, J = 6.7 Hz, 2H), 2.74 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 147.74, 135.42, 134.13, 133.16, 133.16, 131.06, 128.82, 128.82, 125.07, 124.02, 124.02, 121.69, 118.99, 118.99, 113.82, 101.85, 57.55, 56.43, 38.85. HRMS (EI) m/z calcd for $C_{19}H_{19}N_3O_2$ $(M)^+$ 321.1477, found 321.1476.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(2-(trifluoromethyl)phenyl)prop -2-en-1-amine hydrochloride (28a).

Yield: 43%. **28a** was synthesized by the general procedure given above as white solid. m.p. 144-146 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.1 Hz, 1H), 7.89 – 7.75 (m, 3H), 7.61 (dt, J = 15.2, 7.7 Hz, 3H), 7.40 (dt, J = 18.9, 7.3 Hz, 2H), 7.01 (d, J = 15.8 Hz, 1H), 6.62 – 6.46 (m, 1H), 4.70 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 4.17 (dd, J = 12.9, 7.1 Hz, 1H), 3.99 (dd, J = 12.8, 7.8 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 155.44, 147.80, 136.00, 134.12, 132.24, 128.59, 127.83, 126.30, 125.45, 125.41, 125.30, 125.17, 123.36, 121.75, 119.20, 111.40, 109.84, 57.18, 48.21, 38.42. HRMS (ESI) m/z calcd for $C_{20}H_{19}F_3NO$ $(M+H)^+$ 346.1419, found 346.1418.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(2-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (28b).

Yield: 83%. **28b** was synthesized by the general procedure given above as white solid. m.p. 179-180 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.66 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.25 (d, J = 3.2 Hz, 1H), 7.04 (d, J = 7.0 Hz, 1H), 7.01 – 6.96 (m, 1H), 6.93 (d, J = 6.8 Hz, 1H), 6.46 (d, J = 3.2 Hz, 1H), 6.41 – 6.31 (m, 1H), 3.91 (s, 2H), 3.32 (d, J = 4.6 Hz, 2H), 2.30 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, MeOD) δ 136.02, 135.33, 131.96, 131.48, 128.66, 128.42, 127.46, 127.15, 125.22, 125.16, 124.12, 122.54, 121.61, 120.73,

119.31, 118.60, 101.13, 59.34, 58.88, 41.03. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1498.

(E)-N-(benzofuran-3-ylmethyl)-3-(2-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (29a).

Yield: 53%. **29a** was synthesized by the general procedure given above as white solid. m.p. 151-152 ^oC. ^1H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.52 (dd, J = 7.7, 1.5 Hz, 1H), 7.46 – 7.29 (m, 3H), 7.21 (d, J = 15.9 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 6.40 (dt, J = 15.1, 7.5 Hz, 1H), 4.58 (d, J = 50.9 Hz, 2H), 4.18 – 3.90 (m, 2H), 3.87 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 157.29, 155.43, 147.80, 136.07, 130.02, 127.32, 126.29, 125.17, 123.69, 123.35, 120.29, 119.18, 116.55, 111.40, 110.76, 109.78, 58.12, 54.50, 48.12, 38.29. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO_2$ $(M+H)^+$ 308.1651, found 308.1649.

(E)-N-((1H-indol-7-yl)methyl)-3-(2-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (29b).

Yield: 74%. **29b** was synthesized by the general procedure given above as white solid. m.p. 154-155 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.67 (d, J = 5.2 Hz, 1H), 7.50 (s, 1H), 7.36 (s, 1H), 7.26 (d, J = 2.4 Hz, 2H), 7.12 (d, J = 4.8 Hz, 2H), 7.04 – 6.87 (m, 2H), 6.56 (s, 1H), 6.37 (s, 1H), 4.48 (s, 1H), 3.86 – 3.25 (m, 6H), 2.71 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 157.19, 135.57, 134.44, 129.74, 129.14, 127.16, 125.17,

124.18, 123.96, 121.84, 120.34, 119.07, 118.40, 113.66, 110.77, 101.97, 58.64, 56.12, 54.59, 38.51. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2O$ $(M)^+$ 306.1732, found 306.1733.

(E)-N-(benzofuran-3-ylmethyl)-3-(3-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (30a).

Yield: 53%. **30a** was synthesized by the general procedure given above as white solid. m.p. 136-137 ^oC . ^1H NMR (400 MHz, MeOD) δ 8.14 (s, 1H), 7.83 (d, J = 7.0 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.43 (t, J = 8.1 Hz, 2H), 7.40 – 7.32 (m, 3H), 6.91 (d, J = 15.8 Hz, 1H), 6.52 – 6.36 (m, 1H), 4.61 (d, J = 36.8 Hz, 2H), 4.04 (d, J = 55.0 Hz, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.51, 147.98, 139.02, 137.38, 134.43, 129.99, 128.53, 128.04, 126.46, 125.25, 125.23, 123.45, 119.39, 118.29, 111.48, 109.90, 57.32, 48.11, 38.50. HRMS (ESI) m/z calcd for $C_{19}H_{19}ClNO$ $(M+H)^+$ 312.1155, found 312.1154.

(E)-N-((1H-indol-7-yl)methyl)-3-(3-chlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (30b).

Yield: 64%. **30b** was synthesized by the general procedure given above as white solid. m.p. 186-190 ^oC. ^1H NMR (400 MHz, MeOD) δ 7.58 (d, J = 7.8 Hz, 1H), 7.46 (s, 1H), 7.36 – 7.24 (m, 5H), 7.13 (d, J = 6.9 Hz, 1H), 7.08 – 7.02 (m, 1H), 6.67 (d, J = 12.8 Hz, 1H), 6.51 (d, J = 3.2 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 4.22 (d, J = 12.0 Hz, 2H), 3.58 (d, J = 7.5 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 138.89, 137.41, 135.58, 134.42, 129.96, 129.43, 128.50, 126.42, 125.50, 125.23,

124.36, 122.43, 119.18, 118.24, 112.20, 102.20, 57.59, 55.83, 38.31. HRMS (EI) m/z calcd for $C_{19}H_{19}ClN_2$ $(M)^+$ 310.1237, found 310.1234.

(E)-N-(benzofuran-3-ylmethyl)-3-(3-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (31a).

Yield: 43%. **31a** was synthesized by the general procedure given above as white solid. m.p. 161-162 ^oC . ^1H NMR (400 MHz, MeOD) δ 8.11 (s, 1H), 7.81 (d, J = 7.5 Hz, 1H), 7.64 – 7.58 (m, 2H), 7.45 – 7.34 (m, 3H), 7.24 – 7.11 (m, 2H), 7.08 (d, J = 15.9 Hz, 1H), 6.56 – 6.41 (m, 1H), 4.58 (s, 2H), 4.02 (s, 2H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.45, 147.81, 138.59, 136.98, 134.41, 129.45, 128.49, 128.64, 126.45, 125.15, 125.35, 123.58, 119.28, 118.36, 111.31, 109.79, 57.82, 47.89, 38.51 . HRMS (ESI) m/z calcd for $C_{19}H_{19}FNO$ $(M+H)^+$ 296.1451, found 296.1452.

(E)-N-((1H-indol-7-yl)methyl)-3-(3-fluorophenyl)-N-methylprop-2-en-1-amine hydrochloride (31b).

Yield: 52%. **31b** was synthesized by the general procedure given above as white solid. m.p. 186-187 ^oC. ^1H NMR (500 MHz, MeOD) δ 7.72 (d, J = 7.9 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.34 – 7.26 (m, 3H), 7.16 (t, J = 7.6 Hz, 1H), 7.11 – 7.05 (m, 1H), 6.90 (d, J = 6.8 Hz, 1H), 6.59 (d, J = 3.1 Hz, 1H), 6.46 – 6.37 (m, 1H), 4.67 (s, 2H), 4.15 – 3.94 (m, 2H), 2.82 (d, J = 6.4 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 139.05, 137.69, 135.49, 130.14, 129.32, 125.39, 124.32, 122.83, 122.80, 122.32, 119.07, 118.00, 115.25, 112.88, 112.05, 102.06, 57.45, 55.71, 38.14. HRMS (EI) m/z calcd for $C_{19}H_{19}FN_2$ $(M)^+$ 294.1532, found 294.1533.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(m-tolyl)prop-2-en-1-amine hydrochloride (32a).

Yield: 47%. **13c** was synthesized by the general procedure given above as yellow oil . ^{1}H-NMR (400 MHz, MeOD) δ 8.12 (s, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.47 – 7.33 (m, 4H), 7.19 (d, J = 7.9 Hz, 2H), 6.90 (d, J = 15.8 Hz, 1H), 6.32 (dt, J = 15.5, 7.6 Hz, 1H), 4.67 (d, J = 13.9 Hz, 1H), 4.51 (d, J = 13.9 Hz, 1H), 4.11 (dd, J = 13.0, 7.0 Hz, 1H), 3.93 (dd, J = 12.9, 7.9 Hz, 1H), 2.89 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.53, 147.95, 139.12, 137.35, 134.23, 129.87, 128.54, 128.29, 126.39, 125.27, 125.14, 123.25, 119.45, 118.15, 111.36, 109.84, 57.45, 48.19, 38.75, 18.29. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO$ $(M+H)^+$ 292.1701, found 292.1702.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(m-tolyl)prop-2-en-1-amine hydrochloride (32b).

Yield: 78%. **32b** was synthesized by the general procedure given above as white solid. m.p. 196-197 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, J = 7.1 Hz, 1H), 7.33 (d, J = 3.2 Hz, 1H), 7.29 – 7.14 (m, 4H), 7.13 – 7.04 (m, 2H), 6.71 (d, J = 6.8 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 6.39 – 6.28 (m, 1H), 4.29 (s, 2H), 3.67 (d, J = 6.4 Hz, 2H), 2.57 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 138.02, 137.31, 136.03, 135.49, 130.95, 128.86, 128.70, 128.20, 126.98, 124.77, 123.56, 123.11, 121.11, 120.78, 118.90, 116.21, 58.61, 57.07, 39.43, 19.99. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2$ $(M)^+$ 290.1783, found 290.1784.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(3-nitrophenyl)prop-2-en-1-amine hydrochloride (33a).

Yield: 35%. **33a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.37 (t, J = 1.8 Hz, 1H), 8.19 (dd, J = 8.2, 2.1 Hz, 1H), 8.11 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.85 – 7.80 (m, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 7.5 Hz, 1H), 7.44 – 7.33 (m, 2H), 7.01 (d, J = 15.7 Hz, 1H), 6.64 – 6.53 (m, 1H), 4.55 (s, 2H), 4.04 (t, J = 14.6 Hz, 2H), 2.88 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 155.42, 148.61, 147.52, 137.35, 137.20, 132.46, 129.64, 126.45, 125.07, 123.26, 122.81, 121.01, 120.67, 119.30, 111.33, 110.39, 57.22, 48.27, 38.77. HRMS (ESI) m/z calcd for $C_{19}H_{19}N_2O_3$ $(M+H)^+$ 323.1396, found 323.1399.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(3-nitrophenyl)prop-2-en-1-amine hydrochloride hydrochloride (33b).

Yield: 86%. **33b** was synthesized by the general procedure given above as white solid. m.p. 186-188 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 8.23 (t, J = 1.9 Hz, 1H), 8.08 (d, J = 6.9 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.26 (d, J = 3.2 Hz, 1H), 7.04 (d, J = 6.6 Hz, 1H), 6.98 (d, J = 3.6 Hz, 1H), 6.67 (d, J = 6.4 Hz, 1H), 6.54 (d, J = 6.6 Hz, 1H), 6.47 – 6.43 (m, 1H), 3.91 (s, 2H), 3.32 (d, J = 6.4 Hz, 1H), 2.31 (d, J = 8.0 Hz, 4H); ^{13}C NMR (126 MHz, MeOD) δ 148.50, 138.66, 135.23, 134.46, 131.84, 131.15, 129.28, 129.10, 128.34, 124.10, 121.75, 121.53, 120.31, 119.89, 119.49, 118.56, 58.85, 58.56, 40.86. HRMS (EI) m/z calcd for $C_{19}H_{19}N_3O_2$ $(M)^+$ 321.1477, found 321.1476.

(E)-N-(benzofuran-3-ylmethyl)-N-methyl-3-(3-(trifluoromethyl)phenyl)prop -2-en-1-amine hydrochloride (34a).

