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Synthesis and evaluation of dihydroimidazolo and dihydrooxazolo ring-fused 2-pyridones—targeting pilus biogenesis in uropathogenic bacteria

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ABSTRACT

Dihydrothiazolo ring-fused 2-pyridones have previously been shown to inhibit pilus assembly in uropathogenic *Escherichia coli*. Methods have now been developed to synthesize both dihydroimidazolo and dihydrooxazolo ring-fused 2-pyridones. To obtain the nitrogen analogs, Cbz-protected imidazolines were reacted with an acyl-Meldrum's acid derivative under acidic conditions. To prepare the oxygen analogs, a one-pot procedure was developed that allowed synthesis of dihydrooxazolo ring-fused 2-pyridones starting from acylated serine derivatives. After hydrolysis to their corresponding carboxylic acids and lithium carboxylates, biological evaluation revealed that the sulfur could be replaced by an oxygen atom and still maintains the ability to inhibit pilus assembly in uropathogenic *E. coli*. However, introducing a secondary amine instead of oxygen resulted in a substantial decrease in biological activity.

1. Introduction

Bacterial resistance is recognized as one of the major health threats in modern times.[1,2] Dealing with the rapidly increasing number of resistant pathogens necessitates not only the development of new antibacterial agents but also finding new targets and strategies to battle bacterial infections. One such strategy is the development of so-called virulence inhibitors.[3–8] These make the bacteria non-pathogenic without affecting survival. This approach is believed to reduce the evolutionary pressure on the bacteria, as compared to traditional antibacterial agents, and thereby, delay development of resistance.

Bicyclic sulfur containing 2-pyridones **1** and **2** are virulence inhibitors that belong to a class of compounds known as pilicides (Fig. 1), which prevent the assembly of pili in uropathogenic *Escherichia coli* (UPEC).[6,9] These compounds have also been used as chemical tools to regulate pili expression in order to investigate the functional properties of the pilus rod.[10,11] Pili/fimbriae are multiprotein fibers present on the surface of bacteria and are crucial for adhesion and invasion of the host,[12,13] and have also been shown to play an important role in evading host defenses.[14] In brief, pili are assembled via a highly conserved mechanism called the chaperone-usher pathway, where an escort protein, chaperone, folds and transports pili subunits to an outer membrane assembly site, where they are incorporated into the growing pilus rod.[13,15] Pilicides target the periplasmic chaperone to block the formation of pili.[16] Importantly, this key protein has a high level of structural preservation among pathogens utilizing the chaperone-usher pathway.[12,17]

Previous pilicides contain a rigid bicyclic 2-pyridone framework, constructed by reacting Δ^2-thiazolines with acylketenes generated from acyl-Meldrum's acid derivatives (Fig. 1).[18] This reaction has been performed using both solid-phase techniques and microwave irradiation (MWI),[19,20] allowing the preparation of small libraries of substituted ring-fused 2-pyridones in a fast and parallel manner. Initial evaluations indicated that compounds **1** and **2** were the most promising.[20,21] Further functionalization at the readily available C-6 has resulted in a new set of substituted pilicides (class **A**, Fig. 1),[22,23] of which several had maintained or even improved activity as pilicides.[16,23] Based on an amino-functionalized 2-pyridone, N-terminal extended peptide mimetics have also been designed and synthesized (class **B**, Fig. 1).[24] Several of these showed enhanced affinities for the chaperone as measured by relaxation edited ^{1}H NMR spectroscopy, however, the ability to prevent pilus assembly in vivo was significantly decreased when compared to the parent compounds **1** and **2**.

By transforming the carboxylic acid at C-3 to other functionalities (class **C**, Fig. 1) we have been able to show that this functionality is vital to maintain the ability to prevent pilus assembly.[25] The use, however, of carboxylic acid isosteres such as tetrazoles or acyl sulfonamides can improve the potency.[26] Interestingly, desulfurization with Raney nickel to the monocyclic 2-pyridone **D** (Fig. 1) resulted in a compound with a considerable loss of biological activity when compared to the bicyclic parent compound, clearly indicating the importance of the bicyclic 2-pyridone system.[26]

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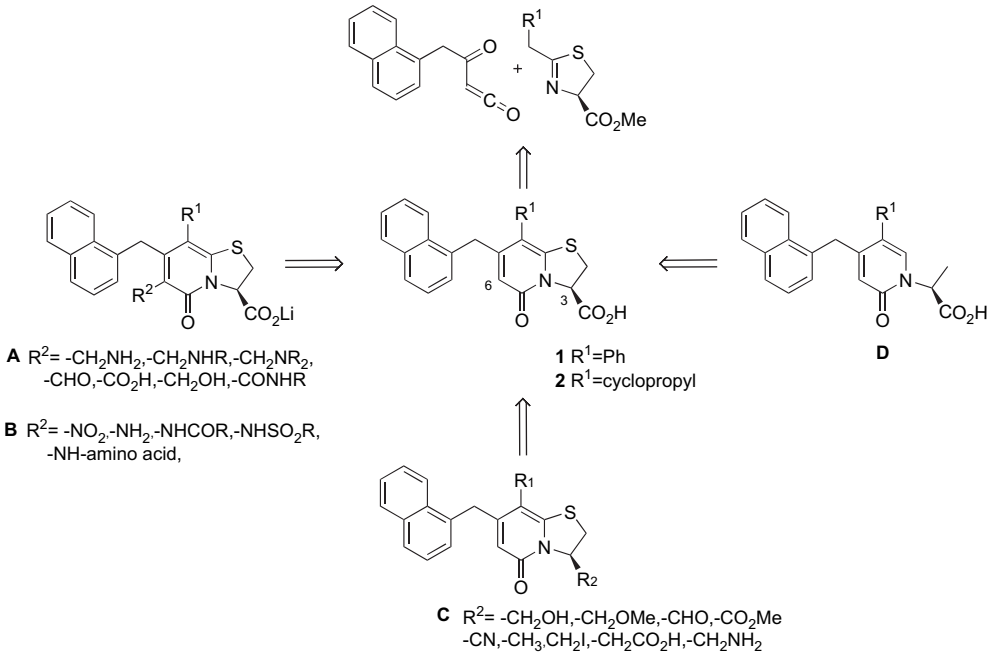


Figure 1. Based on the first two lead compounds **1** and **2**, further functionalization has resulted in new compounds, here divided into four different classes A–D. These have been evaluated as so-called pilicides, compounds that prevent the formation of adhesive protein organelles called pili.

Earlier we have shown that the imine component in the acylketene imine condensation can be exchanged from thiazolines to 3,4-dihydroisoquinolines or β-carbolines, thus resulting in multi-ring-fused systems.[27] To further investigate the scope and limitation of this reaction, and at the same time generate compounds that would allow us to study the importance of the heteroatom in the fused 2-pyridone scaffold from a pilicide point of view, we draw our attention to imidazolines and oxazolines and their reactivity with acylketenes generated in situ from acyl-Meldrum's acid derivatives. In this paper we describe the synthesis of dihydroimidazolo and dihydrooxazolo ring-fused 2-pyridones. In addition, their ability to inhibit pilus assembly in uropathogenic *E. coli* and thus acting as pilicides is also reported.

