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Sequencing [4+1]-Cycloaddition and Aza-Michael Addition Reactions: A Diastereoselective Cascade for the Rapid Access of Pyrido[2',1':2,3]/Thiazolo[2',3':2,3]imidazo[1,5-a]quinolone Scaffolds as Potential Antibacterial and Anticancer Motifs

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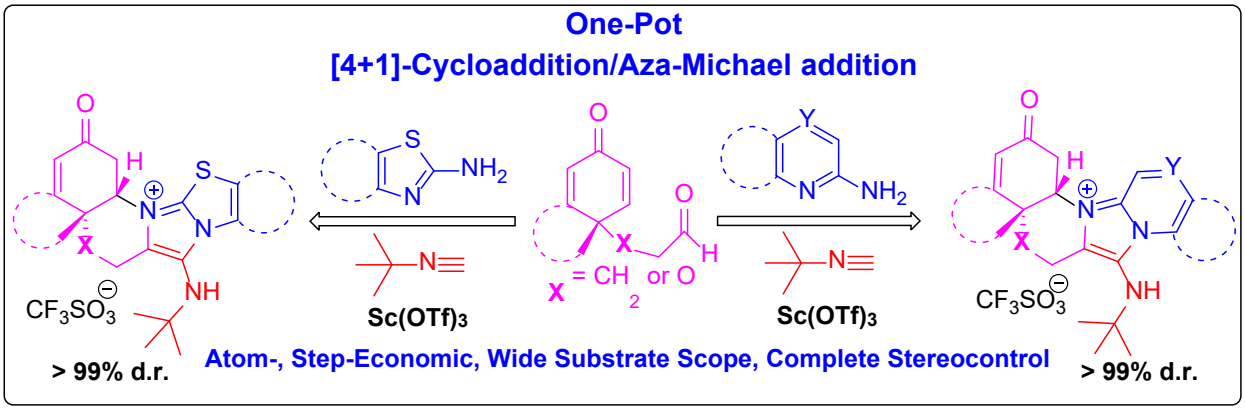


ABSTRACT: The design and synthesis of a quality compound library containing a small number of skeletally diverse scaffolds, whose members rapidly deliver new chemical probes active against multiple phenotypes, is paramount in drug discovery. In this context, an efficient one-pot strategy for the synthesis of a mini library of sp^3 enriched hexahydropyrido[2',1':2,3]imidazo[1,5-a]quinolinium and hexahydrothiazolo[2',3':2,3] imidazo[1,5-a]quinolinium architectures, is described. This new one-pot method features a combination of $Sc(OTf)_3$-catalyzed [4+1]-cycloaddition with aza-Michael addition reactions. The cascade results in a rapid and diastereoselective formation of these scaffolds *via* desymmetrization of the oxidative-dearomatization products of phenols. Phenotypic screening of the mini library against multidrug resistant bacteria and a panel of cancer cell lines identified potential antibacterial and anticancer lead drug candidates. Further investigation of the anticancer

leads, indicated their activity as tubulin-polymerization inhibitors, representing a promising approach for cancer therapy.

INTRODUCTION

The last decade has witnessed a burgeoning interest in the establishment of diversity-oriented synthesis (DOS) strategies for the assembly of nature-inspired and drug-like scaffolds needed for drug discovery campaigns.[1] One such strategy is the use of a single pluripotent starting material that can be ornamented *via* reactions with several reagents, thereby enabling the construction of skeletally and stereochemically diverse compound collections.[2] On the other side, multicomponent reactions (MCRs) hold a privileged position in DOS, allowing the formation of many new bonds and bringing together more than two reactants in one-step.[3] A particularly attractive DOS strategy, is a reaction that combines both strategies in one. Such a strategy should produce a large set of skeletally and stereochemically diverse molecular scaffolds, not achievable by either strategy alone. Within our group, we have developed several starting material- and MCR-based DOS approaches utilizing few pluripotent building blocks.[4] In continuation of a program aiming at the development of efficient synthetic methodologies needed for our drug discovery campaign, we herein present a new strategy for the efficient and diastereoselective synthesis of pyrido[2',1':2,3]imidazo[1,5-a]quinolone and analogues thereof. The latter class of compounds are among the biologically valuable frameworks that are found in a large number of natural products and pharmaceutically active compounds (compounds **A-H**; Figure 1).[5] These include antiviral, antimicrobial, antitumor, and neuroactive pharmaceuticals (Figure 1).[6] Other interesting isosters, are the natural products ellipticine, pazellipticine and 6-methylimidazo[1,2-a:5,4-b']dipyridin-2-amine (Glu-P-1).[7] These were reported to exhibit cytotoxic,[8] genotoxic, and mutagenic activities.[9] Given that structures in this class display an array of biological activities (Figure 1),[5-7] the development of a modular, step-, and atom-economic methodology for their access would be a significant achievement.[7a,7b,10] Such a protocol would facilitate a comprehensive SAR studies for the discovery of new chemical probes for multiple disease states. Only a few synthetic methods for the access of pyrido[2',1':2,3]imidazo[1,5-a]quinolone scaffolds have been reported in the literature. Among others, are the elegant contributions from Anil,[11a] Roman,[11b] Daniel[11c] research groups. Unfortunately, none of these reports introduced 3D-shapes into the core scaffolds of these compounds. The need for high sp^3 content (3D-shapes) containing compounds, has recently been suggested in many reports as a favorable way of

decreasing clinical toxicity and compound attrition rate in clinical trials.[12] Therefore, we envisioned an efficient and modular strategy for the access of sp^3-enriched imidazo[1,5-a]quinoline (type **VII**) could be developed *via* a cascade process combining [4+1]-cycloaddition with aza-Michael addition utilizing synthons of type **III** (Figure 2, *vide infra*). Herein, we report on the synthesis details of this cascade and the biological screening of the designed mini library as potential anticancer and antibacterial lead drug candidates.

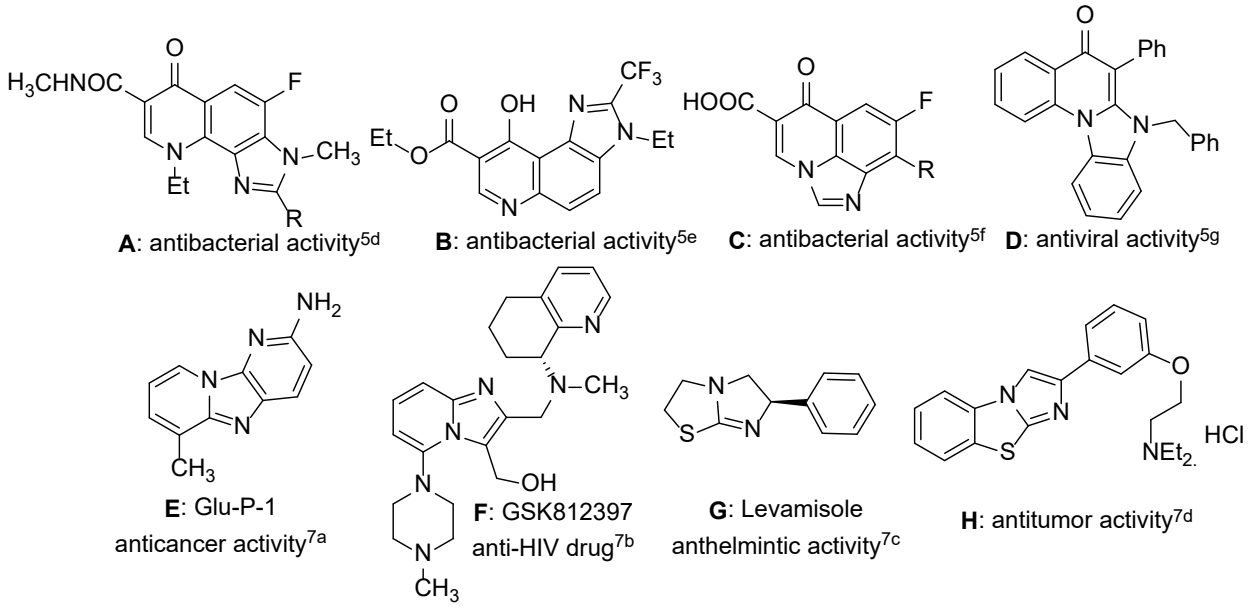


Figure 1. Representative examples of biologically active imidazo[1,5-a]quinolone and imidazopyridines/thiazole derivatives.

RESULTS AND DISCUSSION

Rational Design and Synthesis. The oxidative-dearomatization products of phenols, used in this study, were utilized by many groups which resulted in the construction of complex nature-inspired scaffolds.[13] Recently, our group has reported three-directional routes utilizing the pluripotent building block **III** for the construction of skeletally and stereochemically diverse compound collections (Figure 2).[14a] In this report, we described a one-pot build/couple/pair scheme that distinctively allows access to diverse collections of complex scaffolds of the types **IV**-**VI**, with complete diastereocontrol. These complex molecular shapes were accessed *via* desymmetrization of the oxidative-dearomatization products of phenols. In brief, the pluripotent building block **II** was synthesized *via* the oxidative-dearomatization of phenol **I**. The aldehyde

group in **II**, served as a key branching point which was transformed to the imine **III** (Figure 2). The latter was subjected to three cascades of reactions. The first included desymmetrization of **III** through coupling with various tryptamine derivatives under acid catalyzed conditions, to generate the nature-inspired octahydroindolo[2,3-a]quinolizine **IV** (Figure 2). In the second route, a novel one-step transformation leading to the diastereoselective preparation of oxocane scaffolds of type **V** was discovered. The third round involved the employment of amino acids as one of the reaction components which allowed for the rapid access of polysubstituted piperazinones of type **VI** with complete enantio-control (Figure 2). Inspired by these cascades, we envisioned that the aldehyde group in intermediate **II**, could be utilized as a branching point for a [4+1]-cycloaddition reaction to generate intermediate **5** (Scheme 1). The latter sets the stage for Michael addition reaction to deliver the tetracyclic product of type **VI**. This initiative commonality with the many reports from our group that described the rapid synthesis of diverse collection of privileged and nature-inspired architectures.[4c,14] The ultimate goal of these initiatives is to establish a quality and diverse compound collections needed for our drug discovery campaign. In this context, we envisioned to synthesize a pilot library of polyfunctionalized and conformationally constrained imidazo[1,5-a]quinoline analogues.