Yield: 58%. **34a** was synthesized by the general procedure given above as white solid. m.p. 121-123 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.1 Hz, 1H), 7.88 – 7.73 (m, 3H), 7.61 (dt, J = 15.2, 7.7 Hz, 3H), 7.40 (dt, J = 18.9, 7.3 Hz, 2H), 7.01 (d, J = 15.8 Hz, 1H), 6.62 – 6.45 (m, 1H), 4.70 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 4.23 – 4.13 (m, 1H), 3.99 (dd, J = 12.8, 7.8 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.48, 148.06, 138.84, 136.41, 130.64, 130.24, 129.35, 126.48, 125.47, 125.23, 125.03, 123.44, 123.34, 119.46, 118.89, 111.46, 109.88, 57.28, 48.14, 38.52. HRMS (ESI) m/z calcd for $C_{20}H_{19}F_3NO$ $(M+H)^+$ 346.1419, found 346.1418.

(E)-N-((1H-indol-7-yl)methyl)-N-methyl-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-amine hydrochloride (34b).

Yield: 82%. **34b** was synthesized by the general procedure given above as white solid. m.p. 129-131 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.65 (s, 2H), 7.49 (dd, J = 7.5, 3.8 Hz, 3H), 7.25 (d, J = 3.1 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.63 (d, J = 15.8 Hz, 1H), 6.53 – 6.42 (m, 2H), 3.88 (s, 2H), 3.28 (s, 2H), 2.31–2.10 (m, 3H); ^{13}C NMR (101 MHz, MeOD) δ 138.12, 135.33, 131.38, 129.40, 128.98, 128.43, 125.15, 124.13, 123.51, 123.47, 122.53, 122.49, 121.61, 120.78, 119.28, 118.58, 101.12, 59.26, 58.88, 41.11. HRMS (EI) m/z calcd for $C_{20}H_{19}F_3N_2$ $(M)^+$ 344.1500, found 344.1503.

(E)-N-(benzofuran-3-ylmethyl)-3-(3-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (35a).

Yield: 23%. **35a** was synthesized by the general procedure given above as white solid. m.p. 153-154 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.82 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.49 – 7.34 (m, 2H), 7.29 (t, J = 7.9 Hz, 1H), 7.08 (dd, J = 10.7, 4.8 Hz, 2H), 6.95 – 6.86 (m, 2H), 6.47 – 6.29 (m, 1H), 4.68 (d, J = 14.0 Hz, 1H), 4.52 (d, J = 13.7 Hz, 1H), 4.13 (dd, J = 12.9, 7.2 Hz, 1H), 4.01 – 3.89 (m, 1H), 3.81 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 160.13, 155.51, 147.99, 140.75, 136.62, 129.48, 128.45, 126.43, 125.26, 123.45, 119.31, 116.50, 114.31, 112.05, 111.49, 109.86, 57.55, 54.36, 48.05, 38.38. HRMS (ESI) m/z calcd for $C_{20}H_{22}NO_2$ $(M+H)^+$ 308.1651, found 308.1652.

(E)-N-((1H-indol-7-yl)methyl)-3-(3-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (35b).

Yield: 75%. **35b** was synthesized by the general procedure given above as white solid. m.p. 154-155 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.71 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.27 (t, J = 7.7 Hz, 2H), 7.14 (t, J = 7.6 Hz, 1H), 7.07 (d, J = 7.7 Hz, 1H), 7.04 (s, 1H), 6.88 (s, 2H), 6.58 (d, J = 3.2 Hz, 1H), 6.40 – 6.29 (m, 1H), 4.64 (s, 2H), 4.01 (d, J = 7.2 Hz, 2H), 2.81 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 160.09, 140.35, 136.72, 135.60, 129.43, 129.37, 125.47, 124.38, 122.32, 119.26, 119.16, 116.83, 114.22, 112.39, 112.00, 102.12, 57.80, 55.77, 54.36, 38.17. HRMS (EI) m/z calcd for $C_{20}H_{22}N_2O$ $(M)^+$ 306.1732, found 306.1733.

(E)-N-(benzofuran-3-ylmethyl)-3-(2,4-dichlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (36a).

Yield: 46%. **36a** was synthesized by the general procedure given above as white solid. m.p. 146-148 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 8.13 (s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.40 (ddt, J = 9.9, 8.5, 4.1 Hz, 3H), 7.27 (d, J = 15.7 Hz, 1H), 6.43 (dt, J = 15.6, 7.7 Hz, 1H), 4.69 (d, J = 13.9 Hz, 1H), 4.55 (d, J = 13.8 Hz, 1H), 4.19 (dd, J = 13.3, 6.8 Hz, 1H), 4.02 (dd, J = 13.5, 7.8 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.51, 148.05, 135.04, 134.90, 133.74, 132.20, 129.12, 128.39, 127.44, 126.42, 125.27, 123.48, 120.65, 119.37, 111.49, 109.79, 57.20, 48.15, 38.53. HRMS (ESI) m/z calcd for $C_{19}H_{18}Cl_2NO$ $(M+H)^+$ 346.0765, found 346.0763.

(E)-N-((1H-indol-7-yl)methyl)-3-(2,4-dichlorophenyl)-N-methylprop-2-en-1-amine hydrochloride (36b).

Yield: 68%. **36b** was synthesized by the general procedure given above as white solid. m.p. 176-177 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.61 (d, J = 8.5 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.47 (s, 1H), 7.35 – 7.29 (m, 2H), 7.12 (d, J = 7.0 Hz, 1H), 7.04 (t, J = 3.6 Hz, 1H), 6.98 (s, 1H), 6.50 (d, J = 3.2 Hz, 1H), 6.46 – 6.35 (m, 1H), 4.09 (s, 2H), 3.50 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 135.38, 134.20, 133.35, 133.12, 132.51, 128.88, 128.88, 128.09, 128.09, 127.18, 127.18, 125.22, 124.35, 123.41, 121.32, 118.88, 57.96, 56.76, 39.18. HRMS (EI) m/z calcd for $C_{19}H_{18}Cl_2N_2$ $(M)^+$ 344.0847, found 344.0838.

(E)-N-(benzofuran-3-ylmethyl)-3-(2-fluoro-4-(trifluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (37a).

Yield: 35%. **37a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.15 (d, J = 5.1 Hz, 1H), 7.89 – 7.75 (m, 3H), 7.61 (dt, J = 15.2, 7.7 Hz, 3H), 7.40 (dt, J = 18.9, 7.3 Hz, 2H), 7.01 (d, J = 15.8 Hz, 1H), 6.61 – 6.46 (m, 1H), 4.70 (d, J = 14.0 Hz, 1H), 4.56 (d, J = 13.7 Hz, 1H), 4.23 – 4.12 (m, 1H), 3.99 (dd, J = 12.8, 7.8 Hz, 1H), 2.92 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.54, 148.05, 135.04, 133.74, 132.20, 129.89, 129.12, 128.35, 127.44, 126.42, 125.27, 124.58, 123.48, 120.65, 119.39, 111.49, 109.79, 57.20, 48.19, 38.53. HRMS (ESI) m/z calcd for $C_{20}H_{18}F_4NO$ $(M+H)^+$ 364.1325, found 364.1326.

(E)-N-((1H-indol-7-yl)methyl)-3-(2-fluoro-4-(trifluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (37b).

Yield: 69%. **37b** was synthesized by the general procedure given above as white solid. m.p. 154-155 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.76 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.47 (s, 2H), 7.33 (d, J = 3.2 Hz, 1H), 7.16 (d, J = 7.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 6.4 Hz, 1H), 6.64 – 6.54 (m, 1H), 6.52 (d, J = 3.2 Hz, 1H), 4.29 (s, 2H), 3.71 (s, 2H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 160.91, 158.42, 135.44, 128.82, 128.58, 128.54, 127.00, 124.71, 124.36, 122.96, 120.94, 120.81, 118.87, 116.57, 112.87, 112.61, 101.63, 58.56, 57.52, 39.86. HRMS (EI) m/z calcd for $C_{20}H_{18}F_4N_2$ $(M)^+$ 362.1406, found 362.1408.

(E)-N-(benzofuran-3-ylmethyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (38a).

Yield: 42%. **38a** was synthesized by the general procedure given above as white solid. m.p. 166-168 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.54 – 7.34 (m, 4H), 6.92 (d, J = 16.4 Hz, 1H), 6.63 – 6.50 (m, 1H), 4.63 (s, 2H), 4.49 (s, 1H), 3.96 (s, 1H), 3.48 (s, 1H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.52, 148.08, 137.63, 128.58, 127.30, 126.42, 125.28, 124.71, 123.48, 123.06, 123.02, 121.21, 119.32, 114.62, 114.41, 111.50, 109.78, 56.97, 47.52, 38.62. HRMS (ESI) m/z calcd for $C_{20}H_{18}F_4NO$ $(M+H)^+$ 364.1325, found 364.1326.

(E)-N-((1H-indol-7-yl)methyl)-3-(3-fluoro-4-(trifluoromethyl)phenyl)-N-methylprop-2-en-1-amine hydrochloride (38b).

Yield: 35%. **38b** was synthesized by the general procedure given above as white solid. m.p. 119-120 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.69 – 7.56 (m, 2H), 7.41 (d, J = 12.4 Hz, 2H), 7.32 (d, J = 3.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 6.8 Hz, 1H), 6.55 (s, 1H), 6.51 (t, J = 7.4 Hz, 1H), 4.26 (s, 2H), 3.67 (d, J = 6.7 Hz, 2H), 2.55 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 160.71, 158.40, 135.37, 128.77, 128.51, 128.42, 127.01, 124.69, 124.28, 122.92, 120.91, 120.79, 118.83, 116.53, 112.82, 112.59, 101.61, 58.53, 57.49, 39.81. HRMS (EI) m/z calcd for $C_{20}H_{18}F_4N_2$ $(M)^+$ 362.1406, found 362.1405.

(E)-N-(benzofuran-3-ylmethyl)-3-(2-fluoro-4-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (39a).

Yield: 47%. **39a** was synthesized by the general procedure given above as white solid. m.p. 150-151 ^{o}C. ^{1}H-NMR (400 MHz, MeOD) δ 8.14 (s, 1H), 7.83 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.39 (tt, J = 17.3, 8.7 Hz, 2H), 7.32 – 7.21 (m, 1H), 7.08 (dd, J = 9.8, 5.0 Hz, 2H), 6.93 (s, 1H), 6.47 – 6.31 (m, 1H), 4.60 (d, J = 43.9 Hz, 2H), 3.99 (dd, J = 41.1, 32.3 Hz, 2H), 3.82 (d, J = 6.1 Hz, 3H), 2.91 (d, J = 9.1 Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 160.03, 155.41, 147.87, 140.65, 136.52, 129.38, 126.33, 125.15, 123.35, 119.26, 119.15, 116.40, 114.21, 111.95, 111.38, 109.76, 57.45, 54.26, 47.91, 38.29. HRMS (ESI) m/z calcd for $C_{20}H_{21}FNO_2$ $(M+H)^+$ 326.1556, found 326.1554.

(E)-N-((1H-indol-7-yl)methyl)-3-(2-fluoro-4-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (39b).

Yield: 45%. **39b** was synthesized by the general procedure given above as white solid. m.p. 108-111 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.71 (d, J = 7.8 Hz, 1H), 7.52 (t, J = 8.7 Hz, 1H), 7.39– 7.31 (m, 1H), 7.27 (d, J = 7.2 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 15.9 Hz, 1H), 6.75– 6.60 (m, 2H), 6.58 (d, J = 3.2 Hz, 1H), 6.35 – 6.25 (m, 1H), 4.64 (s, 2H), 4.05 (d, J = 6.7 Hz, 2H), 3.81 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 135.60, 132.71, 129.40, 128.63, 125.48, 124.37, 122.38, 119.16, 116.48, 115.40, 115.28, 112.21, 110.48, 102.15, 101.20, 100.94, 58.23, 55.70, 54.85, 38.05. HRMS (EI) m/z calcd for $C_{20}H_{21}FN_2O$ $(M)^+$ 324.1638, found 324.1635.

(E)-N-(benzofuran-3-ylmethyl)-3-(3-fluoro-4-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (40a).

Yield: 51%. **40a** was synthesized by the general procedure given above as yellow oil. ^{1}H-NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.80 (d, J = 7.1 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.54 – 7.34 (m, 4H), 6.92 (d, J = 16.4 Hz, 1H), 6.63 – 6.50 (m, 1H), 4.63 (s, 2H), 4.49 (s, 1H), 3.96 (s, 1H), 3.48 (s, 1H), 2.83 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 155.51, 148.15, 148.09, 146.41, 136.73, 130.94, 129.29, 128.47, 126.96, 124.83, 123.32, 123.01, 119.50, 113.21, 113.03, 111.25, 58.13, 55.29, 48.53, 39.36. HRMS (ESI) m/z calcd for $C_{20}H_{18}F_4NO$ $(M+H)^+$ 364.1325, found 364.1326.

(E)-N-((1H-indol-7-yl)methyl)-3-(3-fluoro-4-methoxyphenyl)-N-methylprop-2-en-1-amine hydrochloride (40b).