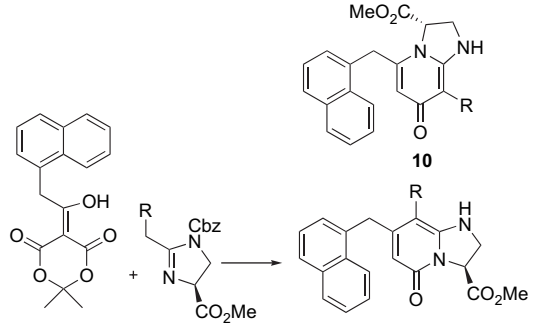
2. Results

2.1. Synthesis of analogs

To our knowledge no reports of dihydroimidazolo[2,3-*a*]pyridin-5-ones (Table 1) or dihydrooxazolo[2,3-*a*]pyridin-5-ones (Table 2) with a carboxylic acid functionality at C-3 have been described in the literature. Nevertheless, reports of the preparation of compounds without the carboxylic acid functionality have been published; Jones et al. prepared imidazolo[2,3-*a*]pyridin-5-ones by annulations of imidazolines with β-ketoesters.[28,29] These systems have also been synthesized by using a similar method based on reacting heterocyclic ketene aminals with α,β-unsaturated esters.[30,31] However, since our previously developed acylketene imine condensation has proven to be mild and effective allowing synthesis of bicyclic thiazolo ring-fused 2-pyridones in a parallel manner,[18–20] we wished to explore the possibilities of expanding this method to also allow the preparation of nitrogen and oxygen analogs.

To synthesize the imidazolo[2,3-*a*]pyridin-5-ones a suitably protected imidazololine was required as a building block, and in contrast to the thiazoline and oxazoline derivatives this structure is not based on a natural amino acid. We therefore decided to first test the conditions and the protective group strategy for the acylketene imine condensation on a cheaper and more readily available starting material. Thus, commercially available tolazoline was chosen as the starting material. Both the *N*-Boc **4a** and the *N*-Cbz **4b** protected derivatives were prepared.[32] These protecting groups were chosen to complement each other. The *N*-Boc could be too labile due to the acidic conditions used in the 2-pyridone forming step, but there was still a possibility that the conditions would allow both the 2-pyridone formation and a subsequent deprotection in one pot. The *N*-Cbz alternative on the other hand would be

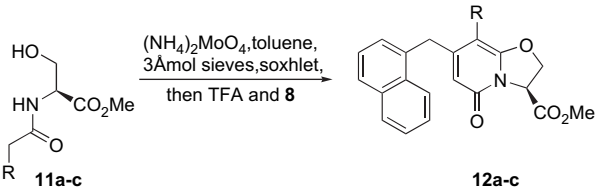
Table 1
Synthesis of dihydroimidazolo[2,3-*a*]pyridin-5-ones **9a–c**



Entry	R	Method	Product	Yield **9** (%)	Yield **10** (%)
1	Ph	A[a]	**9a**	53[c]	13
2	Ph	B[b]	**9a**	70[d]	—[f]
3	Cyclopropyl	A[a]	**9b**	42[e]	—[f]
4	Cyclopropyl	B[b]	**9b**	38[e]	—[f]
5	H	A[a]	**9c**	61[e]	—[f]
6	H	B[b]	**9c**	17[e]	—[f]

[a] Method A: (i) MW, 120 °C, 5 min, TFA, DCE; (ii) Pd/C, H_2 (atm), MeOH.
[b] Method B: (i) 64 °C, 14 h, ½ satd HCl·DCE; (ii) Pd/C, H_2 (atm), MeOH.
[c] Enantiomeric excess: 63% as determined by chiral HPLC see Supplementary data for more details.
[d] Enantiomeric excess: 61% as determined by chiral HPLC see Supplementary data for more details.
[e] Enantiomeric excess not determined.
[f] Not formed.

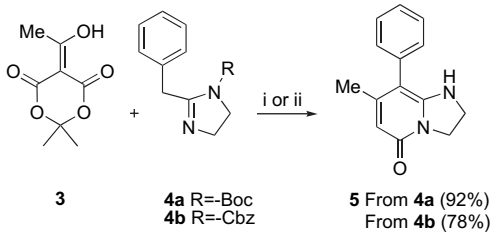
Table 2
One-pot synthesis of dihydrooxazolo[2,3-*a*]pyridin-5-ones **12a–c** from *N*-acylated serine derivatives **11a–c**



Entry	Compound	R	TFA (equiv)	Time (h)	Product	Yield (%)	ee (%)
1	**11a**	Ph	5	8	**12a**	78	2[a]
2	**11b**	Cyclopropyl	5	9	**12b**	32	—[b]
3	**11c**	H	5	7	**12c**	16	—[b]
4	**11a**	Ph	1	5	**12a**	62	16[a]
5	**11a**	Ph	0.1	5	**12a**	28	91[a]

[a] Enantiomeric excess determined by chiral HPLC see Supplementary data for more details.
[b] Enantiomeric excess not determined.

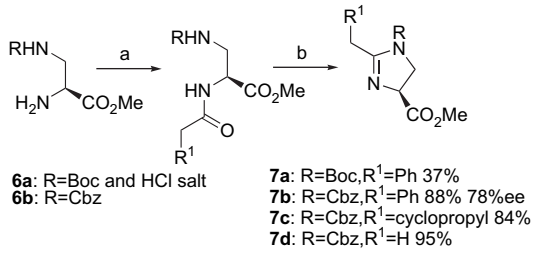
a more robust alternative that would withstand the acidic conditions in the acylketene imine condensation but would then need a subsequent deprotection step. With the *N*-Boc-protected imidazoline **4a** and the *N*-Cbz-protected imidazoline **4b** in hand we allowed them to react with acyl-Meldrum's acid derivative **3** under microwave irradiation at 120 °C for 5 min using trifluoroacetic acid as the acid component (Scheme 1). To our delight, both imidazolines reacted well and gave the desired 2-pyridone **5** in good to excellent yields after standard deprotection conditions (Scheme 1). Especially the *N*-Boc strategy appeared ideal at this point, since the deprotection could simply be conducted in the same pot by just adding more trifluoroacetic acid and allow the mixture to stand in room temperature for 30 min.



Scheme 1. Reagents and conditions: (i) TFA (0.75%), DCE, MW 120 °C, 5 min, then more TFA, rt, 30 min; (ii) (a) TFA (1.5%), DCE, MW 120 °C, 5 min; (b) Pd/C, H_2 (atm), MeOH.

Based upon the results from the model system we decided to continue our study with the *N*-Boc-protected imidazoline **7a** (Scheme 2). This imidazoline was prepared starting from *N*-Boc-protected diaminopropionic acid methyl ester **6a**, which was acylated and then ring-closed using triflic anhydride and triphenylphosphine oxide.[33] Unfortunately, we experienced some deprotection of the *N*-Boc group in the latter step. In addition, efforts to react the *N*-Boc-protected imidazoline **7a** with acyl-Meldrum's acid derivative **8** (Table 1) resulted in a very poor yield of the desired 2-pyridone, which further confirmed that this was not the appropriate protecting group for our purposes. Consequently, we decided to instead use the more acid stable Cbz protective group, and starting from diaminopropionic acid **6b** the *N*-Cbz-protected imidazolines **7b–d** were prepared in excellent yields (Scheme 2).