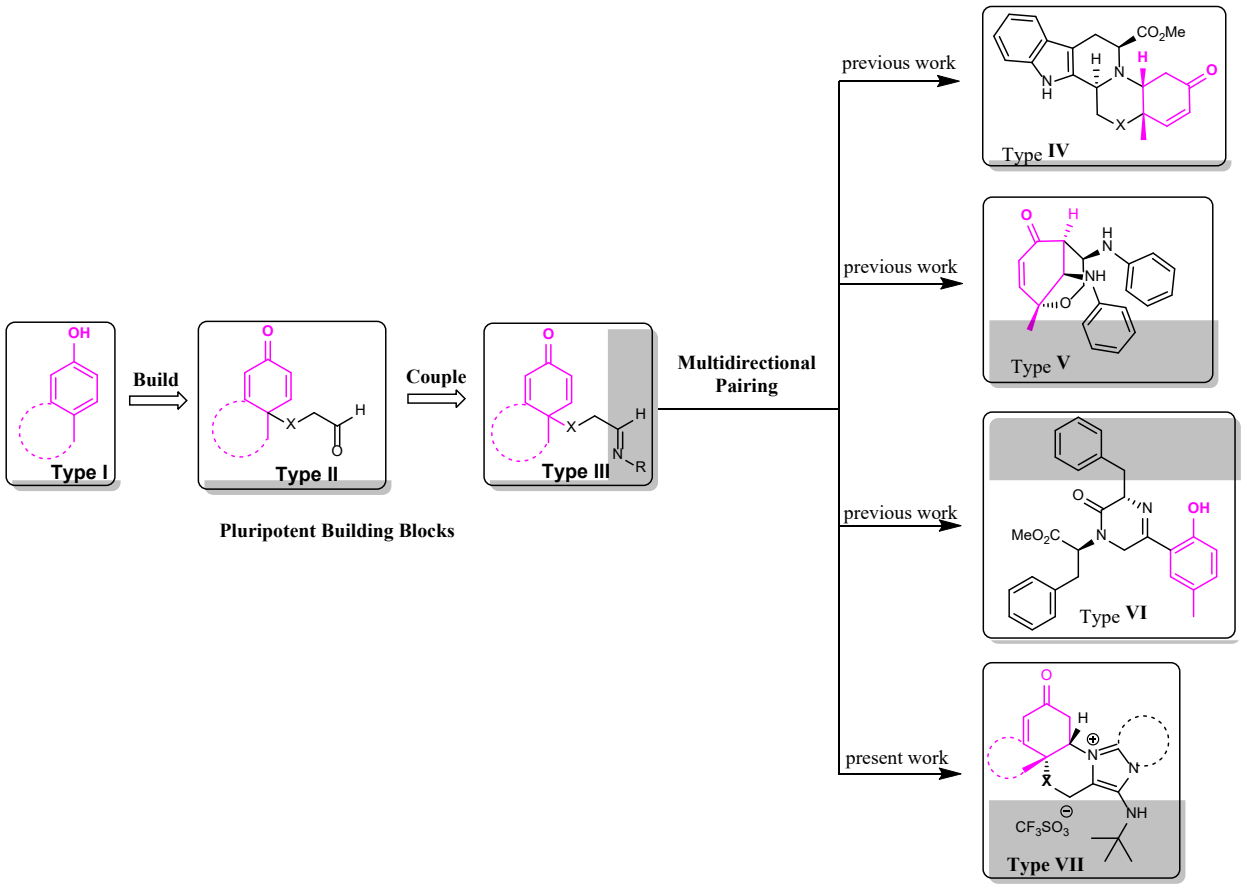
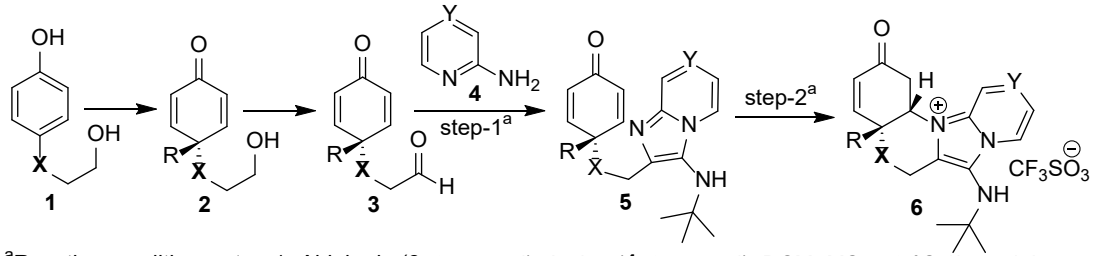


Figure 2. Three directional build/couple/pair protocol for the rapid construction of diverse molecular shapes.

Scheme 1. One-pot synthesis of pyrido[2,1:2,3]imidazo[1,5-a]quinolones



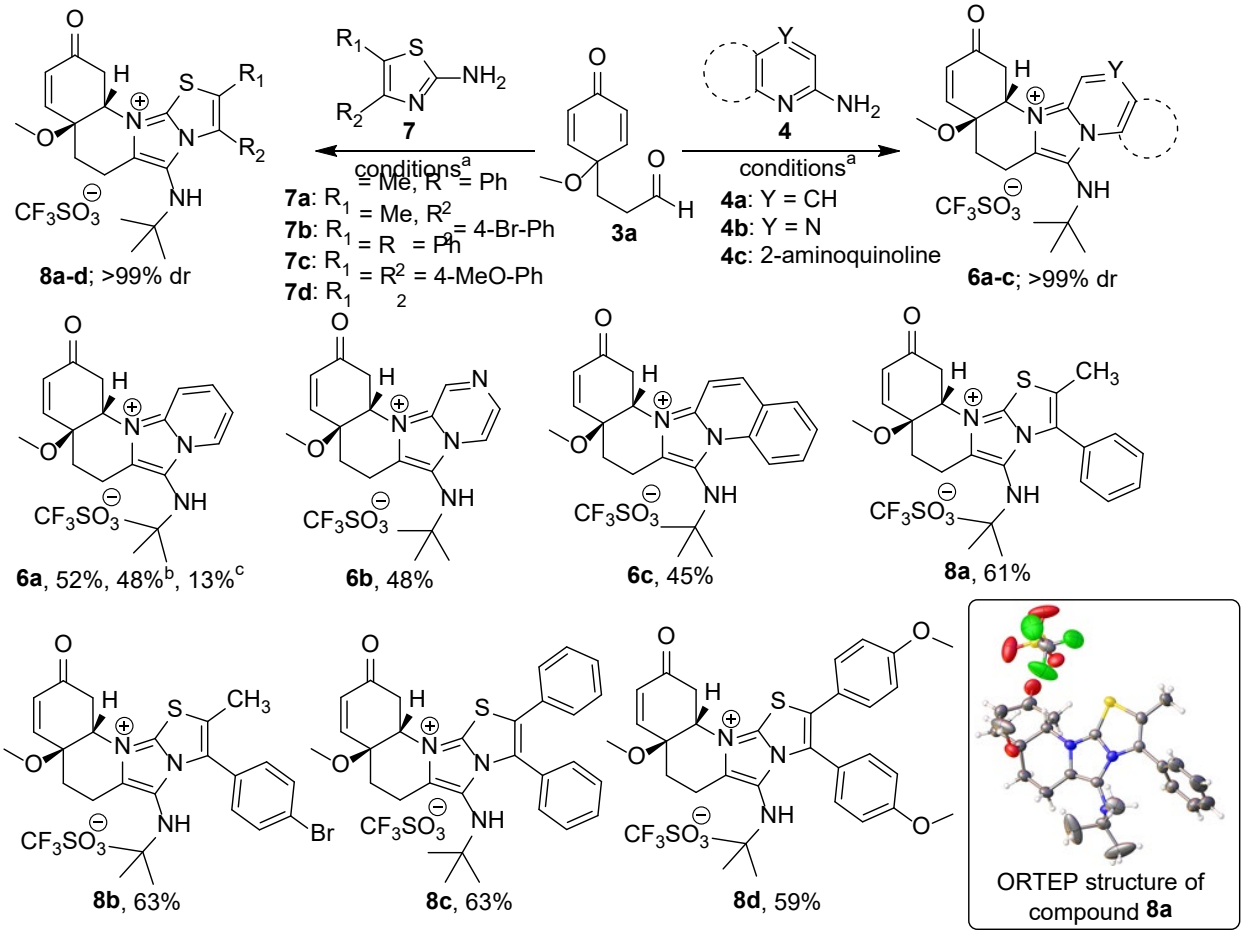
[a]Reaction conditions: step-1- Aldehyde (**3**, 0.5 mmol), Amine (**4**, 0.5 mmol), DCM, MS, -78 °C 1h, and then $Sc(OTf)_3$ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78 °C to rt, 5h; step-2- $Sc(OTf)_3$ (20 mol%), rt, 10h