Yield: 64%. **40b** was synthesized by the general procedure given above as white solid. m.p. 117-118 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.49 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 3.2 Hz, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 8.6 Hz, 1H), 7.00 (t, J = 6.6 Hz, 2H), 6.47 (s, 3H), 6.20– 6.04 (m, 2H), 3.90 (s, 2H), 3.84 (s, 3H), 3.28 (d, J = 6.9 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, MeOD) δ 147.42, 135.39, 133.16, 130.24, 128.52, 124.31, 123.55, 122.76, 122.72, 122.17, 119.84, 119.16, 118.71, 113.14, 112.95, 112.77, 59.03, 58.09, 55.27, 40.42. HRMS (EI) m/z calcd for $C_{20}H_{21}FN_2O$ $(M)^+$ 324.1638, found 324.1637.

3-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N-methylprop-2-yn-1-amine hydrochloride (41a).

Yield: 51%. **41a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 7.70 – 7.56 (m, 7H), 7.46 (dd, J = 10.3, 4.8 Hz, 2H), 7.37 (dd, J = 8.3, 6.4 Hz, 1H), 7.32 (dd, J = 7.6, 1.6 Hz, 1H), 7.27 – 7.18 (m, 1H), 6.97 – 6.82 (m, 2H), 5.64 (t, J = 9.1 Hz, 2H), 4.41 (s, 2H), 2.92 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 155.37, 145.47, 140.35, 138.70, 135.72, 134.56, 130.25, 130.25, 129.31, 129.31, 127.51, 127.51, 126.24, 127.17, 126.34, 126.34, 126.08, 126.08, 124.30, 124.27, 85.24, 82.59, 65.58, 59.64, 39.89. HRMS (EI) m/z calcd for $C_{25}H_{21}NO$ $(M)^+$ 351.1623, found 351.1624.

N-((1H-indol-7-yl)methyl)-3-([1,1'-biphenyl]-4-yl)-N-methylprop-2-yn-1-amine hydrochloride (41b).

Yield: 29%. **41b** was synthesized by the general procedure given above as white solid. m.p. 163-167 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.71 – 7.59 (m, 7H), 7.46 (t, J = 7.6 Hz, 2H), 7.40 – 7.34 (m, 2H), 7.27 (d, J = 7.1 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.57 (d, J = 3.2 Hz, 1H), 4.59 (s, 2H), 4.20 (s, 2H), 2.92 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 140.69, 140.29, 137.28, 136.44, 130.87, 130.32, 130.32, 130.27, 130.27, 129.76, 128.89, 127.75, 127.75, 127.80, 127.80, 127.32, 126.58, 123.21, 120.27, 114.15, 85.49, 82.56, 56.72, 39.68, 18.80. HRMS (EI) m/z calcd for $C_{25}H_{22}N_2$ $(M)^+$ 350.1783, found 350.1782.

3-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N-methylpropan-1-amine hydrochloride (42a).

Yield: 35%. **42a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 7.62 – 7.53 (m, 4H), 7.43 (t, J = 7.6 Hz, 2H), 7.23 (dddd, J = 13.9, 11.2, 9.5, 4.5 Hz, 5H), 6.88 – 6.81 (m, 2H), 4.62 (s, 1H), 4.27 (s, 1H), 3.17 – 3.02 (m, 2H), 2.78 (s, 3H), 2.69 (dd, J = 9.4, 5.6 Hz, 2H), 2.12 – 1.94 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 155.28, 145.41, 140.31, 137.70, 135.59, 134.21, 128.56, 128.56, 127.51, 127.51, 126.24, 127.17, 126.34, 126.34, 126.08, 126.08, 124.30, 124.27, 112.03, 110.25, 65.58, 59.64, 39.89, 31.58, 28.56. HRMS (EI) m/z calcd for $C_{25}H_{25}NO$ $(M)^+$ 355.1936, found 355.1936.

N-((1H-indol-7-yl)methyl)-3-([1,1'-biphenyl]-4-yl)-N-methylpropan-1-amine hydrochloride (42b).

Yield: 42%. **42b** was synthesized by the general procedure given above as white solid. m.p. 154-155 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.64 – 7.61 (m, 1H), 7.59 – 7.56 (m, 2H), 7.52 – 7.48 (m, 2H), 7.42 (d, J = 6.8 Hz, 2H), 7.32 (d, J = 6.9 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.05 (dd, J = 8.7, 6.4 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 4.38 (s, 2H), 3.05 – 2.99 (m, 2H), 2.70 (d, J = 7.5 Hz, 2H), 2.68 (s, 3H), 2.09 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 140.81, 140.39, 137.18, 136.24, 130.87, 130.19, 130.19, 129.76, 129.28, 129.28, 128.89, 128.05, 128.05, 127.32, 126.58, 124.39, 123.21, 120.27, 114.15, 102.41, 56.72, 42.15, 39.68, 31.89, 27.58. HRMS (EI) m/z calcd for $C_{25}H_{22}N_2$ $(M)^+$ 354.2096, found 354.2097.

(E)-3-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N,2-dimethylprop-2-en-1-amine hydrochloride (43a).

Yield: 41%. **43a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.57 (m, 5H), 7.44 (dd, J = 7.9, 6.3 Hz, 5H), 7.37 – 7.31 (m, 2H), 7.29 – 7.22 (m, 1H), 6.92 (ddd, J = 12.5, 9.5, 4.6 Hz, 1H), 6.82 (d, J = 24.1 Hz, 1H), 2.89 (s, 3H), 2.04 (dd, J = 39.4, 1.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 154.35, 140.47, 140.30, 138.70, 135.78, 134.90, 130.26, 130.20, 129.31, 129.31, 128.56, 128.56, 127.24, 127.17, 126.54, 126.54, 126.49, 126.49, 124.30, 120.22, 115.59, 65.25, 59.54, 39.76, 15.74. HRMS (EI) m/z calcd for $C_{26}H_{25}NO$ $(M)^+$ 367.1936, found 367.1938.

(E)-N-((1H-indol-7-yl)methyl)-3-([1,1'-biphenyl]-4-yl)-N,2-dimethylprop-2-en-1-amine hydrochloride (43b).

Yield: 38%. **43b** was synthesized by the general procedure given above as white solid. m.p. 164-165 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, J = 7.9 Hz, 1H), 7.63 (t, J = 7.2 Hz, 4H), 7.47 – 7.38 (m, 5H), 7.37 – 7.30 (m, 2H), 7.17 (t, J = 7.6 Hz, 1H), 6.82 (s, 1H), 6.57 (t, J = 8.0 Hz, 1H), 4.72 (s, 2H), 3.99– 2.90 (m, 2H), 2.87 (s, 3H), 2.02 (d, J = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 140.79, 140.31, 137.24, 136.42, 135.55, 130.85, 130.32, 130.32, 130.27, 130.27, 129.76, 128.89, 127.86, 127.86, 127.80, 127.80, 126.58, 123.21, 120.25, 114.20, 103.07, 65.89, 56.72, 39.68, 18.80. HRMS (EI) m/z calcd for $C_{25}H_{22}N_2$ $(M)^+$ 366.2096, found 366.2097.

(E)-4-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N-methylbut-3-en-1-amine hydrochloride (44a).

Yield: 32%. **44a** was synthesized by the general procedure given above as yellow oil. ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, J = 7.9 Hz, 1H), 7.64 – 7.55 (m, 4H), 7.49 – 7.37 (m, 5H), 7.35 – 7.24 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.58 – 6.35 (m, 2H), 6.28 – 6.15 (m, 1H), 4.65 (s, 2H), 3.37 (t, J = 6.4 Hz, 2H), 2.92 – 2.82 (m, 3H), 2.72 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 140.16, 135.59, 135.70, 133.16, 129.29, 129.29, 128.50, 127.98, 127.98, 127.83, 127.83, 126.94, 126.94, 126.44, 126.36, 125.50, 124.43, 123.38, 122.41, 119.18, 112.14, 102.19, 57.89, 53.59, 41.28, 31.28. HRMS (ESI) m/z calcd for $C_{26}H_{25}NO$ $(M+H)^+$ 367.1936, found 367.1937.

(E)-N-((1H-indol-7-yl)methyl)-4-([1,1'-biphenyl]-4-yl)-N-methylbut-3-en-1-amine hydrochloride (44b).

Yield: 64%. **44b** was synthesized by the general procedure given above as white solid. m.p. 169-172 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, J = 7.9 Hz, 1H), 7.64 – 7.55 (m, 4H), 7.49 – 7.37 (m, 5H), 7.35 – 7.24 (m, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.58 – 6.35 (m, 2H), 6.28 – 6.15 (m, 1H), 4.65 (s, 2H), 3.37 (t, J = 6.4 Hz, 2H), 2.92 – 2.82 (m, 3H), 2.72 – 2.62 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 140.44, 140.36, 135.77, 135.70, 133.16, 129.40, 128.50, 128.50, 127.03, 126.74, 126.74, 126.44, 126.44, 126.36, 126.36, 125.50, 124.43, 123.38, 122.41, 119.18, 112.14, 102.19, 56.46, 55.22, 38.87, 27.76. HRMS (EI) m/z calcd for $C_{26}H_{26}N_2$ $(M)^+$ 366.2096, found 366.2090.

(2E,4E)-5-([1,1'-biphenyl]-4-yl)-N-(benzofuran-3-ylmethyl)-N-methylpenta-2,4-dien-1-amine hydrochloride (45a).

Yield: 52%. **45a** was synthesized by the general procedure given above as yellow solid. m.p. 155-158 ^{o}C. ^{1}H NMR (400 MHz, MeOD) δ 7.60 (m, 5H), 7.51 (d, J = 8.1 Hz, 2H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.14 (dd, J = 20.8, 7.8 Hz, 2H), 6.97 – 6.88 (m, 1H), 6.75 (d, J = 7.6 Hz, 2H), 6.64 (d, J = 16.0 Hz, 1H), 6.55 – 6.40 (m, 1H), 5.94 (s, 1H), 4.61 (s, 2H), 3.38 (d, J = 6.5 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 155.47, 147.93, 138.69, 135.74, 135.59, 135.46, 129.44, 128.55, 128.51, 127.11, 126.95, 126.95, 126.87, 126.87, 126.58, 126.18, 126.18, 125.53, 124.40, 122.46, 119.27, 119.18, 112.01, 102.21, 57.37, 48.17, 38.10. HRMS (EI) m/z calcd for $C_{27}H_{25}NO$ $(M)^{+}$ 379.1936, found 379.1937.

(2E,4E)-N-((1H-indol-7-yl)methyl)-5-([1,1'-biphenyl]-4-yl)-N-methylpenta-2, 4-dien-1-amine hydrochloride (45b).

Yield: 33%. **45b** was synthesized by the general procedure given above as white solid. m.p. 193-199 ^{o}C ^{1}H NMR (400 MHz, MeOD) δ 7.72 (d, J = 7.7 Hz, 1H), 7.67 – 7.59 (m, 4H), 7.56 (d, J = 8.3 Hz, 2H), 7.46 – 7.38 (m, 3H), 7.33 (t, J = 7.3 Hz, 1H), 7.28 (d, J = 7.1 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.00 (dd, J = 12.6, 10.5 Hz, 1H), 6.80 (d, J = 12.8 Hz, 1H), 6.73 (dd, J = 15.0, 10.5 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 5.94 (dt, J = 15.2, 7.7 Hz, 1H), 4.63 – 4.38 (m, 4H), 2.80 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 141.27, 141.00, 140.30, 135.64, 135.59, 135.86, 129.44, 128.53, 128.53, 127.18, 126.97, 126.97, 126.88, 126.88, 126.58, 126.38, 126.38, 125.53, 124.40,

122.46, 119.26, 119.18, 112.03, 102.21, 57.59, 55.51, 37.98. HRMS (EI) m/z calcd for $C_{27}H_{26}N_2$ $(M)^+$ 378.2096, found 378.2098.

1-(3a,7a-dihydrobenzofuran-2-yl)-N-methylmethanamine (48a)

To a solution of 3a,7a-dihydrobenzofuran-3-carbaldehyde (18.2 g, 123 mmol) in methanol (20 mL) was slowly treated with methanamine (31g, 33%, in methanol), and then the reaction was stirred at room temperature for 4 h. Thereafter, $NaBH_4$ (9.4g, 246 mmol) was added in batches at 0 ^oC and the reaction was heated to r.t. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed. The residue was then purified via flash chromatography on silica gel, eluting with EtOAc/petroleum ether (1/25, v/v) to give **48a** as yellow oil. Yield: 42%.^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.63 (dt, J = 15.3, 4.5 Hz, 1H), 7.58 (s, 1H), 7.34-7.27 (m, 1H), 7.26-7.24 (m, 1H), 3.90(d, J = 0.9 Hz, 2H), 2.51(d, J = 4.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 157.06, 145.21, 143.44, 130.15, 129.52, 124.73, 118.02, 117.62, 55.59, 33.90.