Starting with the previously developed method (TFA and MW at 120 °C for 5 min followed by deprotection of the Cbz group by hydrogenation) the desired 2-pyridone **9a** was obtained in 53% yield (Table 1). This time, however, the 2-pyridone **9a** was also accompanied by the isomeric 4-pyridone **10** in a 5:1 ratio (Table 1). However, lowering the temperature to 64 °C (conventional



Scheme 2. Reagents and conditions: (a) for **7a**: BnCOCl, TEA, CH_2Cl_2, rt; compound **7a** was synthesized from the commercially available HCl salt; for **7b**: BnCOCl, TEA, CH_2Cl_2, 0 °C; for **7c**: DCC, HOAt, cyclopropylacetic acid, CH_2Cl_2, rt; for **7d**: Ac_2O, TEA, CH_2Cl_2, 0 °C; (b) for **7a** and **7b**: Tf_2O, Ph_3PO, CH_2Cl_2, 0 °C; for **7c** and **7d**: Tf_2O, polymer supported Ph_3PO, CH_2Cl_2, 0 °C.

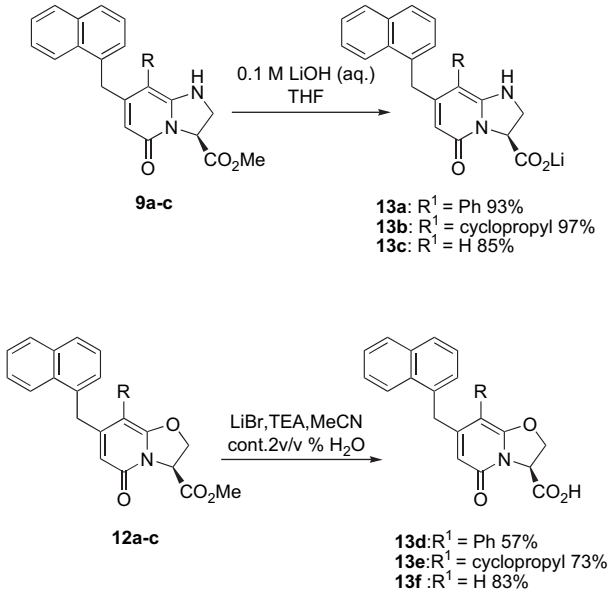
heating) and using a half saturated HCl (g) solution of 1,2-dichloroethane, prevented the formation of this by-product and **9a** was isolated in 70% yield. These two sets of conditions were then used to prepare the cyclopropyl substituted 2-pyridone **9b** and the hydrogen substituted 2-pyridone **9c**, which were included to further evaluate the synthetic method (entries 3–6, Table 1). Both the alkyl substituted 2-pyridone **9b** and the hydrogen substituted 2-pyridone **9c** were isolated in lower yields than the aryl substituted 2-pyridone **9a** but for these two, no formation of the isomeric 4-pyridones were observed under the microwave irradiation conditions (Table 1). The enantiomeric purity was measured for compound **9a** using chiral HPLC and a drop in enantiomeric excess from the starting imidazoline **7b** was observed (78% ee to 63% and 61% ee, respectively, for both methods, entries 1 and 2, Table 1).

To prepare the corresponding oxygen analogs a recently developed dehydrative cyclization using molybdenum oxide as catalyst was employed to obtain the desired oxazolines.[34] Thus, serine derivative **11a** was cyclized to the corresponding oxazoline using 10 mol % of $(NH_4)_2MoO_4$ in toluene at reflux with removal of water (Table 2). However, previous efforts to convert oxazolines to 2-pyridones by reacting them with acyl-Meldrum's acid derivatives in HCl (g) saturated or partly saturated 1,2-dichloroethane solutions had been sluggish, resulting in very poor yields or more commonly in no formation of the desired 2-pyridones. Therefore, we were seeking a one-pot procedure thus avoiding the isolation of the oxazoline. Hence, after 6 h at reflux the formation of the oxazoline was complete (monitored by ^1H NMR spectroscopy) and to this reaction mixture acyl-Meldrum's acid derivative **8** and trifluoroacetic acid were added. To our delight, after additional 2 h at reflux this resulted in the formation of 2-pyridone **12a**, which was isolated in 78% yield (entry 1, Table 2). This one-pot procedure was then used to prepare 2-pyridones **12b** and **12c** from the acylated serine derivatives **11b** and **11c**. These 2-pyridones had not been obtainable via the old procedure and although the yield dropped to a modest level (32% and 16% yields for **12b** and **12c**, respectively), we were delighted to finally isolate enough material for biological evaluation.

Unfortunately, although this method was practical and resulted in fair yields of isolated substituted dihydrooxazolo fused 2-pyridones, it appeared as the sterocentre at C-3 almost epimerized completely for 2-pyridones **12a–c**, since they displayed low optical rotation. This was further confirmed by chiral HPLC, which showed that the enantiomeric excess was as low as 2% for compound **12a** (entry 1, Table 2). Fortunately, by reducing the amount of acid the enantiomeric excess could be improved to 91%, but this also resulted in a considerable drop in yield (entry 5, Table 2).

At this point we had established synthetic protocols that, besides the synthesis of thiazolo ring-fused 2-pyridones, also allowed synthesis of both the nitrogen and the oxygen analogs. To be able to test these compounds as pilicides the only transformation that remained was to hydrolyze the methyl esters to the corresponding lithium carboxylates or carboxylic acids. For the nitrogen analogs

9a–c we applied the saponification conditions that we had previously used for the main part of our studied thiazolo ring-fused pilicides.[16] Hence, **9a–c** were hydrolyzed (0.1 M LiOH (aq) in THF) to the corresponding lithium carboxylates **13a–c** in good yields (Scheme 3). The hydrolysis of the oxygen analogs **12a–c** was not as straightforward, and the standard saponification (LiOH in THF) resulted in very slow conversion in combination with the formation of several unidentified by-products. It has been shown that addition of hydrogen peroxide to lithium hydroxide may effect reaction rate and selectivity.[35] However, also this experiment resulted in decomposition of the starting material. Fortunately, using a recently published method that takes use of lithium bromide, triethylamine and water in acetonitrile the esters were smoothly converted to the desired carboxylic acids **13d–f** in moderate to good yields (57–83%) (Scheme 3).[36]

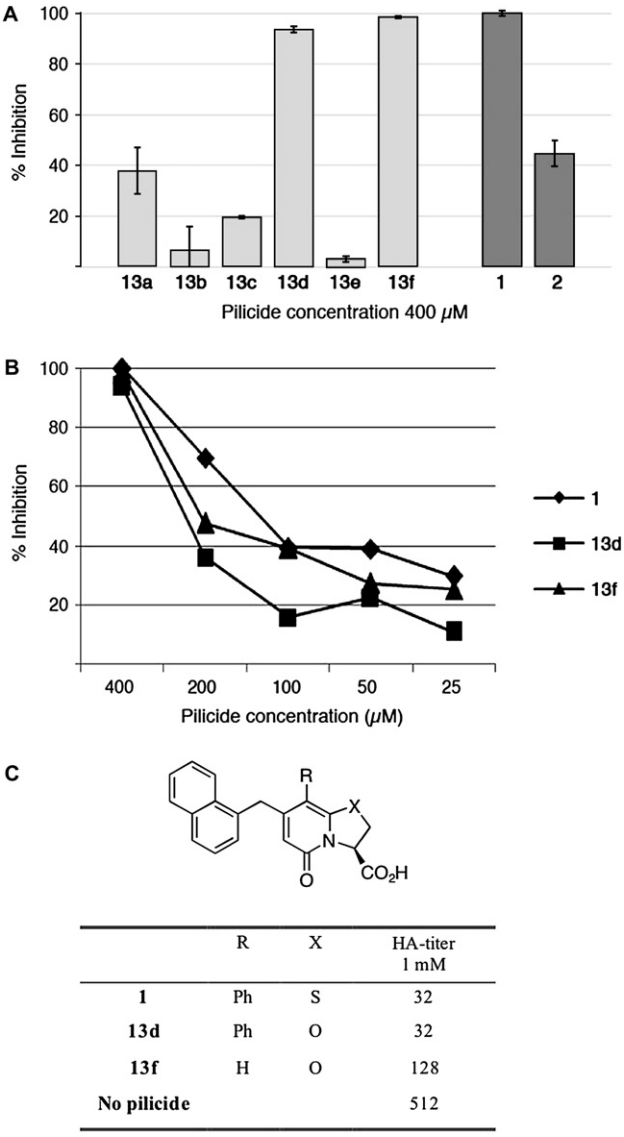


Scheme 3. Hydrolysis of dihydroimidazolo[2,3-*a*]pyridine-5-ones **9a–c** and dihydrooxazolo[2,3-*a*]pyridine-5-ones **12a–c**.