Borrowing inspiration from previous reports while keeping an eye on the various biological activities of imidazo[1,5-a]quinoline analogues[5d-g], it was envisioned that reacting the 4-oxocyclohexa-2,5-dienyloxy)acetaldehyde **3**, and derivatives thereof, with various amino-azines and isocyanides would promote the Groebke–Blackburn–Bienaymé MCR reaction to produce the imidazopyridine intermediate **5**. The latter is suitably poised with a Michael adduct, which would facilitate the subsequent desymmetrization process leading to the formation of the

polycyclic system **6** (Scheme 1). To test this hypothesis, compound **3** was first prepared by oxidative-dearomatization reaction of the 3-hydroxy-1-propyl phenol (**1**) catalyzed by hyperiodinate reagent followed by Dess-Martin oxidation of the resulting primary alcohol **2** (Scheme 1). Thus, reaction of 2-aminopyridine (**4**) with **3** employing 20 mole% of $Sc(OTf)_3$ as a catalyst at -78 °C delivered intermediate **5**. To promote the aza-Michael addition step, a wide set of conditions were examined, however, most were unsuccessful. Nevertheless, we were delighted to find that treating intermediate **5** with an additional 20 mole% of $Sc(OTf)_3$), rapidly furnished the pyrido[2, 1:2,3] imidazo[1,5-a]quinolinium system **6a** in 52% yield with complete stereocontrol (>99% dr, Scheme 2). To optimize the reaction conditions, other lanthanides such as $Yb(Otf)_3$ was also found to be similarly effective and delivered compound **6a** in 48% yield. Furthermore, the loading efficiency of the catalyst was systematically explored. Thus, screening the catalyst loading from 1 to 20 mol% indicated that a 20 mol% of the catalyst is the optimal equivalence needed in each steps for complete consumption of the starting materials.

To briefly comment on the diastereoselectivity of the cascade, the Groebke-Blackburn-Bienaymé/aza-Michael addition sequence provided a single diastereoisomer, presumably through the cis-addition of the imidazo sp^2-hybridized nitrogen on the enone group of intermediate **5**, guided by intramolecularity, as shown in Scheme 1. Apparently, in the tethered intermediate **5**, the sp^2-hybridized nitrogen atom can adopt the right disposition enforces the nucleophilic addition on the α,β-unsaturated system from the energetically favored disposition leading to a single diastereoisomer (compounds **6**/**8**).

Scheme 2. Diastereoselective synthesis of various pyrido/thiazo[2,1:2,3]imidazo[1,5-a]quinolone derivatives

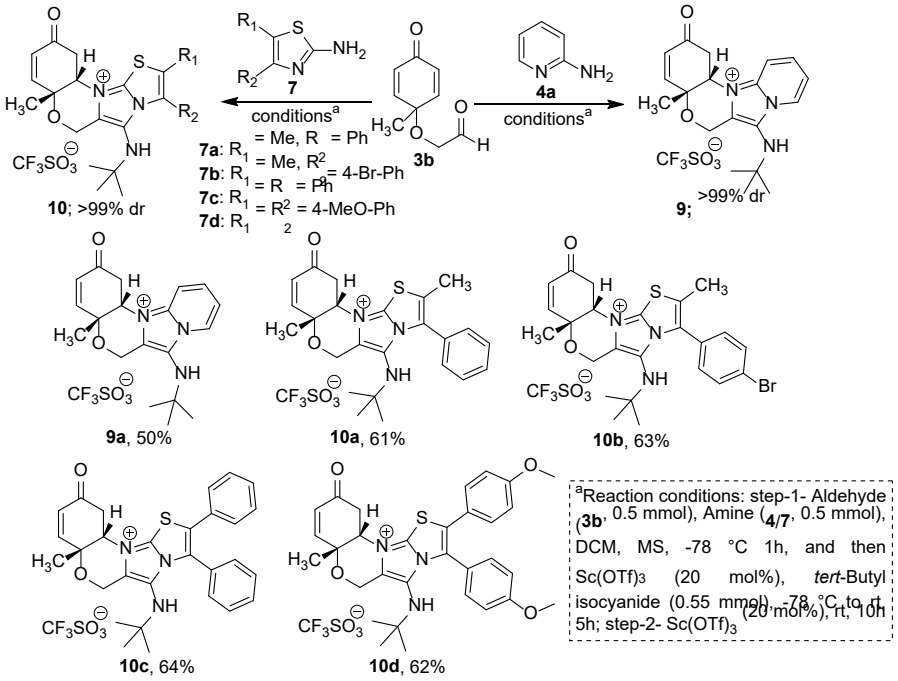


[a]Reaction conditions: step-1- Aldehyde (**3a**, 0.5 mmol), Amine (**4**/**7**, 0.5 mmol), DCM, MS, -78 °C 1h, and then $Sc(OTf)_3$ (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78 °C to rt, 5h; step-2- $Sc(OTf)_3$ (20 mol%), rt, 10h. [b]$Yb(OTf)_3$ was used as a catalyst. [c]5 mol% of $Sc(OTf)_3$

With the optimized conditions in hand, the 2-aminopyrazine (**4b**) and 2-aminoquinoline (**4c**) were reacted with aldehyde **3a**, to deliver compounds **6b** and **6c** each as a single diastereoisomer in 48 and 45 % yield, respectively, scheme 2. To enrich the pilot library with scaffolds bearing additional classes of fused heterocyclic rings, the reaction scope was extended by employing various derivatives of 2-aminothiazole **7a-d** as one of the reaction components. These reactions proceeded smoothly to produce 4 new family members of the hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolinium systems (**8a-d**) in good over all yields and complete diastereocontrol. To unambiguously confirm the structures of these compounds, X-ray crystallographic analysis of compound **8a** was as a representative example (*vide supra*, Scheme 2).

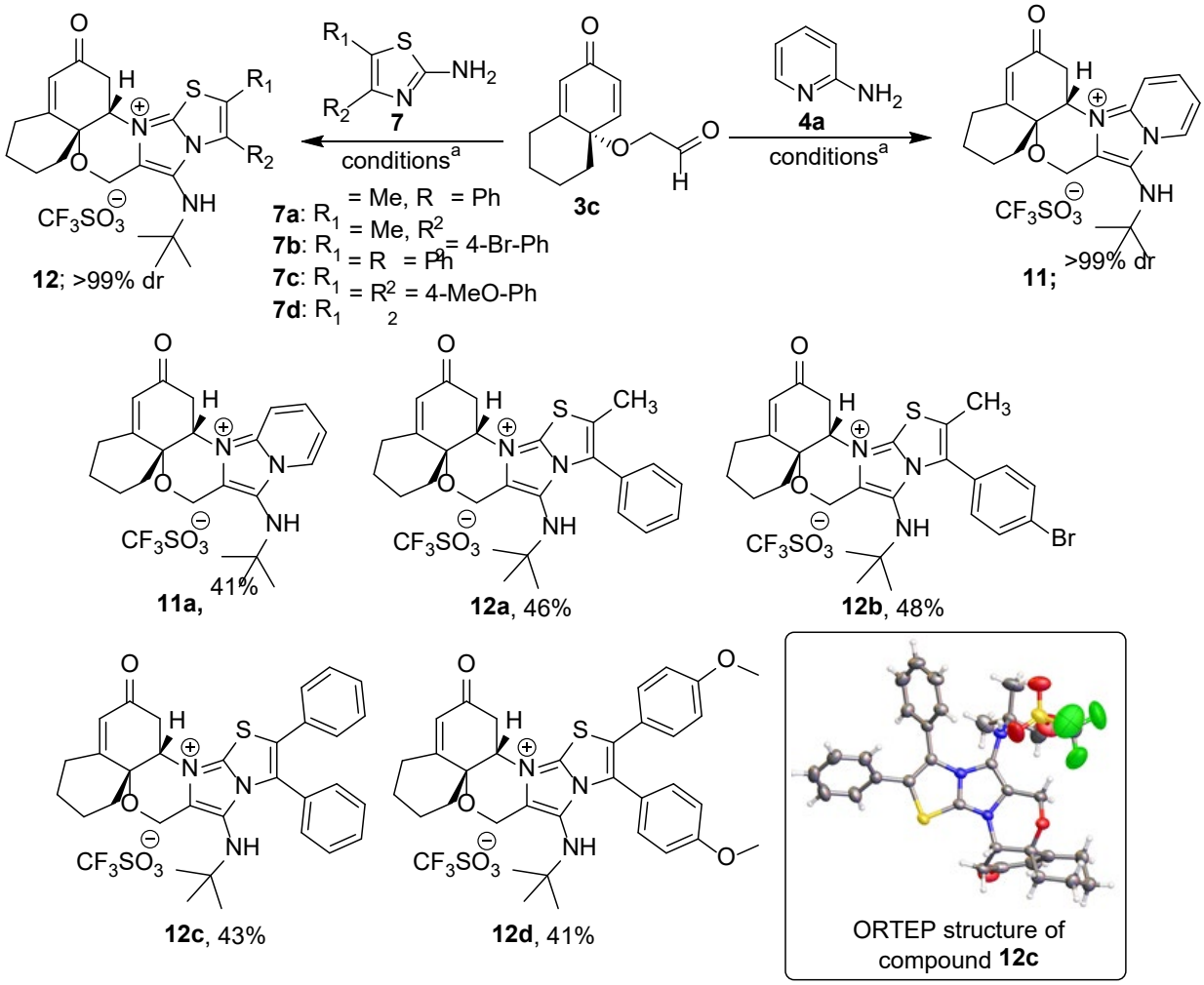
In addition to the structural diversity of the aminoazines used thus far, we incorporated a second diversity element into the pilot library by employing the oxygen-tethered aldehyde **3b**. Hence, we envisioned that applying the same chemistry to this system (Scheme 3), would allow for additional ring-fusion structural diversity within the mini library. To demonstrate this, the aldehyde **3b** was reacted with 2-aminopyridine (**4a**) under the optimized reaction conditions to give rise to the corresponding novel ring system, benzo[d]pyrido[2',1':2,3]imidazo[5,1-b][1,3]oxazinium (**9a**) in 50% yield with complete diastereocontrol (Scheme 3). Similarly, when 2-aminothiazoles **7a-d**, were used as the aminoazine entries, compounds **10a-d** were produced in good yields and with complete stereocontrol.