(E)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-ol (49a).

To a solution of cinnamaldehyde (400.0 mg, 2 mmol) in methanol (10 mL) was treated with sodium borohydride (76.0 mg, 2 mmol) in batches at 0 ^oC. The reaction mixture was stirred at room temperature for 15 min and concentrated. The residue was poured into water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed. The crude was used for next step without further separation giving the title **49a** as yellow oil.

Yield: 59%. ^{1}H NMR (400 MHz, DMSO) δ 7.65 (m, 4H), 6.67 (d, J = 16.1 Hz, 1H), 6.58 (dt, J = 16.0, 4.4 Hz, 1H), 5.14 – 4.92 (m, 1H), 4.18 (m, 2H). ^{13}C NMR (101 MHz, DMSO) δ 141.50, 134.67, 127.14, 127.14, 127.11, 127.11, 125.88, 125.85, 124.35, 61.69.

(E)-1-(3-bromoprop-1-en-1-yl)-4-(trifluoromethyl)benzene (51a).

To a solution of **49a** (303.0 mg, 1.5 mmol) in anhydrous ether (20 mL) was treated with phosphorus tribromide (84.0 μL, 0.9 mmol) at 0 ^{o}C under N_2 atmosphere. The reaction mixture was stirred at room temperature overnight and poured into ice water containing sodium bicarbonate. The mixture was partitioned between EtOAc and water. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and condensed at 30 ^{o}C. The crude was used for next step without further purification affording the **51a** as white solid. Yield: 85%. ^{1}H NMR (400 MHz, DMSO) δ 7.82 (d, J = 8.0 Hz, 2H), 7.77 – 7.73 (d, 2H), 6.99 (d, J = 21.3, 12.3 Hz, 1H), 6.61 – 6.55 (m, 1H), 4.38 (d, J = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 138.72, 134.70, 127.56, 127.47, 127.47, 127.12, 127.12, 125.90, 119.51, 61.65.

Associated Content

Supporting Information.

Experimental procedures and characterizations of derivatives, bacterial growth assays of *S. aureus* Newman and MRSA strains, the hERG inhibition assay, MIC values of derivatives against MRSA strains, pigment inhibition assay, CrtN enzyme

inhibition assay, hydrogen peroxide killing and human whole blood killing, *S. aureus* systemic infection models, anti-fungal assay, cytochrome P450 inhibition assay, pharmacokinetic methods: This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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Abbreviations

S. aureus, *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; STX, staphyloxanthin; CrtN, diapophytoene desaturases; ND4BB, New Drugs for Bad Bugs; CrtM, dehydrosqualene synthase; PK, pharmacokinetics; SAR, structure-activity relationship; IC_{50}, half maximal inhibitory concentration; MIC, minimum inhibitory concentration; HPLC, high-performance liquid chromatography; MS, mass chromatography; CFU, colony-forming unit; PBS, phosphate-buffered saline; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; EtOH, ethanol; EtOAc, ethyl acetate; MeOH, methanol; THF, tetrahydrofuran; CH_2Cl_2, dichloromethane.

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FIGURES

Figure 1. Chemical modification strategies and purpose for lead compound **1** and pigment inhibition activities of analogues **2a**-**j**.

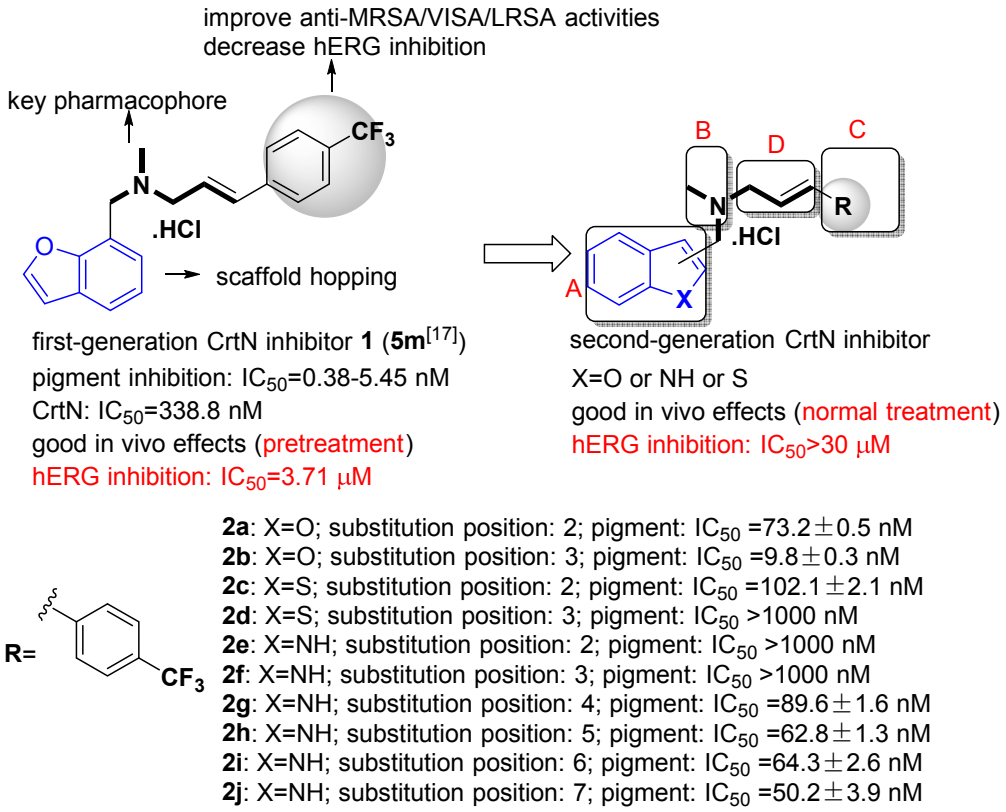


Figure 2. Effects of **23a-b** on the bacterial growth of S. aureus Newman (A and E), USA400 MW2 (B and F), USA300 LAC (C and G), and Mu50 (D and H). Data are presented as means ± SEM, n = 2 independent experiments.

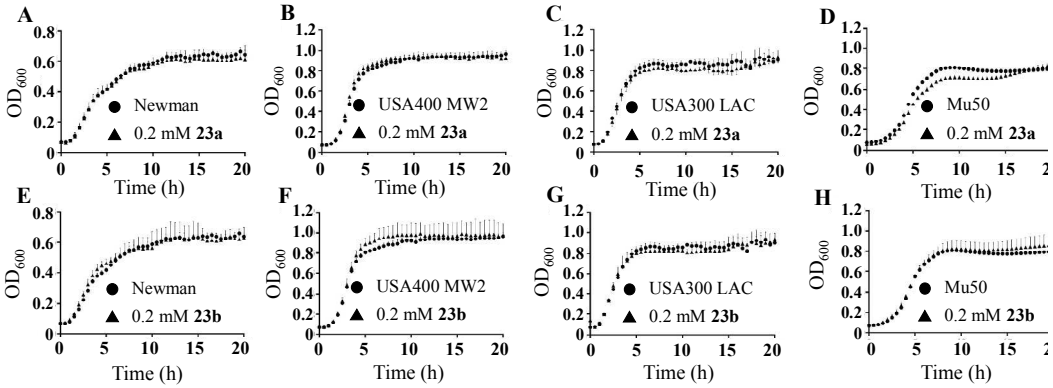


Figure 3. Effects of **23a-b** on susceptibility to hydrogen peroxide killing. *S. aureus* Newman (A), USA400 MW2 (B), USA300 LAC (C), and Mu50 (D); *** $p < 0.001$ via two-tailed t-test (n = three biological replicates, each with two technical replicates).

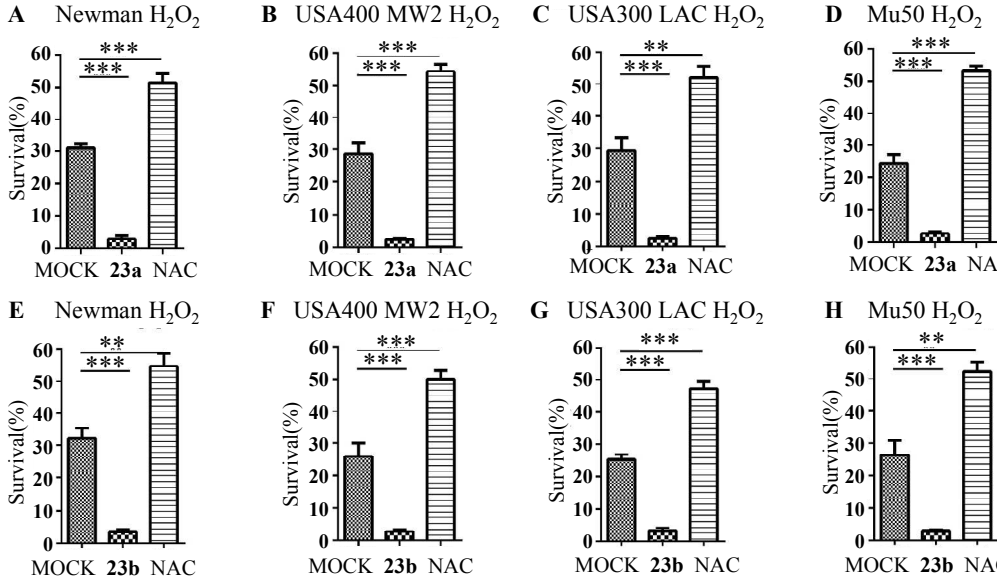


Figure 4. Effects of **23a-b** on susceptibility to human whole blood killing. *S. aureus* Newman (A), USA400 MW2 (B), USA300 LAC (C), and Mu50 (D); *** $p < 0.001$ via two-tailed t-test (n = three biological replicates, each with two technical replicates).

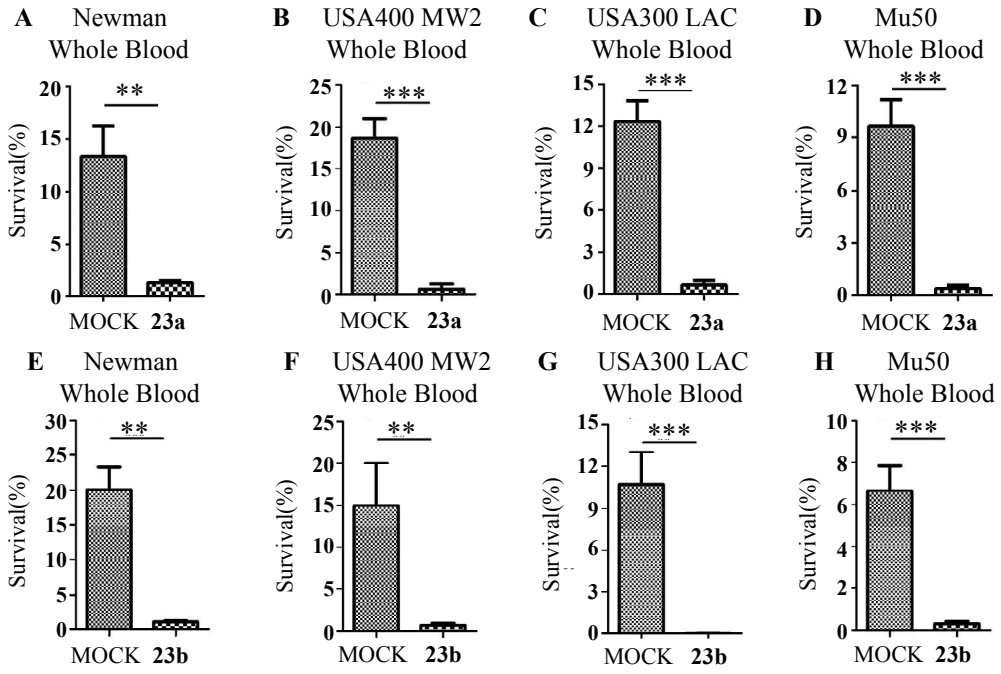


Figure 5. Effects of analogues **23a-b** on *S. aureus* bacteria (A and B), Mu50 (C and D) and NRS271 (E and F) survival in hearts and livers of mice (n=10 for each group) challenged with 2.3×10^7 CFU Newman bacteria, 1.1×10^9 CFU Mu50 bacteria and 2.3×10^8 CFU NRS271 bacteria. **P** = pretreatment, drugs or compounds were intraperitoneally administered 24 h before infection compared with the normal treatment (drugs or compounds were intraperitoneally administered 6 h after infection). Statistical significance was determined by a Mann−Whitney test (two-tailed): ** $p < 0.01$, *** $p < 0.001$. Each symbol represents the value for an individual mouse. Horizontal bars indicate the observation means, and dashed lines mark the limits of detection.