2.2. Biological evaluation

Pili are important for the formation of biofilms,[37] the binding and invasion of host tissues,[38] and the formation of biofilm-like intracellular bacterial communities (IBC's),[39,40] thereby allowing the bacteria to persist in the host and evade host defenses.[14] Effective pilicides have previously been shown to be capable of reducing the formation of biofilms dependent on type 1 pilus formation in an in vitro biofilm assay.[16] This assay can be performed in 96 well plates with small volumes and does not consume too much of the precious potential inhibitors. Although biofilm inhibition can occur by other mechanisms than blocking pili assembly, this assay will still always identify a pilicide. Therefore, this assay is an ideal initial screen. However, to verify that the biofilm inhibition is correlated to decreased piliation, a hemagglutination assay (HA titer) can be performed to evaluate and compare potential pilicides.[16]

The new derivatives **13a–f** and the parent compounds **1** and **2** were initially screened at 400 μM in a biofilm assay (A, Fig. 2). Nitrogen analogs **13a** and **13c** had some effect on the formation of biofilms, but were considerably less effective than the corresponding oxygen analogs **13d** and **13f**. These two oxygen analogs and the parent thiazolo fused compound **1** reduced biofilm formation by over 90% at 400 μM and were further evaluated at lower concentrations (B, Fig. 2), confirming that they behaved in a dose dependent manner.



	R	X	HA-titer 1 mM
1	Ph	S	32
13d	Ph	O	32
13f	H	O	128
No pilicide			512

Figure 2. (A) The heteroatom analogs **13a–f** and the parent sulfide containing compounds **1** and **2** were screened in a biofilm assay. All compounds were tested at 400 μM and inhibition of biofilm formation is shown as percent when compound is present relative to an untreated control. Error bars represent the standard deviation of the mean where shown. (B) The three best compounds from the initial screen were titrated down at lower concentrations to confirm that they have a dose-dependant effect on the formation of biofilms. (C) To confirm that the effect seen in the biofilm formation was due to low pili abundance. Uropathogenic *E. coli* (UTI89) was grown in the presence of compound and HA titers were determined. A low HA titer indicates that less pili are formed, and is thus a verification of an efficient pilicide.

Finally **13d**, **13f**, and **1** were also tested in a HA-assay to verify that the results seen in the biofilm assay were a consequence of low abundance of pili (C, Fig. 2). Indeed all three compounds had an effect on pili formation in *E. coli* (clinical isolate UTI89) as shown by HA titers, and the oxygen analog **13d** was as potent as the corresponding sulfur containing compound **1**. Further confirming that the sulfur atom in thiazolo fused pilicides can be exchanged to oxygen, and still maintain the ability to prevent pilus assembly in uropathogenic *E. coli*.

3. Conclusion

A previously developed method to prepare thiazolo fused 2-pyridones have been further developed to give both oxygen and nitrogen analogs. Both systems were constructed by reacting either

protected imidazolines or oxazolines with an acylketene generated from an acyl-Meldrum's acid derivative. The imidazolo fused 2-pyridones **9a–c** could be synthesized from Cbz-protected imidazolines, by using either trifluoroacetic acid and microwave irradiation, or by performing the reaction at 64 °C with a partly HCl (g) saturated 1,2-dichloroethane solution. The corresponding oxazolo fused 2-pyridones **12a–c** were prepared in a one-pot procedure starting from acylated serine derivatives, which were first ring-closed to the oxazoline using a molybdenum oxide catalyst. This was followed by addition of trifluoroacetic acid and acyl-Meldrum's acid derivative **8**, which gave the desired oxazolo fused 2-pyridones **12a–c**. All compounds were hydrolyzed and evaluated for their ability to prevent pili formation. From these data it could be concluded that exchanging the sulfur toward a secondary amine gave a distinct drop in activity. However, these compounds are still interesting in the future development of pilicides, as this functionality provides a chemical diversification point, which can be used to further substitute and thereby fine-tune the chemical properties to increase affinity and bioavailability. In contrast to the nitrogen analogs the oxazolo fused 2-pyridones had activities comparable to the parent sulfur containing pilicides. The oxygen analog **13d** was as potent as the corresponding sulfur containing compound **1** in a HA-assay. These insights concerning the importance of the sulfur atom will be important for future design and development of pilicides.

4. Experimental

4.1. General

All reactions were carried out under an inert atmosphere with dry solvents under anhydrous conditions, unless otherwise stated. CH_2Cl_2 and 1,2-dichlorethane (DCE) were distilled from calcium hydride. Dimethylformamide (DMF) and acetonitrile (MeCN) were freshly distilled and stored over 3 Å molecular sieves. Trifluoroacetic acid (TFA) and triflic anhydride (Tf_2O) were freshly distilled before use. HCl (g) was passed through concentrated H_2SO_4 prior to use. All microwave reactions were carried out in a monomode reactor (Initiator, Biotage AB) using process vials sealed with Teflon septa and an aluminum crimp top. Reaction times refer to irradiation time at the target temperature, not the total irradiation time. The temperature was measured with an IR sensor. TLC was performed on Silica Gel 60 F_{254} using UV light detection. Flash column chromatography employed normal phase silica gel (Matrex, 60 Å, 35–70 μm, Grace Amicon). The ^1H and ^{13}C NMR spectra were recorded at 298 K with a Bruker DRX-400 spectrometer except compound **13c** where the ^{13}C NMR spectra were recorded on a Bruker Avance DRX-360 spectrometer. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ [residual $CHCl_3$ (δ_H 7.26 ppm) or $CDCl_3$ (δ_C 77.0 ppm) as internal standard], or MeOD-d_4 [residual CD_2HOD (δ_H 3.30 ppm) or CD_3OD (δ_C 49.0 ppm) as internal standard], or DMSO-d_6 [residual DMSO (δ_H 2.50 ppm) or DMSO (δ_C 40.0 ppm) as internal standard]. IR spectra were recorded on an FTIR spectrometer. Enantiomeric purity for selected compounds was determined by chiral HPLC, see Supplementary data for further details. For experimental procedures regarding preparation of serine derivatives **11a–c** and tolazoline derivatives **4a** and **4b** see Supplementary data.