Scheme 3. Diastereoselective synthesis of various pyrido/thiazo[2,1:2,3]imidazo[1,5-a]morpholine derivatives



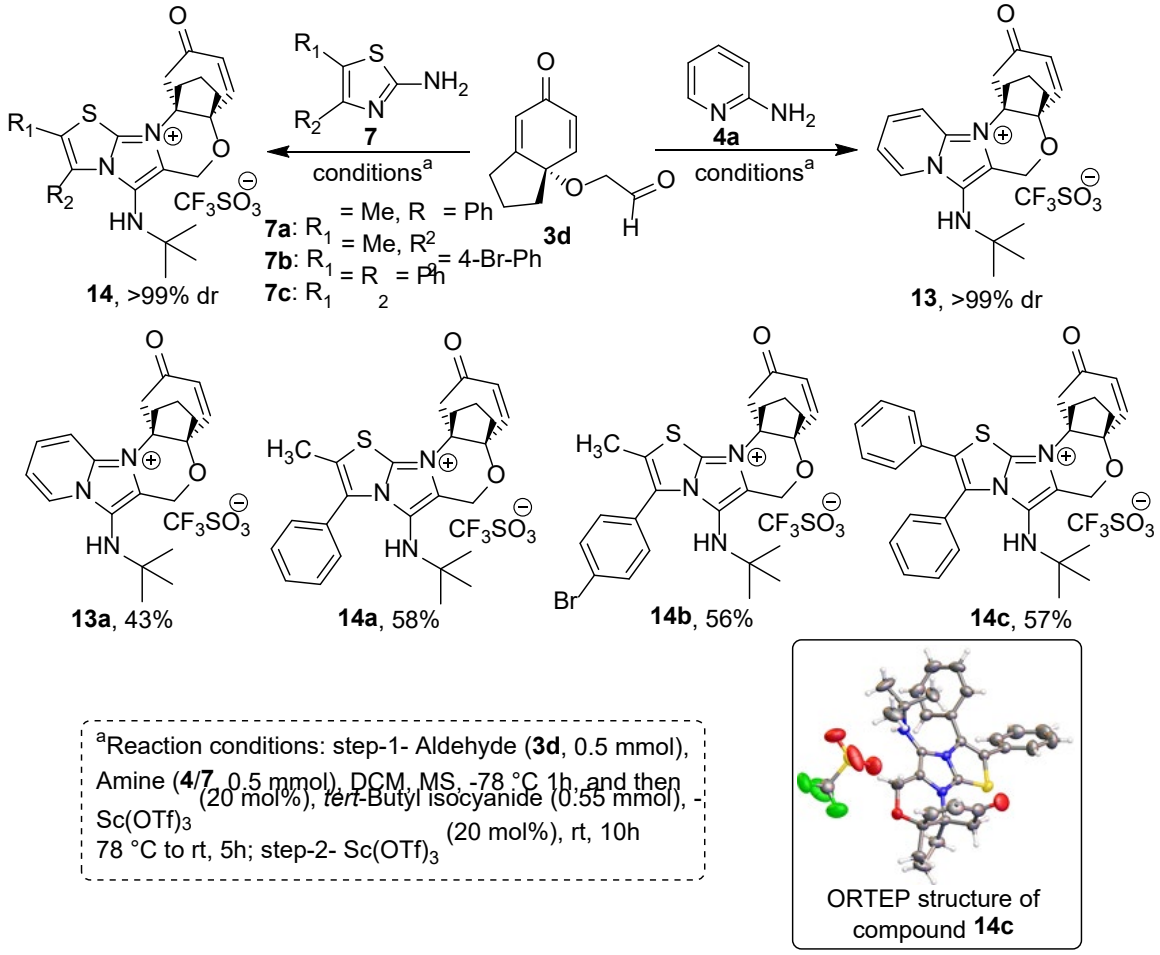
To further expand the mini library to include sp^3-enriched molecular shapes, the hexahydro-7-oxonaphthalen-4a-yloxy)acetaldehyde (**3c**) was synthesized and reacted with various 2-aminoazoles (compounds **4a** and **7a-d**; scheme 4). Under the optimized conditions, this reaction enabled the regioselective synthesis of the pentacyclic imidazo[1,5-d][1,4]oxazinium systems **11a** and **12a-d** in good yields and >99% dr (Scheme 4). The structure of compound **12c** was unambiguously deduced from its X-ray crystallographic analysis (Scheme 4).

Scheme 4. Diastereoselective synthesis of polycyclic imidazo[1,5-d][1,4]oxazinium scaffolds



[a]Reaction conditions: step-1- Aldehyde (**3c**, 0.5 mmol), Amine (**4**/**7**, 0.5 mmol), DCM, MS, -78 °C 1h, and then (20 mol%), *tert*-Butyl isocyanide (0.55 mmol), -78 °C to rt, 5h; step-2- $Sc(OTf)_3$ (20 mol%), rt, 10h

Scheme 5. Diastereoselective synthesis of polycyclic imidazo[1,5-d][1,4]oxazinium scaffolds



Interestingly, when the tetrahydro-5-oxo-1H-inden-7a-yloxy)acetaldehyde (**3d**) was used as a starting material, the regioselectivity was altered relative to that found for the cylohexadienone congener **3c**. Accordingly, the regioisomer **14**, was delivered in fair yield and >99% dr (Scheme 5). The structure of compound **14c** was unequivocally confirmed through 1D-, 2D-NMR spectra (S35-S38; SI) and X-ray analysis (Scheme 5). When the same reaction was performed with the aminopyridine **4a**, similar regio- and diastereo-selectiviy, was observed. Thus, the bridgehead pentacyclic oxazinium system **13** was delivered in 43% yield with complete diastereocontrol. The observed regiochemistry when using aldehyde **3d** as a starting material is notorious compared to that of compound **3c** when reacted with aminoazines **7a-d**. Obviously, the aza-Michael addition reaction of the Greobuck-Blackburn intermediate to deliver compound **12**, proceeded at the least hindered position of the α,β-unsaturated system producing a single regioisomer with complete stereocontrol. While for compounds **13** and **14**, the attack of the sp^2 hybridized nitrogen atom of the azole ring on the α,β-unsaturated system proceeded from the

tetra-substituted carbon rather than from the least hindered tertiary carbon. These findings could be rationalized as contemplated in Figure 3. Clearly, the inherent steric bias contained in intermediates **V** and **VI** (Figure 3), dictated the observed regioselectivity. Apparently, the congested strain in the fused cyclohexane ring in intermediate **III**, hindered the Michael addition at the quaternary center of the α,β-unsaturated system, whereas, the steric compression contained in conformer **VI** prevented the attack at the least hindered position of the α,β-unsaturated ketone (Figure 3). However, the minimal steric strain present in conformer **VIII**, promoted the aza-Michael addition at the more substituted site leading to the bridgehead compounds **13** and **14**.