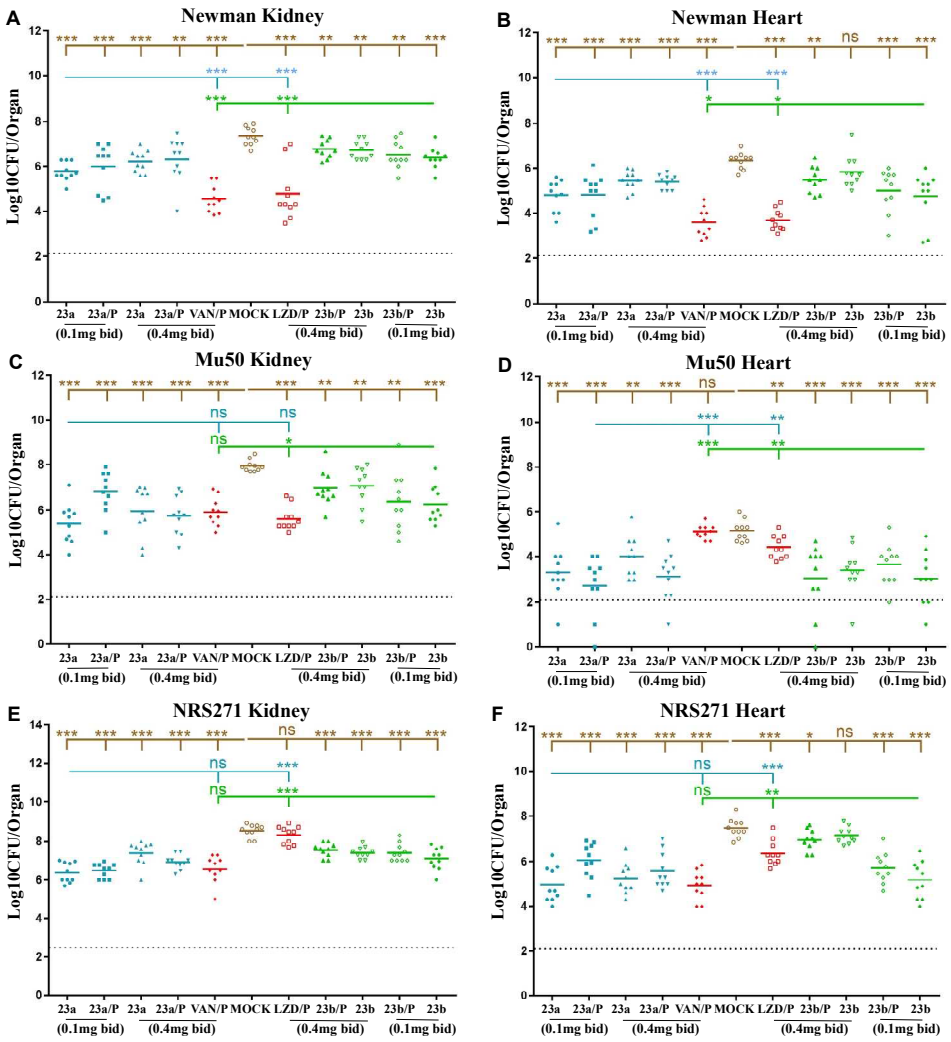


Figure 6. Effects of **23a-b** on Mu50 survival in the kidneys (A) and hearts (B) of mice challenged with 1.3×10^9 CFU Mu50 bacteria. **P** = pretreatment, drugs or compounds were intraperitoneally administered 24 h before infection compared with the normal treatment (drugs or compounds were intraperitoneally administered 6 h after infection). Statistical significance was determined by a Mann-Whitney test (two-tailed): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s. indicates no significant difference. Each symbol represents the value for an individual mouse. Horizontal bars indicate the observation means, and dashed lines mark the limits of detection.

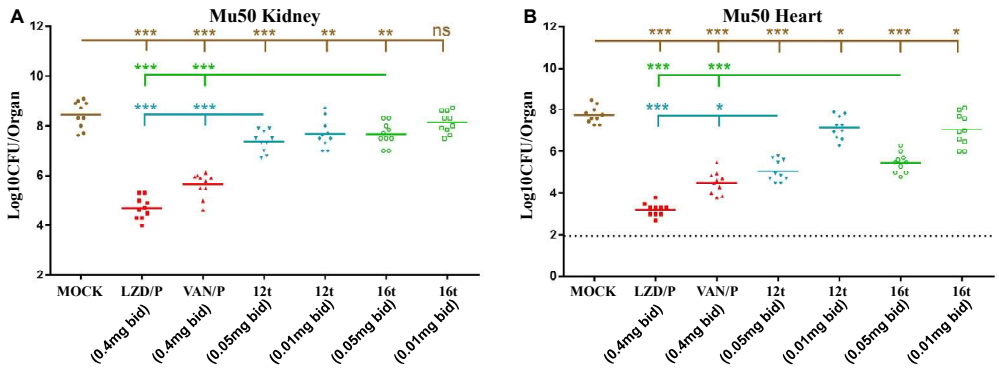


Figure 7. Effects of **1** and **23a** on *S. aureus* survival in protecting mice (n=15) from lethal *S. aureus* infection challenged with 2×10^8 CFU Newman bacteria.

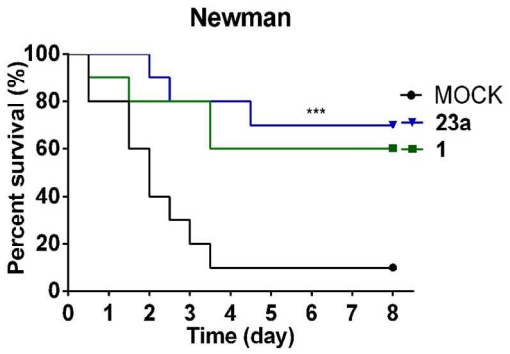


Figure 8. Effects of **23a** on LRSA45 (5.0×10^7 CFU), LRSA202 (7.0×10^7 CFU), NF65Y (3.5×10^8 CFU) and XN108 (2.1×10^8 CFU) survival in the kidneys (A) and hearts (B) of mice. **P** = pretreatment, drugs or compounds were intraperitoneally administered 24 h before infection compared with the normal treatment (drugs or compounds were intraperitoneally administered 6 h after infection). Statistical significance was determined by a Mann−Whitney test (two-tailed): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s. indicates no significant difference. Each symbol represents the value for an individual mouse. Horizontal bars indicate the observation means, and dashed lines mark the limits of detection.

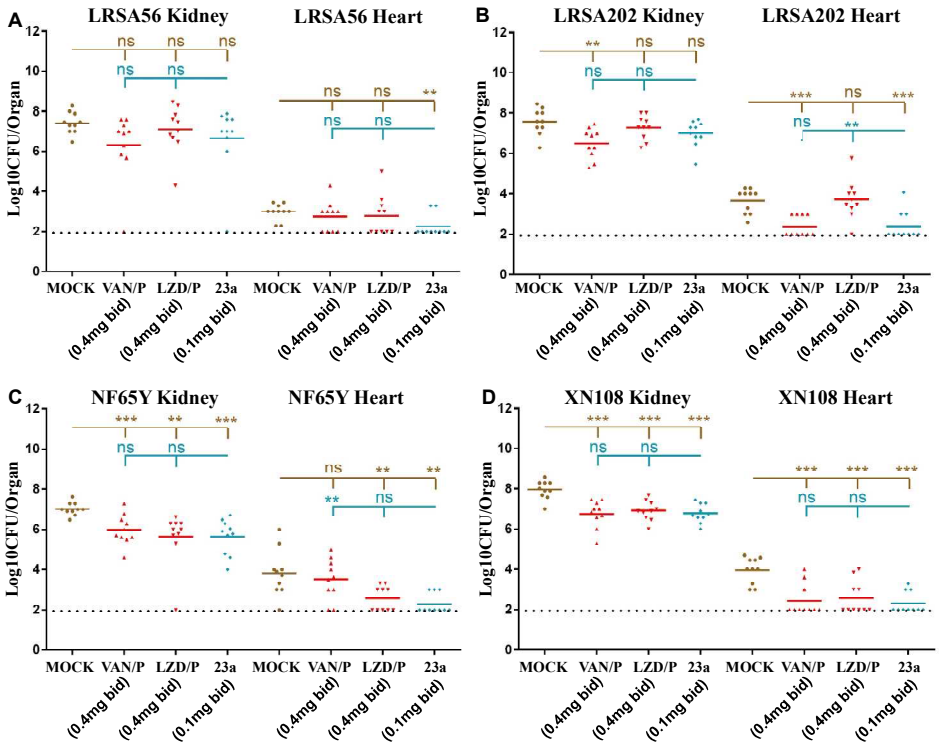


Figure 9. Effects of **23a** on Newman (3.1×10^7 CFU), Mu50 (4.6×10^9 CFU), and NRS271 (3.5×10^8 CFU) survival in the kidneys (A, C and E) and hearts (B, D and F) of mice. **P** = pretreatment, drugs or compounds were intraperitoneally administered 24 h before infection compared with the normal treatment (drugs or compounds were intraperitoneally administered 6 h after infection). Statistical significance was determined by a Mann−Whitney test (two-tailed): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, n.s. indicates no significant difference. Each symbol represents the value for an individual mouse. Horizontal bars indicate the observation means, and dashed lines mark the limits of detection.

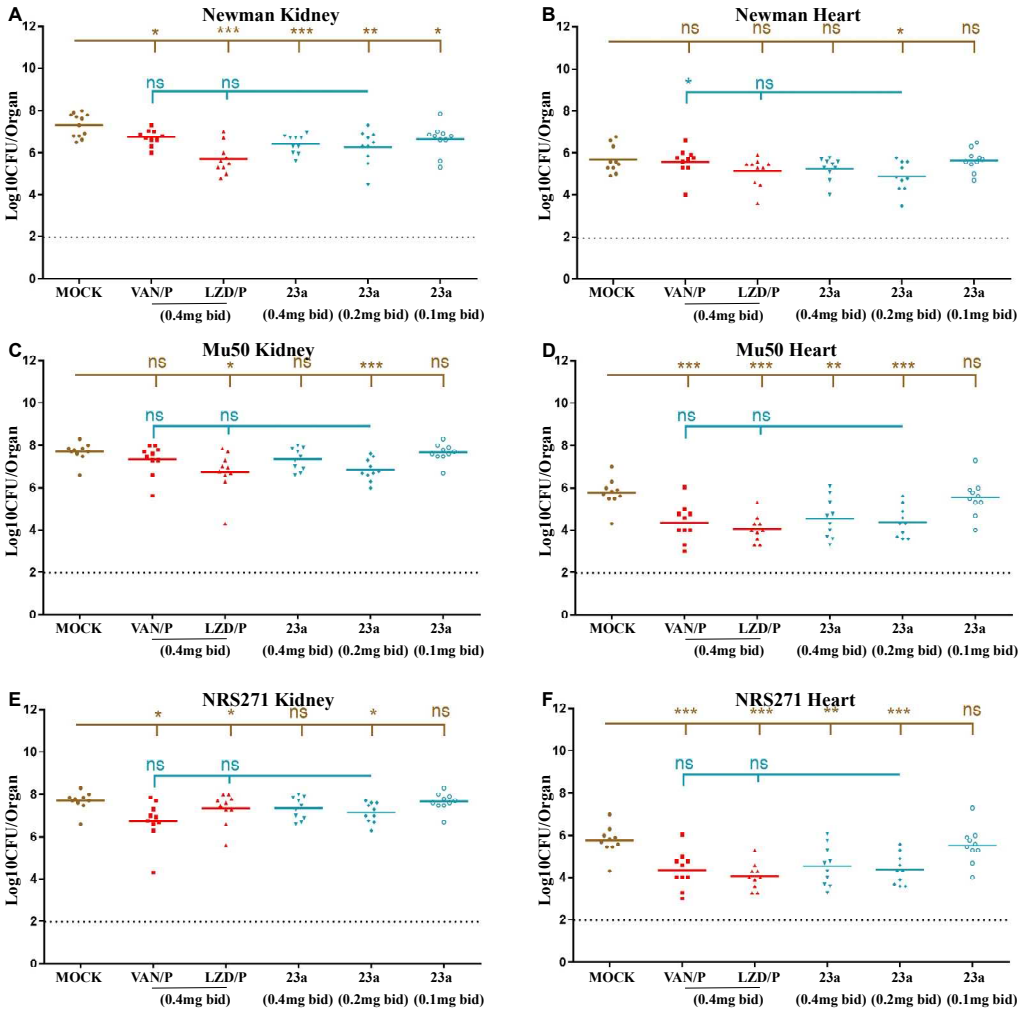


Figure 10. Development of bacterial resistance in Newman towards erythromycin and H_2O_2.