4.2. Preparation of 7-methyl-5-oxo-8-phenyl-2,3-dihydro-5*H*-imidazolo[3,2-*a*]pyridine 5

From Boc-protected tolazoline **4a**: Meldrum's acid derivative **3** (268 mg, 1.44 mmol) was added to a stirred solution of **4a** (125 mg, 0.48 mmol) in DCE (2.4 mL) at room temperature. This was followed by addition of TFA (18 μL, 0.24 mmol) and the solution was then irradiated at 120 °C for 300 s (fixed hold time, normal absorption) using a microwave apparatus. The solution was then allowed to attain room temperature and was diluted with DCE (3.6 mL) and TFA (4 mL) was added. The solution was allowed to stir for 30 min at room temperature and was then diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were concentrated and further purified by column chromatography to yield **5** (100 mg, 92%) as a white solid.

From Cbz-protected tolazoline **4b**: Meldrum's acid derivative **3** (285 mg, 1.53 mmol) was added to a stirred solution of **4b** (150 mg, 0.51 mmol) in DCE (2.6 mL) at room temperature. This was followed by addition of TFA (39 μL, 0.51 mmol) and the solution was then irradiated at 120 °C for 300 s (fixed hold time, normal absorption) using a microwave apparatus. The solution was allowed to attain room temperature and was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2 and the combined organic layers were concentrated. The resulting crude mixture was dissolved in MeOH (20 mL) and a catalytic amount of Pd/C was added and hydrogenation was carried out at atmospheric pressure for 1 h. The catalyst was removed by filtration through Celite and the solid phase was rinsed with MeOH. The filtrate was concentrated and further purified by column chromatography to yield **5** (90 mg, 78%) as a white solid. Mp 162–164 °C (lit.[28] 161–162 °C); IR λ 1745, 1369, 1209, 1114, 1060; ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (s, 3H), 3.65 (t, J=8.4 Hz, 2H), 4.23 (t, J=8.4 Hz, 2H), 4.38 (br s, 1H), 5.82 (s, 1H), 7.20–7.23 (m, 2H), 7.28–7.34 (m, 1H), 7.36–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 42.7, 44.8, 99.8, 106.9, 127.4, 129.0, 130.5, 135.2, 150.1, 152.4, 160.5. HRMS (FAB) calcd for $[M+H]^+$ $C_{14}H_{15}N_2O$ 227.1184, obsd 227.1171.

4.3. Preparation of *N*-β-*Z*-L-diaminopropionic acid methyl ester 6b

N,*N*′-Carbonyldiimidazole (2.5 g, 15.4 mmol) was added to a stirred solution of commercially available *N*-α-Fmoc-*N*-β-*Z*-L-diaminopropionic acid (2.5 g, 5.43 mmol) in CH_2Cl_2 (40 mL) at room temperature. After 90 min, dry MeOH was added. The solution was allowed to stir for an additional 10 min and was then diluted with CH_2Cl_2 and washed with 10% aqueous citric acid. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the crude product, which was used in the next step without further purification.

Diethylamine (25 mL) was added to a solution of the crude methyl ester in MeCN (25 mL) at 0 °C, which was allowed to stir for 1 h at 0 °C. The solution was then concentrated and purified by column chromatography to yield **6b** (1.25 g, 91%) as a colorless oil. $[\alpha]_D^{23}$ 14 (*c* 0.5, MeCN); IR λ 3320, 1729, 1691, 1531, 1253; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (br s, 2H), 3.27–3.37 (m, 1H), 3.49–3.62 (m, 2H), 3.71 (s, 3H), 5.08 (s, 2H), 5.42 (br s, 1H), 7.27–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.4, 52.3, 54.2, 66.8, 128.1 (split), 128.5, 136.4, 156.5, 174.2. HRMS (FAB) calcd for $[M+H]^+$ $C_{12}H_{17}N_2O_4$ 253.1188, obsd 253.1180.

4.4. Preparation of 4-(*S*)-1-*tert*-butoxycarbonyl-2-benzyl-4,5-dihydro-imidazole-4-carboxylic acid methyl ester 7a

The commercially available HCl salt of diaminopropionic acid methyl ester **6a** (300 mg, 1.12 mmol) was dissolved in CH_2Cl_2 (100 mL). Then phenylacetyl chloride (175 μL, 1.32 mmol) followed by triethylamine (330 μL, 2.38 mmol) were added dropwise at 0 °C and the solution was stirred for 1 h and then diluted with CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$, the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and further purified by column chromatography to yield the acylated product (334 mg, 85%) as a colorless oil.

Tf_2O (252 μL, 1.34 mmol) was added to a stirred solution of Ph_3PO (746 mg, 2.68 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The solution was stirred at 0 °C for 10 min and then the acylated product (300 mg, 0.86 mmol) dissolved in CH_2Cl_2 (4 mL) was added. The solution was stirred at 0 °C for 1 h and was then diluted with CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$, and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography to yield **7a** (119 mg, 43%) as a colorless oil. $[\alpha]_D^{23}$ 142 (*c* 1.0, $CHCl_3$); IR λ 2977, 1720, 1369, 1141; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.80 (s, 3H), 3.95 (t, J=11.2 Hz, 1H), 4.06 (dd, J_1=7.6 Hz, J_2=11.2 Hz, 1H), 4.11 (d, J=14.8 Hz, 1H), 4.20 (d, J=14.8 Hz, 1H), 4.66 (dd, J_1=7.6 Hz, J_2=11.2 Hz, 1H), 7.19–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.0, 35.0, 49.2, 52.6, 65.0, 82.5, 126.6, 128.3, 128.9, 135.8, 149.8, 162.0, 171.7. HRMS (FAB) calcd for $[M+H]^+$ $C_{17}H_{23}N_2O_4$ 319.1658, obsd 319.1662.

4.5. Preparation of 4-(*S*)-1-benzyloxycarbonyl-2-benzyl-4,5-dihydro-imidazole-4-carboxylic acid methyl ester 7b

Compound **6b** (135 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (50 mL). Then phenylacetyl chloride (110 μL, 0.59 mmol) followed by triethylamine (74 μL, 0.54 mmol) were added dropwise at 0 °C. The solution was stirred at room temperature for 1 h and then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to yield the acylated product, which was used in the next step without further purification.

Tf_2O (135 μL, 0.54 mmol) was added to a stirred solution of Ph_3PO (448 mg, 1.61 mmol) in CH_2Cl_2 (6 mL) at 0 °C. The solution was stirred at 0 °C for 10 min and then the acylated product (from above) dissolved in CH_2Cl_2 (4 mL) was added. The solution was stirred at 0 °C for 1 h and was then diluted with CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography to yield **7b** (165 mg, 88%) as a colorless oil. $[\alpha]_D^{23}$ 89 (*c* 1.0, $CHCl_3$); IR λ 1727, 1396, 1301, 1201; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.96–4.03 (m, 1H), 4.09–4.23 (m, 3H), 4.70 (dd, J_1=7.6 Hz, J_2=11.1 Hz, 1H), 5.12 (s, 2H), 7.20–7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0, 48.9, 52.7, 65.6, 67.9, 126.7, 128.2, 128.4, 128.5, 128.6, 128.9, 135.2, 135.5, 150.8, 161.5, 171.4. HRMS (FAB) calcd for $[M+H]^+$ $C_{20}H_{21}N_2O_4$ 353.1501, obsd 353.1504.