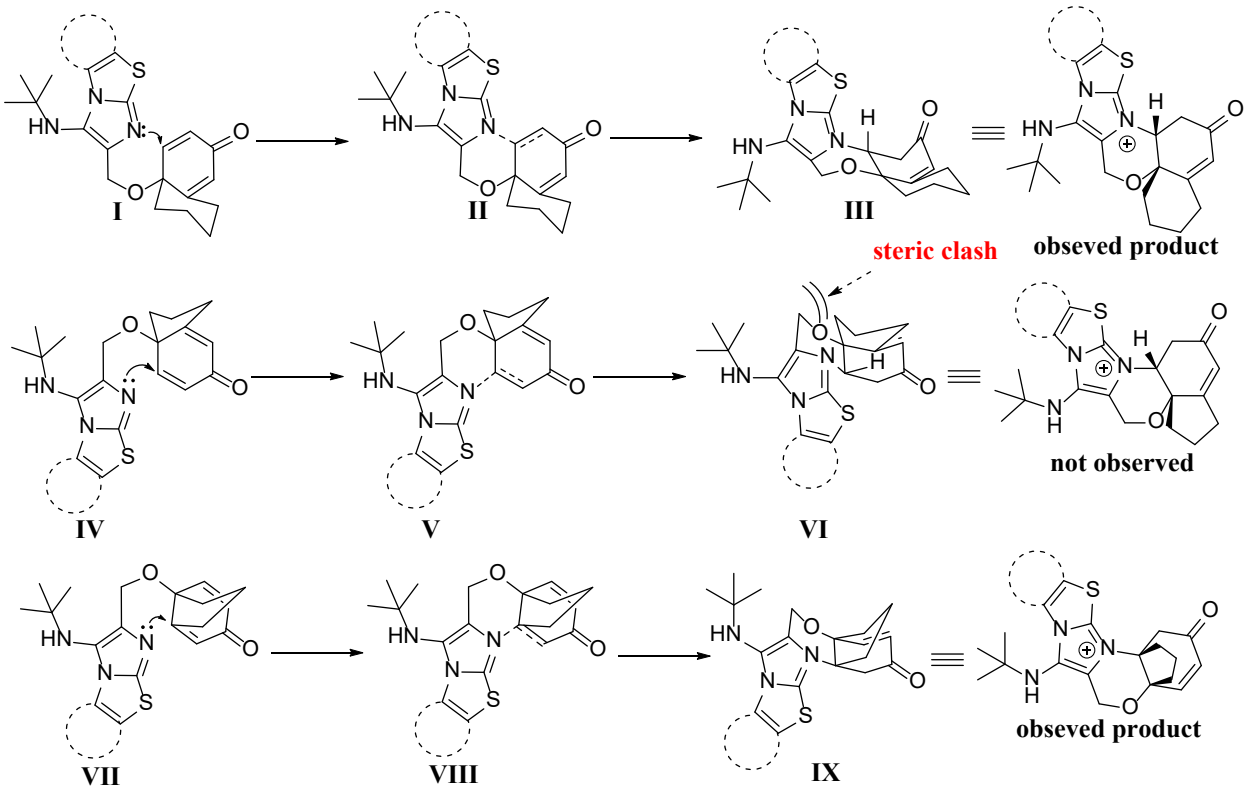


Figure 3. Proposed regiochemical analysis for the formation of the aza-Michael addition products **12/14**.

Phenotypic screening. Multidrug resistant bacteria (MDRB) represent a serious threat to the global health. If not seriously addressed, this silent epidemic is projected to kill up to 300 million people by 2050 with an estimated economic burden of $100 trillion.[15] Due to misuse and overuse of antibiotics, new MDRB species continue to rise, while the discovery of first-in-class

antibiotics to combat these superbugs has drastically declined. On the other side, cancer is the second leading cause of death world-wide after cardiovascular diseases. Although tens of drugs for the treatment of cancer are available in the market, yet the life-span improvement of cancer patients is still very low relative to the amount of time and costs spent on their discovery.

Having established a robust *en route* to the aforementioned compound collections, we aimed to profile these compounds for their activities as potential antiproliferative and antibacterial motifs. Of the 21 compounds tested, compound **8d** showed the most potent antiproliferative activity upon dose-response analysis (Table 1), suggesting that this compound could be a starting point for the development of first-in-class anticancer lead drug candidate. To briefly comment on the structure-activity relationship of the tested pilot compound library, we observed that when the benzo[b]imidazo[1,5-d][1,4]oxazinium core scaffold is fused to thiazole ring (compounds **8d**, **10c-d**, and **14a-b**), the anticancer activity is enhanced when compared to the pyridine fused analogues (compounds **6**, **9**, **11** and **13)**. Furthermore, when the core scaffold, benzo[b]imidazo[1,5-d][1,4]oxazinium, bears a diphenylthiazole ring (compounds **8d, 10c** and **10d**), the anticancer potency is sharply enhanced. Interestingly, a di(methoxyphenyl)thiazole group anchored on the basic framework delivered the most potent anticancer motifs (compounds **8d** and **10d**). Further investigation of the anticancer best hits indicated that these compounds are potential tubulin polymerization destabilizers. The tubulin inhibition dynamics were tested at their IC_{50} concentrations (2.1-4.0 μM) and found to be comparable to that of colchicine, a microtubule-polymerization inhibitor but not analogous to the effect of the microtubule-stabilizer paclitaxel (Figure S6, SI). This finding supports the notion that these compounds might exert their antiproliferative effects through the inhibition of tubulin assembly and suppression of microtubule formation.

Table 1. Cytotoxicity data of active compounds against a panel of human cancer cell lines

Compound	**IC_{50} (μM)[a]**			
	MCF7	**A549**	**HeLa**	**HCT116**
8d	2.1	4.4	2.88	1.7
10c	3.1	4.5	5.4	3.64
10d	2.5	7.4	1.2	3.0

14a	6.9	11.2	2.1	6.1
14b	9.1	14.6	5.1	9.4
Doxorubicin	0.17	0.12	0.29	0.09
[a]Breast cancer (MCF-7), lung cancer (A549), cervical cancer (HeLa), colon cancer (HCT116). **IC_{50} =** Half-maximal inhibitory concentration.				

Furthermore, phenotypic screening of the designed library against three species of multidrug resistant *Staphylococcus aureus* (Gram-positive pathogen) (Table S4) and *E. Coli* (Gram-negative), identified compound **8d** as a potential antibacterial lead drug candidate. Compound **8d** demonstrated high growth inhibition activity against the four species under investigation, with MIC values ranges from 12.5 to 25 μg/mL. However, none of the tested compounds was active against *E. Coli* (Table 2).

Table 2. Antibacterial activity of compound **8d** against *Staphylococcus aureus* (Gram-positive bacteria), *Escherichia coli* (Gram-negative bacteria) and three multidrug resistant strains of methicillin-resistant *Staphylococcus aureus* (MRSA-1, MRSA-2 and MRSA-3)

Compound	**MICs (μg/ml)**				
	***Staphylococcus aureus* (strain ATCC 25923)**	**MRSA-1**	**MRSA-2**	**MRSA-3**	***Escherichia coli* (strain ATCC 25922)**
8d	25	12.5	12.5	25	Non-active
Ciprofloxacin	0.125	32	16	2	0.008

While an in-depth assessment of the biological findings of these motifs is required, the encouraging results support a promising application of these compounds as potential lead drug candidates for the development of antibacterial and anticancer agents.

CONCLUSION

In summary, we have developed a highly efficient synthesis of hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolinium heterocycles and anologues thereof, through a one-pot combination of formal $Sc(OTf)_3$-catalyzed [4+1]-cycloaddition with aza-Michael addition reactions. The use of commercial catalysts, readily available substrates, and a simple procedure bode well for practical application of this strategy. The described protocol allowed for the access of quality compounds with complete stereocontrol, step- and atom-economic control. This approach offered interesting skeletal and stereochemical complexity not achievable by either approach alone. Subsequent phenotypic screening of the mini library identified unique chemotypes, compound **8d**, which effectively suppressed proliferation of cancer cells, and inhibit tubulin polymerization, representing a promising approach for the development of first-in-class lead drug candidates for potential treatment of cancer. In another aspect, the designed mini library, offered a potential opportunity to develop the designed motifs as potent antibiotics against multidrug resistant bacteria. Finally, the established chemistry is projected to enable the discovery of new chemical probes and work along these lines is presently in progress in our laboratories.

EXPERIMENTAL SECTION

General. Chemical reagents and anhydrous solvents were purchased from Sigma-Aldrich and were used without further purification. Solvents for extraction and column chromatography were distilled prior to use. TLC analysis were performed with silica gel plates (0.25 mm, E. Merck, 60 F_{254}) using iodine and a UV lamp for visualization. ^{1}H and ^{13}C NMR experiments were performed on a 500 MHz instrument. Chemical shifts are reported in parts per million (ppm) downstream from the internal tetramethylsilane standard. Spin multiplicities are described as s (singlet), bs (broad singlet), d (doublet), dd (doubledoublet), t (triplet), q (quartet), or m (multiplet). Coupling constants are reported in Hertz (Hz). ESI mass spectrometry was performed on a Q-TOF high resolution mass spectrometer or Q-TOF Ultim LC-MS. Single-crystal X-ray diffraction data were collected using an Oxford Diffraction XCalibur, equipped with (Mo) X-ray Source ($\lambda = 0.71073$ Å) at 293(2) K.

General Reaction Procedure for the Preparation of Compounds 3a-d. Compounds **3a-d** were prepared according to a precedent procedure and the spectroscopic data are matching that published in reference 14a.[14a]

General reaction procedure for the preparation of compounds 6 and 8-14. Aldehyde (**3**, 0.5 mmol, 1.0 eq) and molecular sieves were mixed in DCM (2 mL, 0.25M) and a solution of amine (**4**/**7**, 0.5 mmol, 1.0 eq) in DCM (2.0 mL, 0.25M) was added dropwise at -78 °C. After 1h, scandium triflate (20 mol%, 0.2 eq) and a solution of tert-butyl isocyanide (0.55 mmol, 1.1 eq) in MeOH (0.5 mL, 1.1M) were introduced and stirring was continued for 5h. After completion of step-1, an additional 20 mol% (0.2 eq) of scandium triflate was added and the reaction was continued at rt for 10h. After completion, solvent was removed under vacuum and the crude was purified on flash column chromatography, using a gradient of MeOH/DCM as an eluent to deliver pure products.

Reaction procedure for the preparation of compound 6a at 2mmol scale. Aldehyde (**3a**, 360 mg, 2.0 mmol) and molecular sieves were mixed in DCM (8.0 mL, 0.25M) and a solution of amine (**4a**, 188 mg, 2.0 mmol) in DCM (8.0 mL, 0.25M) was added dropwise at -78 °C. After 1h, scandium triflate (196 mg, 20 mol%) and a solution of tert-butyl isocyanide (183 mg, 2.2 mmol) in MeOH (2.0 mL, 1.1M) were introduced and stirring was continued for 5h. After completion of step-1, an additional 20 mol% (196 mg) of scandium triflate was added and the reaction was continued at rt for 10h. After completion, solvent was removed under vacuum and the crude was purified on flash column chromatography, using a gradient of 3% MeOH in DCM as an eluent to deliver compound **6a** (548 mg, 56% yield).