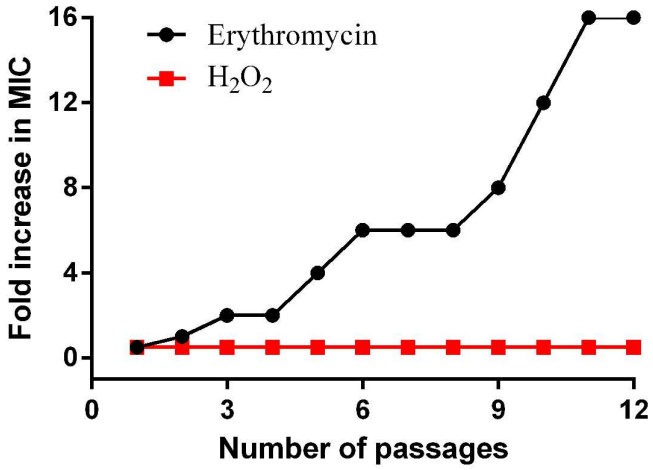
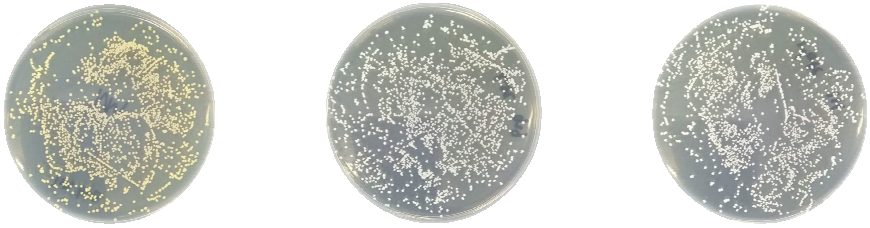


Figure 11. Images of the treated and nontreated (control) TSA plates of 12 passages Newman (1000 CFU), which were under the sequential H_2O_2 + CrtN inhibitors selection pressure. The concentrations of 23a and 23b were 7.5 nM/mL and 10.0 nM/mL (IC_{90} of pigment inhibition).

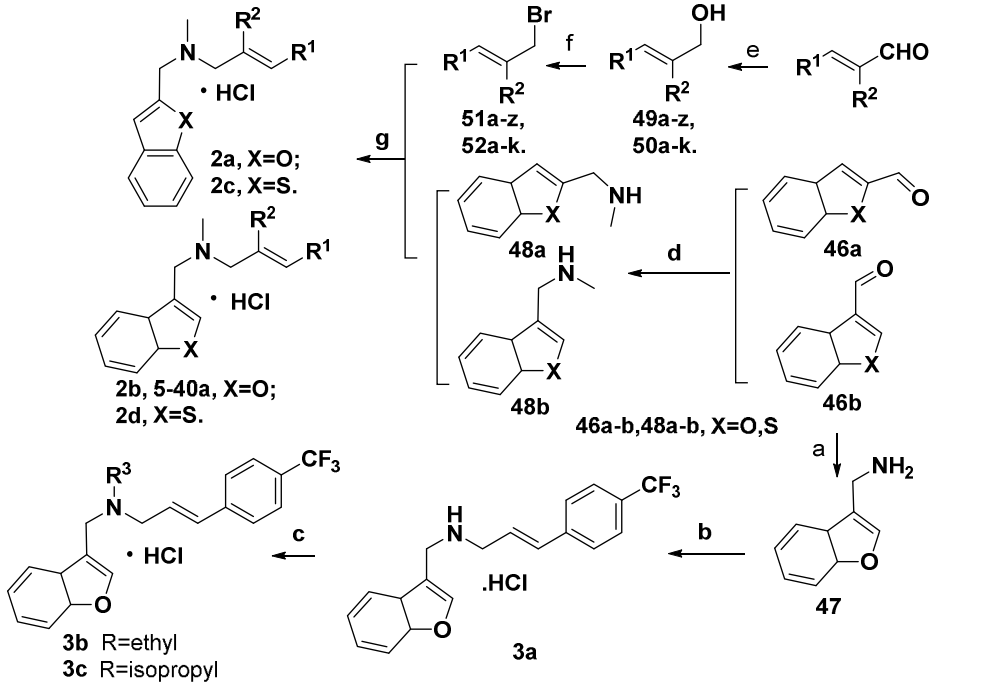


12 passages Newman | **12 passages Newman + 23a** | **12 passages Newman + 23b**

SCHEMES

Scheme 1. Syntheses of Derivatives **2a-d** and **5a-40a**[a]

	R^1	R^2		R^1	
49a, 51a, 2a	4-trifluoromethylphenyl	H	**49r, 51r, 21a**	4-(tert-butyl)phenyl	H
49a, 51a, 2b	4-trifluoromethylphenyl	H	**49s, 51s, 22a**	4-(methoxycarbonyl)pheny	H
49a, 51a, 2c	4-trifluoromethylphenyl	H	**49t, 51t, 23a**	4-phenylphenyl	H
49a, 51a, 2d	4-trifluoromethylphenyl	H	**49u, 51u, 24a**	2-chiorophenyl	H
49b, 51b, 5a	cyclopentyl	H	**49v, 51v, 25a**	2-fluorophenyl	H
49c, 51c, 6a	cyclohexyl	H	**49w, 51w, 26a**	2-methylphenyl	H
49d, 51d, 7a	furan-2-yl	H	**49x, 51x, 27a**	2-nitrophenyl	H
49e, 51e, 8a	thiophene-2-yl	H	**49y, 51y, 28a**	2-trifluoromethylphenyl	H
49f, 51f, 9a	naphthalen-1-yl	H	**49z, 51z, 29a**	2-methoxyphenyl	H
49g, 51g, 10a	naphthalen-1-yl	H	**50a, 52a, 30a**	3-chiorophenyl	H
49h, 51h, 11a	phenyl	H	**50b, 52b, 31a**	3-fluorophenyl	H
49i, 51i, 12a	4-chiorophenyl	H	**50c, 52c, 32a**	3-methylphenyl	H
49j, 51j, 13a	4-fluorophenyl	H	**50d, 52d, 33a**	3-nitrophenyl	H
49k, 51k, 14a	4-bromophenyl	H	**50e, 52e, 34a**	3-trifluoromethylphenyl	H
49l, 51l, 15a	4-methylphenyl	H	**50f, 52f, 35a**	3-methoxyphenyl	H
49m,51m, 16a	4-methoxyphenyl	H	**50g, 52g, 36a**	2,4-dichlorophenyl	H
49n,51n, 17a	4-ethyoxyphenyl	H	**50h, 52h, 37a**	2-fluoro-4-trifluoromethylphenyl	H
49o, 51o, 18a	4-nitrophenyl	H	**50i, 52i, 38a**	3-fluoro-4-trifluoromethylphenyl	H
49p, 51p, 19a	4-difluoromethylphenyl	H	**50j, 52j, 39a**	2-fluoro-4-methoxyphenyl	H
49q, 51q, 20a	4-cyanolphenyl	H	**50k, 52k, 40a**	3-fluoro-4-methoxyphenyl	H



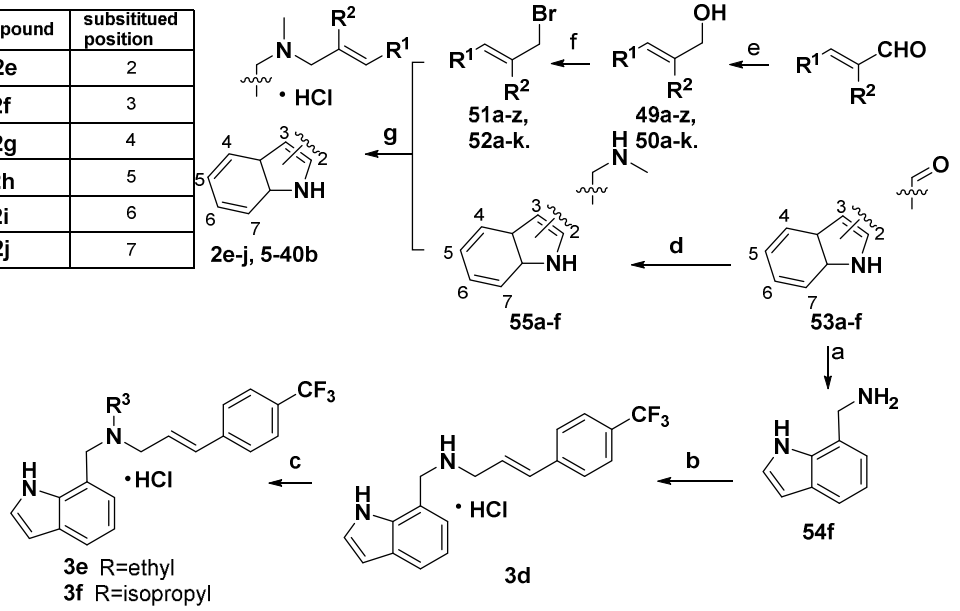
[a]Reagents and conditions**:** (a) ammonia in THF, DCM, $NaBH(OAc)_3$, r. t, 2 h, 30%; (b) (1) K_2CO_3, DMF, r.t., overnight, 43-85%, (2) bubbled into hydrogen chloride gas. (c) iodoethane or 2-iodopropane, NaH, DMF 0 ^oC to r.t, overnight, under

N_2, 50%; (d) methylamine, MeOH, $NaBH_4$, r. t, 0 ^oC, 10 mins, 55%; (e) $NaBH_4$, methanol, 0 ^oC, 30 min; (f) phosphorus tribromide, diethyl ether, 0 ^oC to r.t., overnight, under N_2, 57-84% (2 steps); (g) (1) K_2CO_3, DMF, r.t., overnight, 43-85%, (2) bubbled into hydrogen chloride gas.

Scheme 2. Syntheses of Derivatives **2e-j, 3d-f** and **5b-40b**[a]

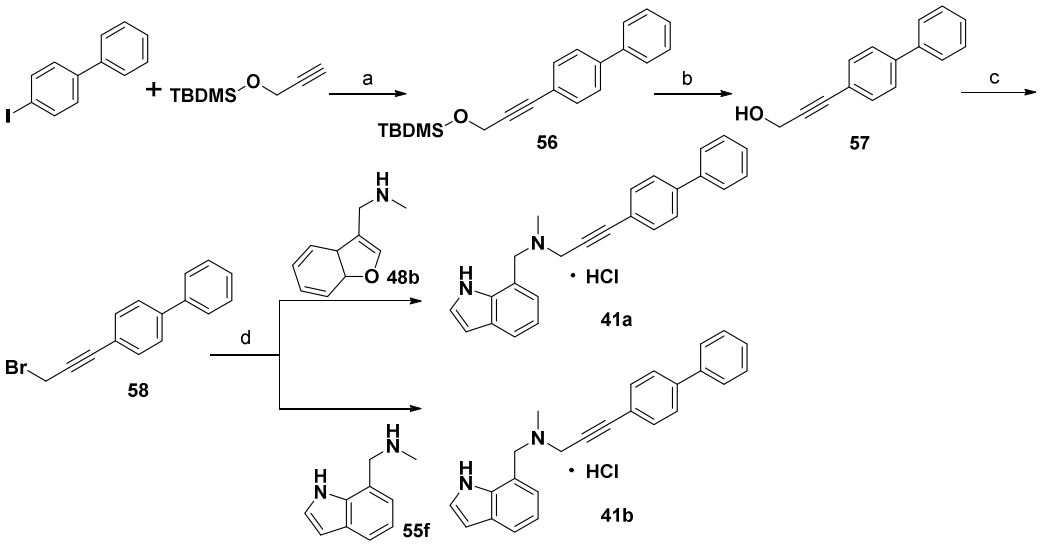
	R^1	R^2		R^1	R^2
2h					
49a, 51a, 2e	4-trifluoromethylphenyl	H	**49q, 51q, 20b**	4-cyanolphenyl	H
49a, 51a, 2f	4-trifluoromethylphenyl	H	**49r, 51r, 21b**	4-(tert-butyl)phenyl	H
49a, 51a, 2g	4-trifluoromethylphenyl	H	**49s, 51s, 22b**	4-(methoxycarbonyl)pheny	H
49a, 51a, 2h	4-trifluoromethylphenyl	H	**49t, 51t, 23b**	4-phenylphenyl	H
49a, 51a, 2i	4-trifluoromethylphenyl	H	**49u, 51u, 24b**	2-chiorophenyl	H
49a, 51a, 2j	4-trifluoromethylphenyl	H	**49v, 51v, 25b**	2-fluorophenyl	H
49b, 51b, 5b	cyclopentyl	H	**49w, 51w, 26b**	2-methylphenyl	H
49c, 51c, 6b	cyclohexyl	H	**49x, 51x, 27b**	2-nitrophenyl	H
49d, 51d, 7b	furan-2-yl	H	**49y, 51y, 28b**	2-trifluoromethylphenyl	H
49e, 51e, 8b	thiophene-2-yl	H	**49z, 51z, 29b**	2-methoxyphenyl	H
49f, 51f, 9b	naphthalen-1-yl	H	**50a, 52a, 30b**	3-chiorophenyl	H
49g, 51g, 10b	naphthalen-1-yl	H	**50b, 52b, 31b**	3-fluorophenyl	H
49h, 51h, 11b	phenyl	H	**50c, 52c, 32b**	3-methylphenyl	H
49i, 51i, 12b	4-chiorophenyl	H	**50d, 52d, 33b**	3-nitrophenyl	H
49j, 51j, 13b	4-fluorophenyl	H	**50e, 52e, 34b**	3-trifluoromethylphenyl	H
49k, 51k, 14b	4-bromophenyl	H	**50f, 52f, 35b**	3-methoxyphenyl	H
49l, 51l, 15b	4-methylphenyl	H	**50g, 52g, 36b**	2,4-dichlorophenyl	H
49m,51m, 16b	4-methoxyphenyl	H	**50h, 52h, 37b**	2-fluoro-4-trifluoromethylphenyl	H
49n,51n, 17b	4-ethyoxyphenyl	H	**50i, 52i, 38b**	3-fluoro-4-trifluoromethylphenyl	H
49o, 51o, 18b	4-nitrophenyl	H	**50j, 52j, 39b**	2-fluoro-4-methoxyphenyl	H
49p, 51p, 19b	4-difluoromethylphenyl	H	**50k, 52k, 40b**	3-fluoro-4-methoxyphenyl	H