4.6. Preparation of 4-(*S*)-1-benzyloxycarbonyl-2-cyclopropylmethyl-4,5-dihydro-imidazole-4-carboxylic acid methyl ester 7c

A flask was charged with HOAt (126 mg, 0.93 mmol), DCC (191 mg, 0.93 mmol), and CH_2Cl_2 (15 mL). This was followed by addition of cyclopropylacetic acid (93 mg, 0.93 mmol) and the mixture was allowed to stir at room temperature for 5 min before **6b** in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 1 h at room temperature and was then diluted with CH_2Cl_2 and washed with ice-cold 1 M HCl and brine. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated. EtOAc was added to the crude mixture, which was cooled to −78 °C and then filtered. The filtrate was concentrated and purified by column chromatography to yield the acylated product (207 mg, 87%).

Tf_2O (125 μL, 0.74 mmol) was added to a stirred solution of polymer supported Ph_3PO (530 mg, 1.48 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and then the acylated product (165 mg, 0.49 mmol) dissolved in CH_2Cl_2 (5 mL) was added. The solution was stirred at 0 °C for 1 h and the beads were then filtered off and washed with CH_2Cl_2. The filtrate was washed with 10% aqueous $NaHCO_3$ and brine and the aqueous layers were extracted with CH_2Cl_2. The combined organic layers were concentrated to yield **7c** (151 mg, 97%) as a colorless oil. $[\alpha]_D^{23}$ 102 (*c* 1.0, $CHCl_3$); IR λ 1722, 1633, 1392, 1301, 1157; ^1H NMR (400 MHz, $CDCl_3$) δ 0.13–0.25 (m, 2H), 0.42–0.54 (m, 2H), 1.08–1.20 (m, 1H), 2.59 (dd, J_1=7.1 Hz, J_2=15.6 Hz, 1H), 2.74 (dd, J_1=6.7 Hz, J_2=15.6 Hz, 1H), 3.76 (s, 3H), 3.95–4.02 (m, 1H), 4.10 (dd, J_1=7.5 Hz, J_2=11.0 Hz, 1H), 4.61–4.69 (m, 1H), 5.17 (s, 2H), 7.29–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 4.3, 4.5, 8.0, 35.2, 48.6, 52.6, 65.5, 67.8, 128.2, 128.5, 128.6, 135.3, 151.0, 162.9, 171.5. HRMS (FAB) calcd for $[M+H]^+$ $C_{17}H_{21}N_2O_4$ 317.1501, obsd 317.1495.

4.7. Preparation of 4-(*S*)-1-benzyloxycarbonyl-2-methyl-4,5-dihydro-imidazole-4-carboxylic acid methyl ester 7d

Compound **6b** (230 mg, 0.91 mmol) was dissolved in CH_2Cl_2 (40 mL). Then acetic anhydride (95 μL, 1.0 mmol) followed by triethylamine (126 μL, 0.91 mmol) were added dropwise at 0 °C. The solution was stirred at 0 °C for 1 h and was then diluted with CH_2Cl_2 and washed with 10% aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were concentrated and further purified by filtering through a short silica plug to yield the acetylated product, which was used in the next step without further purification.

Tf_2O (225 μL, 1.34 mmol) was added to a stirred solution of polymer supported Ph_3PO (986 mg, 2.74 mmol) in CH_2Cl_2 (8 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min and then the acetylated product dissolved in CH_2Cl_2 (8 mL) was added. The solution was stirred at 0 °C for 1 h and then filtered and the beads were washed with CH_2Cl_2. The filtrate was washed with 10% aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were concentrated to yield **7d** (239 mg, 95%) as a colorless oil. $[\alpha]_D^{23}$ 110 (*c* 1.0, $CHCl_3$); IR λ 1773, 1637, 1398, 1315; ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (d, J=1.4 Hz, 3H), 3.79 (s, 3H), 3.96–4.03 (m, 1H), 4.12 (dd, J_1=7.7 Hz, J_2=11.1 Hz, 1H), 4.59–4.66 (m, 1H), 5.19 (s, 2H), 7.32–7.41 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 48.6, 52.8, 65.6, 68.0, 128.4, 128.7, 128.8, 135.4, 151.4, 160.2, 171.5. HRMS (FAB) calcd for $[M+H]^+$ $C_{14}H_{17}N_2O_4$ 277.1188, obsd 277.1183.

4.8. General procedure for the preparation of imidazolo[2,3-*a*]pyridin-5-ones 9a–c

Method A: Meldrum's acid derivative **8** (3 equiv) was added to a stirred solution of imidazolines (**7a–c**) in DCE (0.2 mmol/mL) at room temperature. This was followed by addition of TFA (1 equiv) and the solution was then heated to 120 °C and irradiated at the target temperature for 300 s (fixed hold time, normal absorption) using a microwave apparatus. The solution was allowed to attain room temperature and was then diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were concentrated. The resulting crude mixture was dissolved in MeOH and a catalytic amount of Pd/C was added and hydrogenation was carried out at atmospheric pressure for 2 h. The catalyst was removed by filtration through Celite and the solid phase was rinsed with MeOH. The filtrate was concentrated and further purified by column chromatography to yield **9a–c** in 42–61% yield.

Method B: Meldrum's acid derivative **8** (1.5 equiv) was added to a stirred solution of imidazolines (**7a–c**) in DCE (0.1 mmol/mL) at room temperature. This was followed by addition of HCl (g) saturated DCE (0.1 mmol/mL) and the solution was heated to 64 °C and allowed to stir for 12 h and then more Meldrum's acid derivative **8** (0.5 equiv) was added. Stirring was maintained for an additional 3 h and then cooled to room temperature, diluted with CH_2Cl_2, and

washed with saturated aqueous $NaHCO_3$ and brine. The aqueous layers were extracted with CH_2Cl_2, and the combined organic layers were concentrated. The resulting crude mixture was dissolved in MeOH and a catalytic amount of Pd/C was added and hydrogenation was carried out at atmospheric pressure for 2 h. The catalyst was removed by filtration through Celite and the solid phase was rinsed with MeOH. The filtrate was concentrated and further purified by column chromatography to yield **9a–c** in 17–70% yield.

*4.8.1. (3S)-7-(Naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5H-imidazolo[3,2-a]pyridine-3-carboxylic acid methyl ester **9a***

$[\alpha]_D^{23}$ −44 (*c* 1.0, $CHCl_3$); IR λ 1749, 1646, 1521, 1209; ^1H NMR (400 MHz, $CDCl_3$) δ 3.70–3.75 (m, 1H), 3.81 (s, 3H), 3.91–4.06 (m, 3H), 4.27 (br s, 1H), 5.19 (dd, J_1=4.5 Hz, J_2=10.0 Hz, 1H), 5.53 (s, 1H), 7.23 (d, J=7.0 Hz, 1H), 7.27–7.48 (m, 8H), 7.64–7.68 (m, 1H), 7.72 (d, J=8.4 Hz, 1H), 7.78–7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 47.0, 53.1, 57.8, 99.3, 107.5, 124.0, 125.5, 125.6, 126.0, 127.5, 127.8, 127.9, 128.7, 129.3, 130.8, 132.0, 133.9, 134.7 (split), 150.0, 155.9, 160.1, 169.4. HRMS (FAB) calcd for $[M+H]^+$ $C_{26}H_{23}N_2O_3$ 411.1709, obsd 411.1704.