(4aS,13aS)-7-(Tert-butylamino)-4a-methoxy-2-oxo-1,2,4a,5,6,13a-hexahydropyrido[2',1':2,3]imidazo[1,5-a]quinolin-13-ium trifluoromethanesulfonate (6a). White solid (127 mg, 52% yield, eluent: 3% MeOH in DCM). mp 92−94 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 6.7 Hz, 1H), 7.98 – 7.90 (m, 1H), 7.90 – 7.83 (m, 1H), 7.41 (t, *J* = 6.8 Hz, 1H), 7.01 (d, *J* = 10.4 Hz, 1H), 6.23 (d, *J* = 10.4 Hz, 1H), 5.48 – 5.39 (m, 1H), 3.48 – 3.42 (m, 1H), 3.42 (s, 3H), 3.18 – 3.09 (m, 2H), 2.95 – 2.86 (m, 1H), 2.36 – 2.30 (m, 2H), 1.28 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 193.5, 150.2, 135.7, 133.1, 131.6, 128.5, 126.1, 125.8, 120.6 (q, 1JC-F = 318.7 Hz), 117.1, 110.1, 73.4, 56.2, 52.9, 51.5, 41.3, 30.7, 25.6, 17.6. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{20}H_{26}N_3O_2$ 340.2025, found 340.2029.

(4aS,13aS)-7-(tert-butylamino)-4a-methoxy-2-oxo-1,2,4a,5,6,13a-hexahydropyrazino[2',1':2,3]imidazo[1,5-a]quinolin-13-ium trifluoromethanesulfonate (6b). White solid (117 mg, 48% yield, eluent: 4% MeOH in DCM). mp 196−198 °C. ^{1}H NMR

(500 MHz, CD_3OD) δ 9.59 (s, 1H), 8.85 (d, *J* = 3.5 Hz, 1H), 8.55 (d, *J* = 4.5 Hz, 1H), 7.25 (d, *J* = 10.4 Hz, 1H), 6.33 (d, *J* = 10.4 Hz, 1H), 5.95 (dd, *J* = 12.3, 5.4 Hz, 1H), 3.43 (s, 3H), 3.38 – 3.34 (m, 1H), 3.31 – 3.26 (m, 2H), 3.04 – 2.93 (m, 1H), 2.48 – 2.28 (m, 2H), 1.32 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, CD_3OD) δ 195.0, 152.2, 137.5, 135.8, 132.4, 132.0, 131.2, 128.3, 121.7 (q, 1JC-F = 313.7 Hz),119.3, 74.3, 58.0, 54.5, 51.7, 43.1, 30.6, 26.0, 18.4. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{19}H_{25}N_4O_2$ 341.1977, found 341.1984.

(7aS,11aS)-14-(tert-butylamino)-11a-methoxy-9-oxo-7a,8,9,11a,12,13-hexahydroimidazo[1,2-a:3,4-a']diquinolin-7-ium trifluoromethanesulfonate (6c). Brownish solid (121 mg, 45% yield, eluent: 3% MeOH in DCM). mp 189−191 °C. ^1H NMR (500 MHz, CD_3OD) δ 10.09 (d, *J* = 8.8 Hz, 1H), 8.36 (d, *J* = 9.4 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 9.5 Hz, 1H), 7.96 (t, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 10.4 Hz, 1H), 6.32 (d, *J* = 10.4 Hz, 1H), 5.79 (dd, *J* = 12.4, 5.4 Hz, 1H), 3.45 (s, 3H), 3.31 – 3.18 (m, 3H), 2.97 – 2.89 (m, 1H), 2.49 – 2.42 (m, 1H), 2.39 – 2.26 (m, 1H), 1.30 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, CD_3OD) δ 195.2, 152.4, 137.0, 136.1, 135.1, 132.3, 132.2, 131.6, 131.1, 128.8, 127.5, 126.6, 120.9 (q, 1JC-F = 317.8 Hz), 120.5, 108.8, 74.6, 58.1, 54.0, 51.7, 42.5, 30.2, 26.3, 18.2. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{24}H_{28}N_3O_2$ 390.2181, found 390.2184.

(4aS,12aS)-7-(tert-butylamino)-4a-methoxy-10-methyl-2-oxo-9-phenyl-1,2,4a,5,6,12a-hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolin-12-ium trifluoromethanesulfonate (8a). White solid (178 mg, 61% yield, eluent: 2% MeOH in DCM). mp 193−195 °C. ^1H NMR (500 MHz, acetone-d_6) δ 7.57 – 7.50 (m, 2H), 7.50 – 7.42 (m, 3H), 7.08 (d, *J* = 10.4 Hz, 1H), 6.10 (d, *J* = 10.4 Hz, 1H), 5.50 (dd, *J* = 12.0, 5.7 Hz, 1H), 3.42 (s, 1H), 3.32 (s, 3H), 3.10 (dd, *J* = 16.2, 5.2 Hz, 2H), 3.05 – 2.96 (m, 1H), 2.89 – 2.78 (m, 1H), 2.36 (s, 3H), 2.30 – 2.22 (m, 2H), 0.61 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, acetone-d_6) δ 193.5, 151.1, 151.0, 141.4, 132.7, 131.9, 130.9, 129.6, 129.2, 129.1, 128.0, 127.5, 121.2 (q, 1JC-F = 315.0 Hz), 74.0, 55.7, 55.3, 51.6, 40.3, 30.0, 26.0, 18.3, 13.3. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{25}H_{30}N_3O_2S$ 436.2058, found 436.2047

(4aS,12aS)-9-(4-bromophenyl)-7-(tert-butylamino)-4a-methoxy-10-methyl-2-oxo-1,2,4a,5,6,12a-hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolin-12-ium trifluoromethanesulfonate (8b). White solid (204 mg, 63% yield, eluent: 2.5% MeOH in DCM). mp 200−202 °C. ^1H NMR (500 MHz, acetone-d_6) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* =

8.2 Hz, 2H), 7.22 (d, *J* = 10.4 Hz, 1H), 6.24 (d, *J* = 10.4 Hz, 1H), 5.64 (dd, *J* = 12.2, 5.6 Hz, 1H), 3.71 (s, 1H), 3.46 (s, 3H), 3.30 – 3.20 (m, 2H), 3.20 – 3.10 (m, 1H), 3.03 – 2.94 (m, 1H), 2.52 (s, 3H), 2.43 – 2.35 (m, 2H), 0.79 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, acetone-d_6) δ 193.5, 151.1, 151.0, 141.5, 134.7, 132.1, 131.9, 131.6, 129.6, 128.2, 127.2, 124.7, 121.0 (q, 1JC-F = 316.5 Hz), 74.0, 55.7, 55.3, 51.6, 40.3, 26.0, 18.3, 13.3. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{25}H_{29}BrN_3O_2S$ 514.1163, found 514.1153.

(4aS,12aS)-7-(tert-butylamino)-4a-methoxy-2-oxo-9,10-diphenyl-1,2,4a,5,6,12a-hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolin-12-ium trifluoromethanesulfonate (8c). White solid (194 mg, 63% yield, eluent: 2.5% MeOH in DCM). mp 198−200 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 3H), 7.40 – 7.34 (m, 2H), 7.33 – 7.29 (m, 3H), 7.18 (d, *J* = 7.2 Hz, 2H), 6.95 (d, *J* = 10.4 Hz, 1H), 6.28 (d, *J* = 10.4 Hz, 1H), 5.03 – 4.97 (m, 1H), 3.45 (s, 3H), 3.40 – 3.32 (m, 1H), 3.29 – 3.21 (m, 2H), 3.11 – 3.01 (m, 1H), 2.48 – 2.39 (m, 1H), 2.37 – 2.29 (m, 1H), 0.72 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.4, 148.8, 140.0, 132.1, 131.6, 130.4, 130.2, 129.9, 129.8, 129.48, 129.47, 129.2, 128.9, 128.65, 128.64, 126.7, 120.8 (q, 1JC-F = 320.0 Hz),73.1, 55.8, 54.6, 51.3, 39.2, 30.1, 25.6, 18.3. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{30}H_{32}N_3O_2S$ 498.2215, found 498.2228.

(4aS,12aS)-7-(tert-butylamino)-4a-methoxy-9,10-bis(4-methoxyphenyl)-2-oxo-1,2,4a,5,6,12a-hexahydrothiazolo[2',3':2,3]imidazo[1,5-a]quinolin-12-ium trifluoromethanesulfonate (8d). White solid (208 mg, 59% yield, eluent: 3.0% MeOH in DCM). mp 190−192 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.54 – 7.34 (m, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 7.00 – 6.87 (m, 3H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.24 (d, *J* = 10.4 Hz, 1H), 5.00 – 4.92 (m, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.42 (s, 3H), 3.36 – 3.27 (m, 1H), 3.25 – 3.10 (m, 3H), 3.08 – 2.97 (m, 1H), 2.42 – 2.24 (m, 2H), 0.72 (s, 9H). $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$) δ 193.4, 161.1, 160.6, 149.0, 139.7, 131.6, 131.4, 131.1, 130.1, 129.8, 129.4, 128.9, 121.2, 120.8 (q, 1JC-F = 318.7 Hz),118.8, 114.7, 114.1, 73.1, 55.59, 55.57, 55.5, 54.7, 51.3, 39.2, 30.2, 25.6, 18.2. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{32}H_{36}N_3O_4S$ 558.2426, found 558.2416.