compound	subsititued position
2e	2
2f	3
2g	4
2h	5
2i	6
2j	7



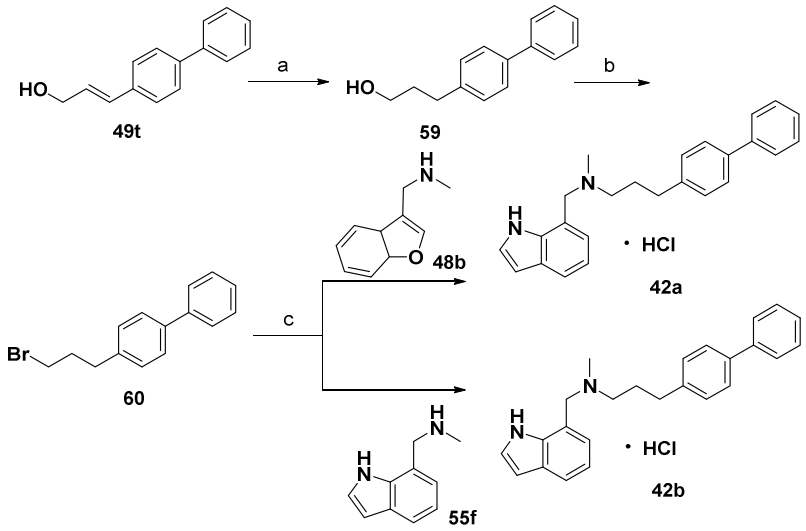
[a]Reagents and conditions: (a) ammonia in THF, DCM, $NaBH(OAc)_3$, r. t, 2h, 30%; (b) (1) K_2CO_3, DMF, r.t., overnight, 43-85%, (2) bubbled into hydrogen chloride gas. (c) iodoethane or 2-iodopropane, NaH, DMF 0 °C to r.t, overnight, under N_2, 50%; (d) methylamine, MeOH, $NaBH_4$, r. t, 0 °C, 10 mins, 55%; (e) $NaBH_4$, methanol, 0 °C, 30 min; (f) phosphorus tribromide, diethyl ether, 0 °C to r.t., overnight, under N_2, 57-84% (2 steps); (g) (1) K_2CO_3, DMF, r.t., overnight, 43-85%, (2) bubbled into hydrogen chloride gas.

Scheme 3. Syntheses of Derivatives **41a-b**[a]



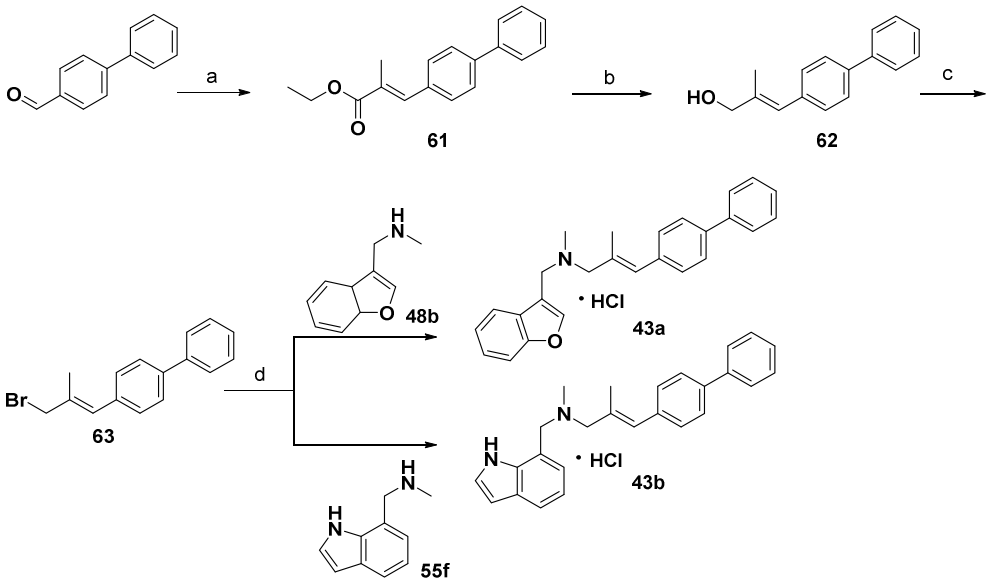
[a]Reagents and conditions: (a) CuI, $Pd(PPh_3)_4$, DMF, TEA, 90 °C; (b) TBAF/THF; (c). PBr_3, Et_2O; (d) (1) K_2CO_3, DMF, r.t., overnight, 41-45%, (2) bubbled into hydrogen chloride gas.

Scheme 4. Syntheses of Derivatives **42a-b**[a]



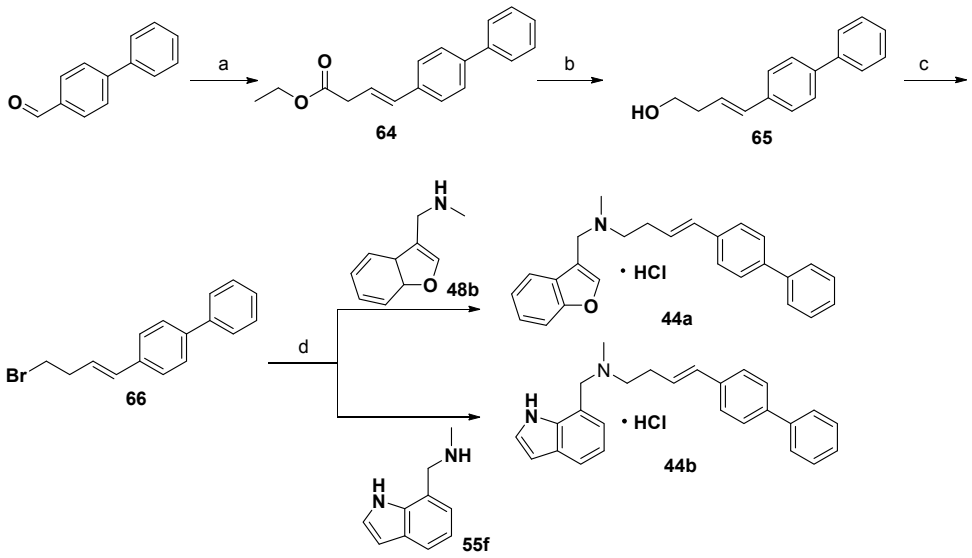
[a]Reagents and conditions: (a) H_2, Pd/C, MeOH; (b) PBr_3, CCl_4, reflux, 4 h; (c). (1) K_2CO_3, DMF, r.t., overnight, 25-35%, (2) bubbled into hydrogen chloride gas..

Scheme 5. Syntheses of Derivatives **43a-b**[a]



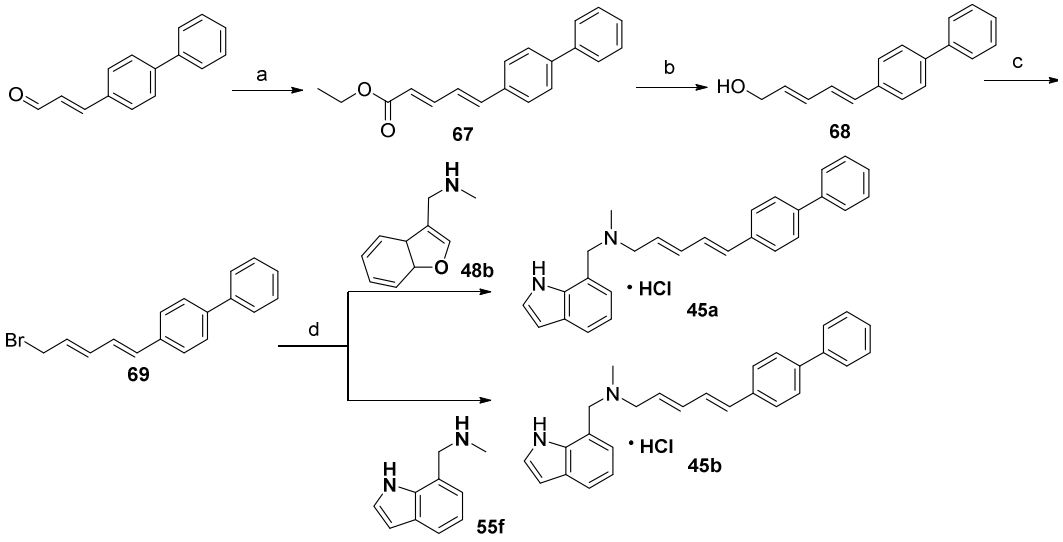
[a]Reagents and conditions: (a) ethyl 2-(triphenyl-l5-phosphanylidene)propanoate, toluene, 100 ^oC; (b) DIABL-H, DCM, 0 ^oC; (c). PBr_3, Et_2O; (d)(1) K_2CO_3, DMF, r.t., overnight, 41-55%, (2) bubbled into hydrogen chloride gas.

Scheme 6. Syntheses of Derivatives **44a-b**[a]



[a]Reagents and conditions: (a)(1) (2-carboxyethyl)triphenylphosphonium, NaH in THF/DMSO, (2) EtOH/H_2SO_4; (b) DIABL-H, DCM, 0 ^oC; (c). CBr_4, PPh_3, DCM; (d) (1) K_2CO_3, DMF, r.t., overnight, (2) bubbled into hydrogen chloride gas.

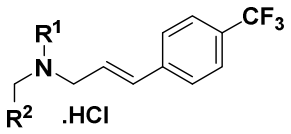
Scheme 7. Syntheses of Derivatives **45a-b**[a]



[a]Reagents and conditions: (a) ethyl 2-(triphenyl-l5-phosphanylidene)acetate, , toluene, 100 ^{o}C; (b) DIABL-H, DCM, 0 ^{o}C; (c). PBr_3, Et_2O; (d)(1) K_2CO_3, DMF, r.t., overnight, 28-37%, (2) bubbled into hydrogen chloride gas.

TABLES

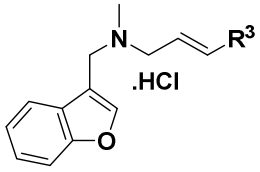
Table 1. Chemical structures of drivatives **3a-f** and their pigment inhibitory activities against *S. aureus* Newman.

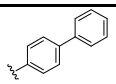
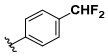


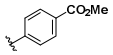
Compd	R^1	R^2	IC_{50}[a](nM)
3a	H		> 1000
3b	ethyl		> 1000
3c	isopropyl		> 1000
3d	H		> 1000
3e	ethyl		117.9 ± 8.9
3f	isopropyl		> 1000

[a]The values given are the IC_{50} values for pigment inhibition in *S. aureus* Newman. The values are reported as the average ± S.D.