*4.8.2. (3S)-5-(Naphthalen-1-ylmethyl)-7-oxo-8-phenyl-2,3-dihydro-7H-imidazolo[3,2-a]pyridine-3-carboxylic acid methyl ester **10***

$[\alpha]_D^{23}$ −39 (*c* 0.7, $CHCl_3$); IR λ 2919, 1633, 1536, 1508, 1434; ^1H NMR (400 MHz, $CDCl_3$) δ 3.74–3.82 (m, 2H), 3.83 (s, 3H), 4.19 (br s, 2H), 4.64 (br s, 1H), 4.90 (dd, J_1=2.5 Hz, J_2=8.3 Hz, 1H), 5.85 (s, 1H), 7.20–7.26 (m, 1H), 7.30–7.39 (m, 3H), 7.41–7.47 (m, 3H), 7.48–4.57 (m, 2H), 7.83 (d, J=8.3 Hz, 1H), 7.87–7.95 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.1, 47.8, 53.5, 59.6, 106.0, 116.2, 123.3, 125.6, 126.1, 126.7, 127.0, 127.3, 128.5, 128.7, 128.9, 130.0, 130.8, 131.9, 133.6, 134.0, 143.4, 153.1, 169.5, 177.7. HRMS (FAB) calcd for $[M+H]^+$ $C_{26}H_{23}N_2O_3$ 411.1709, obsd 411.1712.

*4.8.3. (3S)-7-(Naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5H-imidazolo[3,2-a]pyridine-3-carboxylic acid methyl ester **9b***

$[\alpha]_D^{23}$ −134 (*c* 1.0, $CHCl_3$); IR λ 1749, 1643, 1521, 1207; ^1H NMR (400 MHz, $CDCl_3$) δ 0.48–0.61 (m, 2H), 0.77–0.94 (m, 2H), 1.37–1.46 (m, 1H), 3.70–3.85 (m, 4H), 3.95–4.01 (m, 1H), 4.31 (d, J=16.9 Hz, 1H), 4.45 (d, J=16.9 Hz, 1H), 4.75 (br s, 1H), 5.12 (dd, J_1=4.3 Hz, J_2=9.9 Hz, 1H), 5.46 (s, 1H), 7.26–7.30 (m, 1H), 7.37–7.42 (m, 1H), 7.43–7.49 (m, 2H), 7.75 (d, J=8.3 Hz, 1H), 7.83–7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.5, 7.0, 7.1, 36.4, 47.2, 53.0, 57.3, 96.1, 108.1, 123.9, 125.5, 125.6, 126.0, 127.3 (split), 128.7, 132.1, 133.9, 134.7, 151.0, 158.4, 159.9, 169.5. HRMS (FAB) calcd for $[M+H]^+$ $C_{23}H_{23}N_2O_3$ 375.1709, obsd 375.1701.

*4.8.4. (3S)-7-(Naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5H-imidazo[3,2-a]pyridine-3-carboxylic acid methyl ester **9c***

$[\alpha]_D^{23}$ −69 (*c* 1.0, $CHCl_3$); IR λ 1741, 1654, 1535, 1209; ^1H NMR (400 MHz, $CDCl_3$) δ 3.63–3.69 (m, 1H), 3.76 (s, 3H), 3.80–3.87 (m, 1H), 4.15 (s, 2H), 4.58 (br s, 1H), 5.05 (dd, J_1=4.1 Hz, J_2=9.9 Hz, 1H), 5.20 (s, 1H), 5.81 (s, 1H), 7.30–7.54 (m, 4H), 7.77 (d, J=8.2 Hz, 1H), 7.80–7.87 (m, 1H), 7.88–7.95 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 47.0, 53.0, 57.0, 84.9, 106.4, 124.1, 125.4, 125.7, 126.2, 127.6, 127.8, 128.6, 132.1, 133.9, 134.4, 151.9, 157.7, 160.8, 169.3. HRMS (FAB) calcd for $[M+H]^+$ $C_{20}H_{19}N_2O_3$ 335.1396, obsd 335.1386.

4.9. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester 12a

$(NH_4)_2MoO_4$ (16 mg, 0.08 mmol) was added to a stirred solution of serine derivative **11a** (200 mg, 0.84 mmol) in toluene (84 mL). The solution was heated to reflux with azeotropic removal of water using a Soxhlet apparatus containing activated 3 Å molecular sieves. After 6 h at reflux, the reaction mixture was cooled to room temperature for 5 min and Meldrum's acid derivative **8** (527 mg, 1.69 mmol) followed by TFA (325 μl, 4.22 mmol) were added. The solution was heated to reflux for 2 h and then allowed to attain room temperature, filtered through Celite, and concentrated under reduced pressure. Purification by column chromatography yielded pyridone **12a** (268 mg, 78% yield) as a colorless foam. $[\alpha]_D^{23}$ −6 (*c* 1.1, $CHCl_3$); IR λ 1752, 1666, 1508, 1207; ^1H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.03 (d, J=17.0 Hz, 1H), 4.10 (d, J=17.0 Hz, 1H), 4.65 (dd, J_1=4.6 Hz, J_2=9.4 Hz, 1H), 4.80 (t, J_1=9.3 Hz, 1H), 5.22 (dd, J_1=4.6 Hz, J_2=9.4 Hz, 1H), 5.71 (s, 1H), 7.24 (d, J=7.2 Hz, 1H), 7.33–7.46 (m, 8H), 7.62 (m, 1H), 7.74 (d, J=8.3 Hz, 1H), 7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0, 53.4, 57.1, 71.4, 99.9, 111.3, 123.8, 125.4, 125.6, 126.1, 127.7, 127.9 (split), 128.7 (split), 130.8, 131.8, 132.5, 133.9, 134.1, 153.6, 157.1, 159.1, 168.2. HRMS (FAB) calcd for $[M+H]^+$ $C_{26}H_{22}NO_4$ 412.1549, obsd 412.1550.

When **12a** was prepared using 0.1 equiv of TFA, which resulted in 91% ee the optical rotation was $[\alpha]_D^{23}$ −63 (*c* 1.0, $CHCl_3$).

4.10. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester 12b

$(NH_4)_2MoO_4$ (19 mg, 0.01 mmol) was added to a stirred solution of serine derivative **11b** (190 mg, 0.94 mmol) in toluene (95 mL). The solution was heated to reflux with removal of water using a Soxhlet apparatus containing activated 3 Å molecular sieves. After 5 h at reflux, the reaction mixture was cooled in room temperature for 5 min and Meldrum's acid derivative **8** (590 mg, 1.89 mmol) followed by TFA (360 μL, 4.67 mmol) were added. The solution was heated to reflux for 2 h and then allowed to attain room temperature for 40 min. Then more Meldrum's acid derivative **11** (295 mg, 0.94 mmol) was added and the reaction mixture was heated to reflux for an additional 90 min. The solution was allowed to attain room temperature, filtered through Celite, and concentrated. Purification by column chromatography gave 2-pyridone **12b** as a brown oil (114 mg, 32% yield). $[\alpha]_D^{23}$ −18 (*c* 1.0, $CHCl_3$); IR λ 1752, 1671, 1594, 1509, 1211; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68–0.76 (m, 2H), 0.80–0.93 (m, 2H), 1.40–1.47 (m, 1H), 3.78 (s, 3H), 4.37 (d, J=17.2 Hz, 1H), 4.50 (d, J=17.2 Hz, 1H), 4.66 (dd, J_1=4.5 Hz, J_2=9.5 Hz, 1H), 4.75 (t, J=9.5 Hz, 1H), 5.12 (dd, J_1=4.5 Hz, J_2=9.5 Hz, 1H), 5.61 (s, 1H), 7.28 (d, J=7.3 Hz, 1H), 7.37–7.52 (m, 3H), 7.74–7.87 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.3, 6.6, 6.6, 36.4, 53.1, 56.6, 71.0, 97.9, 111.1, 123.7, 125.4, 125.5, 126.0, 127.3, 127.4, 128.7, 131.9, 133.8, 134.0, 154.3, 158.9, 159.6, 168.3. HRMS (FAB) calcd for $[M+H]^+$ $C_{23}H_{22}NO_4$ 376.1549, obsd 376.1550.