(4aR,13aS)-7-(tert-butylamino)-4a-methyl-2-oxo-1,4a,5,13a-tetrahydro-2H-benzo[d]pyrido[2',1':2,3]imidazo[5,1-b][1,3]oxazin-13-ium trifluoromethanesulfonate (9a). White solid (118 mg, 50% yield, eluent: 3.5% MeOH in DCM). mp 138−140 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.75 (d, *J* = 6.7 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.92 – 7.84 (m, 1H), 7.44 (t, *J*

= 6.8 Hz, 1H), 6.78 (d, *J* = 10.2 Hz, 1H), 6.18 (d, *J* = 10.2 Hz, 1H), 5.26 – 5.10 (m, 3H), 2.96 (d, *J* = 7.5 Hz, 2H), 1.65 (s, 3H), 1.23 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 193.8, 147.7, 136.5, 133.9, 130.9, 126.4, 124.6, 123.6, 120.6 (q, 1JC-F = 317.5 Hz),117.6, 110.7, 69.7, 57.4, 56.3, 54.7, 39.9, 30.5, 21.8. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{19}H_{24}N_3O_2$ 326.1868, found 326.1874.

(4aR,12aS)-7-(tert-butylamino)-4a,10-dimethyl-2-oxo-9-phenyl-1,2,4a,12a-tetrahydro-6H-benzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (10a). White solid (174 mg, 61% yield, eluent: 3% MeOH in DCM). mp 170−172 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 7.71 – 7.65 (m, 2H), 7.65 – 7.59 (m, 3H), 7.12 (dd, *J* = 10.4, 1.3 Hz, 1H), 6.21 (d, *J* = 10.4 Hz, 1H), 5.18 – 5.06 (m, 3H), 3.61 (s, 1H), 3.47 (dd, *J* = 17.6, 4.0 Hz, 1H), 3.29 (dd, *J* = 17.6, 5.2 Hz, 1H), 2.51 (s, 3H), 1.81 (s, 3H), 0.71 (s, 9H). ^{13}C{1H} NMR (126 MHz, acetone-d_6) δ 192.9, 149.8, 142.7, 132.7, 132.5, 132.0, 131.1, 129.3, 128.2, 128.1, 127.7, 126.3, 122.4 (q, 1JC-F = 320.0 Hz),72.6, 59.7, 58.3, 55.6, 38.4, 23.7, 13.2. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{24}H_{28}N_3O_2S$ 422.1902, found 422.1892.

(4aR,12aS)-9-(4-bromophenyl)-7-(tert-butylamino)-4a,10-dimethyl-2-oxo-1,2,4a,12a-tetrahydro-6H-benzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (10b). White solid (204 mg, 63% yield, eluent: 2.5% MeOH in DCM). mp 160−162 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 5.5 Hz, 2H), 7.60 – 7.31 (m, 2H), 6.88 (d, *J* = 10.1 Hz, 1H), 6.20 (d, *J* = 10.1 Hz, 1H), 5.14 – 4.93 (m, 2H), 4.90 – 4.78 (m, 1H), 3.35 – 3.15 (m, 2H), 2.37 (s, 3H), 1.74 (s, 3H), 0.66 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.7, 149.3, 141.2, 131.8, 131.2 (2C), 130.7, 127.5, 127.2, 125.8, 125.1, 125.0, 120.5 (q, 1JC-F = 316.2 Hz), 71.5, 58.7, 57.6, 54.6, 38.0, 29.6, 23.4, 13.1. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{26}H_{29}BrN_3O_2S$ 526.1163, found 526.1155.

(4aR,12aS)-7-(tert-butylamino)-4a-methyl-2-oxo-9,10-diphenyl-1,2,4a,12a-tetrahydro-6H-benzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (10c). White solid (202 mg, 64% yield, eluent: 3% MeOH in DCM). mp 186−188 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.56 (m, 1H), 7.55 – 7.41 (m, 4H), 7.36 (d, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.21 (d, *J* = 7.3 Hz, 2H), 6.92 (d, *J* = 10.2 Hz, 1H), 6.26 (d, *J* = 10.2 Hz, 1H), 5.19 – 5.03 (m, 2H), 4.94 – 4.83 (m, 1H), 3.40 (d, *J* = 16.8 Hz, 1H), 3.26 (d, *J* = 16.8 Hz, 1H), 2.93 (s, 1H), 1.80 (s, 3H), 0.68 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.8, 149.5, 142.0,

131.4, 131.1, 131.0, 130.7, 130.1, 130.0, 129.0, 129.2, 129.1, 128.4, 127.7, 126.7, 125.5, 120.7 (q, 1JC-F = 318.7 Hz),71.7, 59.0, 57.9, 55.0, 38.2, 29.8, 23.8. HRMS (ESI-TOF) m/z: $[M-CF_3SO_3]^+$ calcd for $C_{29}H_{30}N_3O_2S$ 484.2058, found 484.2049.

(4aR,12aS)-7-(tert-butylamino)-9,10-bis(4-methoxyphenyl)-4a-methyl-2-oxo-1,2,4a,12a-tetrahydro-6H-benzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (10d). (White solid, 214 mg, 62% yield). mp 156−158 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.33 (m, 2H), 7.14 (d, *J* = 6.6 Hz, 2H), 7.04 – 6.95 (m, 2H), 6.91 (d, *J* = 9.8 Hz, 1H), 6.83 (d, *J* = 6.6 Hz, 2H), 6.25 (d, *J* = 9.8 Hz, 1H), 5.17 – 5.00 (m, 2H), 4.88 (d, *J* = 14.4 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.39 (d, *J* = 16.0 Hz, 1H), 3.23 (d, *J* = 16.0 Hz, 1H), 3.01 (s, 1H), 1.80 (s, 3H), 0.72 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 161.4, 160.8, 149.6, 141.6, 131.3, 130.6, 130.4, 127.7, 125.3, 120.8 (q, 1JC-F = 318.7 Hz), 120.7, 118.6, 114.7, 114.5, 71.7, 59.2, 58.1, 55.6, 55.5, 55.1, 38.3, 29.9, 23.9. HRMS (ESI-TOF) m/z: $[M-CF_3SO_3]^+$ calcd for $C_{31}H_{34}N_3O_4S$ 544.2270, found 544.2253.

(7aR,16aS)-10-(tert-butylamino)-2-oxo-1,4,5,6,7,16a-hexahydro-2H,9H-naphtho[8a,1-b]pyrido[2',1':2,3]imidazo[1,5-d][1,4]oxazin-16-ium trifluoromethanesulfonate (11a). (White solid, 41% yield, eluent: 3% MeOH in DCM). mp 103−105 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 4.6 Hz, 1H), 7.92 – 7.86 (m, 1H), 7.51 – 7.43 (m, 1H), 7.33 – 7.25 (m, 1H), 6.05 (s, 1H), 5.30 – 5.12 (m, 2H), 5.03 – 4.90 (m, 1H), 3.01 – 2.84 (m, 2H), 2.78 – 2.65 (m, 1H), 2.59 – 2.47 (m, 2H), 2.05 – 1.96 (m, 1H), 1.78 – 1.67 (m, 2H), 1.63 – 1.52 (m, 2H), 1.27 (s, 9H). ^{13}C {1H} NMR (125 MHz, $CDCl_3$) δ 193.1, 159.6, 136.3, 133.7, 126.6, 126.4, 124.5, 123.6, 120.4 (q, 1JC-F = 317.5 Hz), 117.5, 110.3, 71.1, 56.6, 56.2, 54.7, 39.7, 32.3, 32.0, 30.4, 26.2, 20.5. HRMS (ESI-TOF) m/z: $[M-CF_3SO_3]^+$ calcd for $C_{22}H_{28}N_3O_2$ 366.2181, found 366.2178.

(7aR,15aS)-10-(tert-butylamino)-13-methyl-2-oxo-12-phenyl-1,4,5,6,7,15a-hexahydro-2H,9H-naphtho[8a,1-b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-15-ium trifluoromethanesulfonate (12a). (White solid, 140 mg, 46% yield, elent: 2% MeOH in DCM). mp 162−164 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.34 (m, 5H), 6.01 (s, 1H), 4.94 (d, *J* = 15.4 Hz, 1H), 4.79 – 4.65 (m, 3H), 3.10 – 2.94 (m, 2H), 2.87 (s, 1H), 2.63 – 2.45 (m, 2H), 2.37 (d, *J* = 13.4 Hz, 1H), 2.31 (s, 3H), 2.02 – 1.93 (m, 1H), 1.86 – 1.67 (m, 2H), 1.51 – 1.42 (m, 1H), 0.59 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.8, 161.1, 141.0, 131.8, 130.5, 128.9, 127.2, 126.7, 126.6 (2C), 126.4, 124.8, 120.6 (q, 1JC-F = 318.7 Hz), 72.5, 57.5, 56.6, 54.7, 38.4,

34.3, 32.7, 29.6, 27.6, 20.5, 13.2. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{27}H_{32}N_3O_2S$ 462.2215, found 462.2200.

(7aR,15aS)-12-(4-bromophenyl)-10-(tert-butylamino)-13-methyl-2-oxo-1,4,5,6,7,15a-hexahydro-2H,9H-naphtho[8a,1-b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-15-ium trifluoromethanesulfonate (12b). (White solid, 165 mg, 48% yield, eluent: 2% MeOH in DCM). mp 202−204 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.1 Hz, 2H), 7.52 – 7.24 (m, 2H), 6.00 (s, 1H), 4.97 (d, *J* = 15.4 Hz, 1H), 4.83 – 4.60 (m, 2H), 3.09 – 2.86 (m, 3H), 2.62 – 2.53 (m, 1H), 2.49 (d, *J* = 13.1 Hz, 1H), 2.38 (d, *J* = 13.1 Hz, 1H), 2.30 (s, 3H), 2.01 – 1.94 (m, 1H), 1.85 – 1.66 (m, 2H), 1.50 – 1.41 (m, 1H), 0.63 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.7, 161.0, 140.9, 131.8, 131.0, 127.4, 126.9, 126.7, 126.6, 125.4, 125.2, 125.0, 120.6 (q, 1JC-F = 312.5 Hz), 72.2, 57.5, 56.6, 54.6, 38.4, 34.0, 32.7, 29.7, 27.4, 20.5, 13.2. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{27}H_{31}BrN_3O_2S$ 540.1320, found 540.1306.