Table 2. Structures and pigment inhibition activities of the analogs of compound **4a-40a**

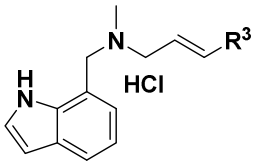


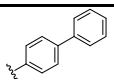
Compd	R^3	$IC_{50}{}^a$ (nM)	Compd	R^3	$IC_{50}{}^a$ (nM)
4a		91.3 ± 3.8	**23a**		2.0 ± 0.1
5a		397.3 ± 20.3	**24a**		359.8 ± 57.8
6a		> 1000	**25a**		> 1000
7a		> 1000	**26a**		86.4 ± 0.6
8a		> 1000	**27a**		74.1 ± 2.7
9a		> 1000	**28a**		> 1000
10a		6.4 ± 0.6	**29a**		> 1000
11a		> 1000	**30a**		> 1000
12a		4.9 ± 0.1	**31a**		> 1000
13a		74.1 ± 2.7	**32a**		> 1000
14a		2.5 ± 0.3	**33a**		> 1000
15a		9.9 ± 1.8	**34a**		> 1000
16a		15.8 ± 2.8	**35a**		> 1000
17a		> 1000	**36a**		6.2 ± 0.5
18a		9.5 ± 3.2	**37a**		9.2 ± 0.4
19a		6.4 ± 0.1	**38a**		> 1000
20a		80.1 ± 4.7	**39a**		> 1000
21a		> 1000	**40a**		> 1000

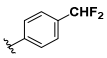
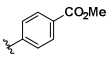
22a		9.5 ± 0.8

[a]The values given are the IC_{50} values for pigment inhibition in *S. aureus* Newman. The values are reported as the average ± S.D.

Table 3. Structures and pigment inhibition activities of the analogs of compound **4b-40b**

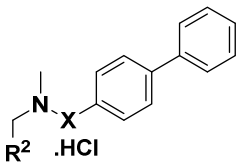


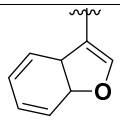
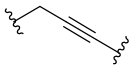
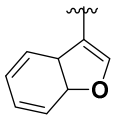
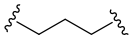
Compd	R^3	IC_{50}[a] (nM)	Compd	R^3	IC_{50}[a] (nM)
4b		> 1000	**23b**		3.3 ± 0.4
5b		> 1000	**24b**		> 1000
6b		> 1000	**25b**		> 1000
7b		> 1000	**26b**		> 1000
8b		> 1000	**27b**		> 1000
9b		> 1000	**28b**		> 1000
10b		131.8 ± 11.6	**29b**		> 1000
11b		> 1000	**30b**		> 1000
12b		142.6 ± 5.6	**31b**		> 1000
13b		> 1000	**32b**		> 1000
14b		83.8 ± 2.5	**33b**		> 1000

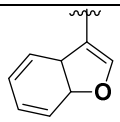
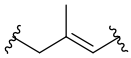
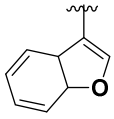
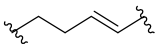
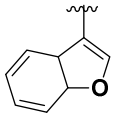
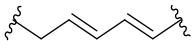
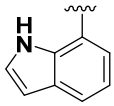
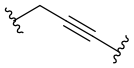
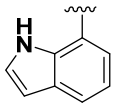
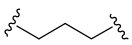
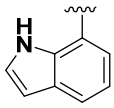
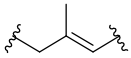
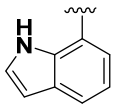
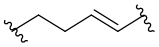
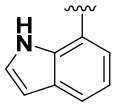
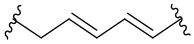
15b		199.0 ± 4.2	**34b**		> 1000
16b		167.0 ± 24.2	**35b**		> 1000
17b		64.8 ± 3.2	**36b**		279.6 ± 0.3
18b		> 1000	**37b**		48.4 ± 0.2
19b		43.5 ± 5.4	**38b**		> 1000
20b		784.7 ± 20.0	**39b**		73.1 ± 0.3
21b		700.0 ± 57.4	**40b**		> 1000
22b		87.8 ± 0.2			

[a]The values given are the IC_{50} values for pigment inhibition in *S. aureus* Newman. The values are reported as the average ± S.D.

Table 4. Structures and pigment inhibition activities of the analogs of compound **41-45a** and **41-45b.**



Compd.	R^2	Linker (X)	*S. aureus* Newman IC_{50} (nM)[a]
41a			> 1000
42a			> 1000

43a			> 1000
44a			> 1000
45a			> 1000
41b			101.8 ± 5.2
42b			> 1000
43b			> 1000
44b			> 1000
45b			19.4 ± 0.2

[a]The values given are the IC_{50} values for pigment inhibition in *S. aureus* Newman.

The values are reported as the average ± S.D.

Table 5. Cytotoxicity of **12a, 14a** and **23a-b** on human embryonic kidney cell (HEK-293) and human hepatocellular carcinoma cell (HepG2).

Compd.	HEK-293	HepG2
	CC_{50}[a] (μM)	IC_{50}[b] (μM)
Amphotericin B	4.2	3.1
12a	42.1	60.2

14a	41.9	33.0
23a	48.1	105.8
23b	26.5	21.9

[a]The values given are the IC_{50} values for Cytotoxicity of HEK-293. [b]The values given are the IC_{50} values for Cytotoxicity of HepG2.

Table 6. Effects of **23a-b** on pigment production of *S. aureus* USA400 MW2, USA300 LAC, Mu50 and NRS271.

Compd.	USA400 MW2 IC_{50}[a] (nM)	USA300 LAC IC_{50}[b] (nM)	Mu50 IC_{50}[c] (nM)	NRS271 IC_{50}[d] (nM)
1	3.4 ± 0.02	5.5 ± 0.4	0.4 ± 0.02	6.7 ± 0.3
23a	7.9 ± 1.2	1.9 ± 0.2	0.8 ± 0.01	5.6 ± 0.9
23b	8.0 ± 0.1	4.0 ± 0.3	0.4 ± 0.04	10.1 ± 0.6

[a]The values given are the IC_{50} values against USA400 MW2. The values are reported as the average ± S.D [b]The values given are the IC_{50} values against USA300 LAC. The values are reported as the average ± S.D. [c]The values given are the IC_{50} values against Mu50. The values are reported as the average ± S.D. [d]The values given are the IC_{50} values against NRS271. The values are reported as the average ± S.D.

Table 7. The results of water solubility, hERG and CrtN inhibition activities (IC_{50}) of **1** and **23a-b.**

Compd.	Water solubility[a] (mg/mL)	hERG inhibition activities IC_{50}[b] (μM)	CrtN IC_{50}[c] (μM)

1	10.0	3.7	0.3
23a	0.2	34.8	0.4 ± 0.01
23b	0.2	> 40	0.2 ± 0.01

[a]The values given are the values of water solubility. [b]The values given are the IC_{50} values of hERG inhibition activity. [c]The values given are the IC_{50} values against CrtN. The values are reported as the average ± S.D.

Table 8. Human miarosome stability of **23a-b.**

Compd.	k	$CL_{int,\ in\ vitro}$ (ml/min/mg)	$CL_{int,\ in\ vivo}$ (ml/min/mg)	$t_{1/2}$ (min)
Midazolam	0.165	0.33	381.0	4.2
23a	0.007	1.23	31.6	50.7
23b	0.014	0.02	17.0	93.7

Table 9. Antifungal activities of **1** and **23a-b.**

	Antifungal Activities, MIC_{80} (μg /mL)		
Compd.	Trichophyton rubrum	Microsporum gypseum	Tinea barbae
Ketoconazole	0.5	2	0.0625
Voriconazole	0.03125	0.25	0.03125
Fluconazole	1	8	2
1	16	32	> 64

23a	64	32	> 64
23b	> 64	> 64	> 64

Table 10. Effects of **23a** on pigment production of NRS271, NRS70, NRS100, NRS108, LRSA56, LRSA202, LRSA205, HS663, NF65Y and XN108**.**

Pigment production, IC_{50} (nM)			
MRSA strains (country)	IC_{50} (nM)	MRSA strains (country)	IC_{50} (nM)
NRS70 (JPN)	1.7 ± 0.01	LRSA205 (CHN)	10.5 ± 0.4
NRS100 (USA)	1.2 ± 0.1	HS663 (CHN)	0.02 ± 0.01
NRS108 (FRA)	5.6 ± 0.02	NF65Y (CHN)	1.0 ± 0.02
LRSA56 (CHN)	1.8 ± 0.1	XN108 (CHN)	0.2 ± 0.04
LRSA202 (CHN)	1.6 ± 0.2		

Table 11. Effects of **23a** on inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4M and CYP3A4T**.**

CYP	Selective Inhibitors	Inhibition Activity IC_{50} (μM)	Compd.	Inhibition Activity IC_{50} (μM)
1A2	α-Naphthoflavon	30	**23a**	5.7
2B6	Ticlopidine	70	**23a**	10.0
2C8	Montelukast	1	**23a**	10.0
2C9	Sulfaphenazole	10	**23a**	10.0

2C19	Omeprazole	35	**23a**	10.0
2D6	Quinidine	5	**23a**	3.2
3A4M	Ketoconazole	80	**23a**	10.0
3A4T	Ketoconazole	80	**23a**	10.0

Table 12. Pharmacokinetic parametears for **23a** after single dosing in rats**.**

dose of **23a** mg/kg	$AUC_{(0\text{-}24h)}$ (h*ng/mL)	$AUC_{(0\text{-}\infty)}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	CL (mL/h/kg)	$T_{1/2}$ (h)	*F* (%)
5 (I.V.)	2805.48	2862.41	4608.78	0.08	1750.00	2.46	-
10 (P.O.)	898.70	930.33	212.56	2.00	-	1.29	16.30
10 (I.P.)	974951.40	1086152.29	130484.03	3.00	-	7.61	

Table 13. Pharmacokinetic parametears for **23a** after single dosing in mice**.**

dose of **23a** mg/kg	$AUC_{(0\text{-}24h)}$ (h*ng/mL)	$AUC_{(0\text{-}\infty)}$ (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	CL (mL/h/kg)	$T_{1/2}$ (h)	*F* (%)
2 (I.V.)	1067.27	1086.95	2230.35	0.08	1840.00	2.05	-

10 (P.O.)	4528.41	4556.40	801.19	2.00	-	3.35	83.84

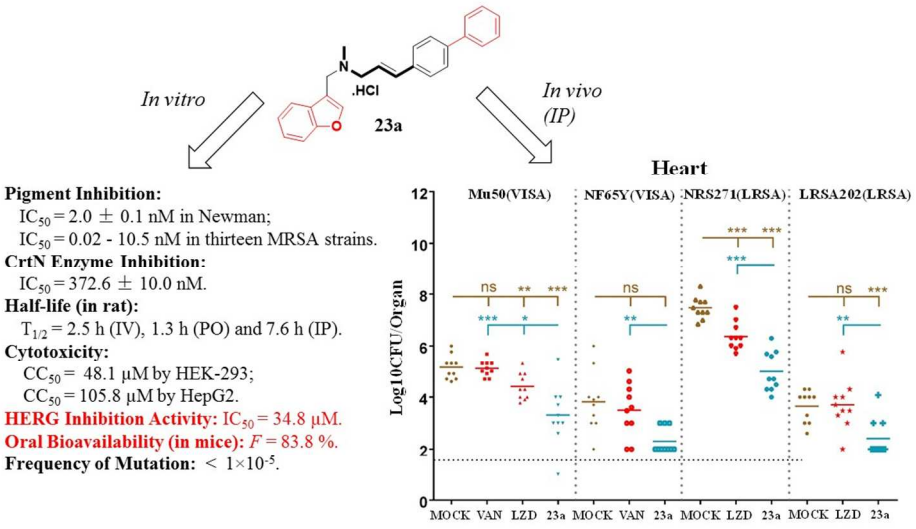
Table 14. Effects of **23a-b** on pigment production of the original and 12 passages of *S. aureus* Newman under IC_{90} concentrations of **23a** or **23b**.

Pigment production, IC_{50} (nM)		
Compd.	Original *S. aureus* Newman, IC_{50}[a] (nM)	12 passages of *S. aureus* Newman, IC_{50}[b] (nM)
23a	2.0 ± 0.1	1.8 ± 0.1
23b	3.3 ± 0.4	2.6 ± 0.2

[a]The values given are the IC_{50} against original *S. aureus* Newman. The values are reported as the average ± S.D. [a]The values given are the IC_{50} against 12 passages of *S. aureus* Newman. The values are reported as the average ± S.D..

Table 15. MIC values of **23a** for enterococcus faecium, *S. aureus* Newman, and pseudomonas aeruginosa.

MIC(μg/mL)			
Compd.	enterococcus faecium	*S. aureus* Newman	pseudomonas aeruginosa
23a	>500μg/mL	>500μg/mL	>500μg/mL



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338x190mm (96 x 96 DPI)