10-(tert-butylamino)-2-oxo-12,13-diphenyl-1,4,5,6,7,15a-hexahydro-2H,9H-naphtho[8a,1-b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-15-ium trifluoromethanesulfonate (12c). White solid (107 mg, 43% yield, eluent: 2.5% MeOH in DCM). mp 192−194 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.31 (dd, *J* = 10.6, 6.5 Hz, 4H), 7.30 – 7.20 (m, 4H), 7.14 – 7.11 (m, 2H), 6.05 –6.02 (m, 1H), 4.99 (d, *J* = 15.5 Hz, 1H), 4.79 – 4.71 (m, 2H), 3.13 – 3.07 (m, 1H), 3.05 – 2.99 (m, 1H), 2.94 (s, 1H), 2.63 – 2.52 (m, 2H), 2.39 (d, *J* = 13.4 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.86 – 1.67 (m, 3H), 1.52 – 1.41 (m, 1H), 0.61 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.8, 161.2, 141.6, 131.1, 130.6, 130.5, 129.9, 129.8, 129.7, 129.1, 128.9, 128.4, 127.7, 126.7, 126.5, 124.9, 120.6 (q, 1JC-F = 321.2 Hz) 72.4, 57.6, 56.7, 54.8, 38.3, 34.2, 32.8, 29.7, 27.6, 20.5. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{32}H_{34}N_3O_2S$ 524.2371, found 524.2367.

(7aR,15aS)-10-(tert-butylamino)-12,13-bis(4-methoxyphenyl)-2-oxo-1,4,5,6,7,15a-hexahydro-2H,9H-naphtho[8a,1-b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-15-ium trifluoromethanesulfonate (12d). White solid (150 mg, 41% yield, eluent: 3% MeOH in DCM). mp 185−187 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 – 7.34 (m, 2H), 7.14 (d, *J* = 7.3 Hz, 2H), 7.03 – 6.92 (m, 2H), 6.83 (d, *J* = 7.3 Hz, 2H), 6.12 (s, 1H), 5.08 (d, *J* = 15.4 Hz, 1H), 4.88 – 4.76 (m, 2H), 3.86 (s, 3H), 3.81 (s, 3H), 3.23 – 3.02 (m, 3H), 2.77 – 2.58 (m, 2H), 2.48 (d, *J* = 12.4 Hz, 1H), 2.13 – 2.02 (m, 1H), 1.99 – 1.75 (m, 2H), 1.60 – 1.49 (m, 1H), 0.74 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 161.2, 160.7, 141.1, 131.1, 130.6, 129.9, 127.8, 126.7 (2C), 124.6,

120.7, 120.6 (q, 1JC-F = 317.5 Hz), 118.4, 115.0 (2C), 114.3, 72.4, 57.5, 56.7, 55.5, 55.4, 54.9, 38.3, 34.2, 32.7, 29.7, 27.5, 20.5. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{34}H_{38}N_3O_4S$ 584.2583, found 584.2555.

(4aS,13aR)-7-(tert-butylamino)-2-oxo-1,2-dihydro-6H-4a,13a-propanobenzo[b]pyrido[2',1':2,3]imidazo[1,5-d][1,4]oxazin-13-ium trifluoromethanesulfonate (13a). White solid (148 mg, 43% yield, eluent: 4.5% MeOH in DCM). mp 156−158 °C. ^{1}H NMR (500 MHz, acetone-d_6) δ 9.06 (d, *J* = 6.8 Hz, 1H), 8.44 (d, *J* = 9.2 Hz, 1H), 8.17 – 8.10 (m, 1H), 7.72 – 7.67 (m, 1H), 7.23 (d, *J* = 10.4 Hz, 1H), 6.23 (dd, *J* = 10.4, 0.9 Hz, 1H), 5.32 (d, *J* = 16.1 Hz, 1H), 5.15 (d, *J* = 16.1 Hz, 1H), 4.57 (s, 1H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.47 (d, *J* = 17.2 Hz, 1H), 2.80 – 2.75 (m, 1H), 2.58 – 2.48 (m, 1H), 2.48 – 2.37 (m, 2H), 2.22 – 2.09 (m, 2H), 1.25 (s, 9H). ^{13}C{1H} NMR (125 MHz, acetone-d_6) δ 193.8, 148.7, 148.6, 137.8, 134.6, 132.0, 127.6, 125.1, 120.6 (q, 1JC-F = 322.5 Hz), 118.3, 113.3, 83.6, 70.4, 58.1, 57.0, 44.6, 37.6, 36.4, 30.1, 21.9. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{21}H_{26}N_3O_2$ 352.2025, found 352.2030.

(4aS,12aR)-7-(tert-butylamino)-10-methyl-2-oxo-9-phenyl-1,2-dihydro-6H-4a,12a-propanobenzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (14a). White solid (173 mg, 58% yield, eluent: 2.5% MeOH in DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.65 (m, 1H), 7.63 – 7.31 (m, 4H), 7.00 (d, *J* = 10.4 Hz, 1H), 6.23 (d, *J* = 10.4 Hz, 1H), 5.08 (d, *J* = 15.2 Hz, 1H), 4.74 (d, *J* = 15.2 Hz, 1H), 3.31 (d, *J* = 16.9 Hz, 1H), 3.22 – 3.04 (m, 2H), 2.67 – 2.54 (m, 1H), 2.53 – 2.42 (m, 1H), 2.37 (s, 3H), 2.35 – 2.17 (m, 3H), 2.06 – 1.91 (m, 1H), 0.60 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 148.2, 139.8, 132.5, 131.3, 130.6 (2C), 128.8, 127.8, 126.9, 126.3, 125.1, 120.8 (q, 1JC-F = 321.3 Hz), 81.7, 69.7, 57.9, 54.5, 43.0, 35.8, 35.6, 29.7, 21.1, 13.3. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{26}H_{30}N_3O_2S$ 448.2058, found 448.2046.

(4aS,12aR)-9-(4-bromophenyl)-7-(tert-butylamino)-10-methyl-2-oxo-1,2-dihydro-6H-4a,12a-propanobenzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (14b). White solid (189 mg, 56% yield, eluent: 2.5% MeOH in DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 – 7.81 (m, 1H), 7.82 – 7.47 (s, 3H), 7.03 (d, *J* = 9.4 Hz, 1H), 6.26 (d, *J* = 9.4 Hz, 1H), 5.27 – 5.03 (m, 1H), 4.90 – 4.67(m, 1H), 3.31 (d, *J* = 16.2 Hz, 1H), 3.25 – 3.01 (m, 2H), 2.82 – 2.62 (m, 1H), 2.57 – 2.46 (m, 1H), 2.40 (s, 3H), 2.36 – 2.21 (m,

3H), 2.07 – 1.92 (m, 1H), 0.68 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.0, 148.2, 139.9, 131.8, 131.4, 131.3 (2C), 127.7, 127.5, 125.5, 125.1, 125.0, 120.5 (q, 1JC-F = 318.7 Hz) 81.7, 69.7, 57.8, 54.3, 49.7, 42.9, 35.7, 29.7, 21.0, 13.3. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{24}H_{27}BrN_3O_2S$ 500.1007, found 500.1003.

(4aS,12aR)-7-(tert-butylamino)-2-oxo-9,10-diphenyl-1,2-dihydro-6H-4a,12a-propanobenzo[b]thiazolo[2',3':2,3]imidazo[1,5-d][1,4]oxazin-12-ium trifluoromethanesulfonate (14c). Off white solid (187 mg, 57% yield, eluent: 3% MeOH in DCM). mp 202−204 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.37 (m, 4H), 7.38 – 7.28 (m, 4H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.06 (d, *J* = 10.4 Hz, 1H), 6.29 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 15.4 Hz, 1H), 4.80 (d, *J* = 15.4 Hz, 1H), 3.40 (d, *J* = 16.9 Hz, 1H), 3.31 (s, 1H), 3.15 (d, *J* = 16.9 Hz, 1H), 2.80 – 2.69 (m, 1H), 2.61 – 2.51 (m, 1H), 2.39 – 2.24 (m, 3H), 2.07 – 1.93 (m, 1H), 0.65 (s, 9H). ^{13}C{1H} NMR (125 MHz, $CDCl_3$) δ 192.9, 148.3, 140.2, 131.9, 131.1, 130.49, 130.46, 129.9, 129.8, 129.11, 129.07, 128.7, 128.4, 128.2, 126.3, 125.3, 120.7 (q, 1JC-F = 322.5 Hz) 81.5, 69.6, 57.8, 54.3, 42.9, 35.7, 35.3, 29.6, 21.0. HRMS (ESI-TOF) m/z: $[M\text{-}CF_3SO_3]^+$ calcd for $C_{31}H_{32}N_3O_2S$ 510.2215, found 510.2209.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of Charge on the ACS Publications website at: DOI: X-ray diffraction data, biological activity data and copies of NMR spectra (PDF).

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Notes

The authors declare no competing financial interest.

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