4.11. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-carboxylic acid methyl ester 12c

$(NH_4)_2MoO_4$ (25 mg, 0.13 mmol) was added to a stirred solution of serine derivative **11c** (210 mg, 1.30 mmol) in toluene (140 mL). The solution was heated to reflux with azeotropic removal of water using a Soxhlet apparatus containing activated 3 Å molecular sieves. After 4 h at reflux, the reaction mixture was cooled at room temperature for 5 min and Meldrum's acid derivative **8** (893 mg, 2.86 mmol) followed by TFA (100 μL, 1.30 mmol) were added. The solution was then heated to reflux for 1 h and then allowed to attain room temperature, filtered through Celite, and concentrated. Purification by column chromatography yielded 2-pyridone **12c** as a yellow oil (74 mg, 17% yield). $[\alpha]_D^{23}$ −37 (*c* 0.5, $CHCl_3$); IR λ 1751, 1673, 1596, 1529, 1218; ^1H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 4.23 (s, 2H), 4.63 (dd, J_1=4.5 Hz, J_2=9.3 Hz, 1H), 4.74 (t, J_1=9.3 Hz, 1H), 5.14 (dd, J_1=4.5 Hz, J_2=9.3 Hz, 1H), 5.50 (d, J=1.1 Hz, 1H), 6.00

(s, 1H), 7.35 (d, J=6.7 Hz, 1H), 7.40–7.51 (m, 3H), 7.79 (d, J=8.3 Hz, 1H), 7.83–7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 53.3, 56.5, 71.3, 84.9, 109.8, 123.8, 125.4, 125.7, 126.2, 127.8 (split), 128.7, 131.9, 133.7, 133.9, 156.5, 158.2, 160.0, 168.1. HRMS (FAB) calcd for $[M+H]^+$ $C_{20}H_{18}NO_4$ 336.1236, obsd 336.1233.

4.12. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-imidazo[3,2-*a*]pyridine-3-lithium carboxylate 13a

LiOH (0.1 M, 1.58 mL, 0.158 mmol) was added dropwise to a stirred solution of **9a** (65 mg, 0.158 mmol) in THF (5.0 mL) at 0 °C. The solution was allowed to attain room temperature while stirring for 2 h and was then concentrated and lyophilized from H_2O to yield lithium carboxylate **13a** (59 mg, 93%). $[\alpha]_D^{23}$ −44 (*c* 0.5, MeOH); IR λ 3270, 1639, 1527, 1396, 1295; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.55 (dd, J_1=3.6 Hz, J_2=9.2 Hz, 1H), 3.62–3.70 (m, 1H), 3.90 (s, 2H), 4.56 (dd, J_1=3.6 Hz, J_2=10.1 Hz, 1H), 4.91 (br s, 1H), 6.31 (s, 1H), 7.26–7.52 (m, 9H), 7.66–7.72 (m, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.87–7.92 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 36.3, 48.2, 61.0, 97.9, 104.7, 124.4, 126.0, 126.1, 126.5, 127.4, 127.9, 128.9, 129.2, 131.4, 132.0, 133.8, 135.9 (split), 151.9, 153.4, 160.2, 171.0.

4.13. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-imidazolo[3,2-*a*]pyridine-3-lithium carboxylate 13b

LiOH (0.1 M, 0.51 mL, 0.05 mmol) was added dropwise to a stirred solution of **9b** (19 mg, 0.05 mmol) in THF (3.0 mL) at 0 °C. The solution was allowed to attain room temperature while stirring for 2 h and was then concentrated and lyophilized from H_2O to yield lithium carboxylate **13b** (18 mg. 97%). $[\alpha]_D^{23}$ −53 (*c* 0.5, MeOH); IR λ 3274, 1644, 1525, 1396, 1294; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.44–0.56 (m, 2H), 0.77–0.89 (m, 2H), 1.36–1.47 (m, 1H), 3.63–3.72 (m, 2H), 4.27 (d, J=7.0 Hz, 1H), 4.37 (d, J=7.0 Hz, 1H), 4.47 (dd, J_1=3.9 Hz, J_2=9.4 Hz, 1H), 4.77 (s, 1H), 6.50 (s, 1H), 7.33 (d, J=6.8 Hz, 1H), 7.44–7.54 (m, 3H), 7.33 (d, J=8.1 Hz, 1H), 7.87–7.97 (m 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 7.6, 8.1, 36.1, 48.5, 60.8, 95.0, 104.8, 124.7, 126.1, 126.2, 126.6, 127.4, 127.8, 129.0, 132.3, 133.9, 136.2, 153.3, 156.3, 160.2, 170.8.

4.14. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-imidazolo[3,2-*a*]pyridine-3-lithium carboxylate 13c

LiOH (0.1 M, 0.90 mL, 0.09 mmol) was added dropwise to a stirred solution of **9c** (30 mg, 0.09 mmol) in THF (4.0 mL) at 0 °C. The solution was allowed to attain room temperature while stirring for 4 h and was then concentrated and lyophilized from H_2O to yield lithium carboxylate **13c** (25 mg, 85%). $[\alpha]_D^{23}$ −69 (*c* 0.4, MeOH); IR λ 2915, 1660, 1527, 1425, 1301; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.54–3.68 (m, 2H), 4.10 (s, 2H), 4.49 (dd, J_1=3.5 Hz, J_2=9.3 Hz, 1H), 5.09 (s, 1H), 5.30 (s, 1H), 6.94 (br s, 1H), 7.36–7.57 (m, 4H), 7.82 (d, J=7.6 Hz, 1H), 7.88–8.06 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 38.3, 47.5, 60.1, 83.2, 103.0, 124.3, 125.6, 125.7, 126.1, 127.1, 127.6, 128.5, 131.8, 133.5, 135.5, 153.7, 155.4, 160.7, 170.7.

4.15. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-phenyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-lithium carboxylate 13d

LiBr (190 mg, 2.19 mmol) and TEA (90 μL, 0.65 mmol) were added to a stirred solution of **12a** (90 mg, 0.22 mmol) in MeCN (1 mL) containing 2 v/v % H_2O. The reaction mixture was allowed to stir for 3 h at room temperature and was then diluted with EtOAc and washed with 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried, concentrated, and further purified by centrifugal chromatography. This product was lyophilized from H_2O to yield carboxylic acid **13d** (50 mg, 57%). $[\alpha]_D^{23}$ −2 (*c* 0.5, $CHCl_3$); IR λ 1652, 1575, 1511, 1396; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.04 (d, J=17.0 Hz, 1H), 4.11 (d, J=17.0 Hz, 1H), 4.68 (dd, J_1=3.6 Hz, J_2=8.8 Hz, 1H), 4.82–4.90 (m, 1H), 5.04 (dd, J_1=3.6 Hz, J_2=9.3 Hz, 1H), 5.29 (s, 1H), 7.29–7.36 (m, 2H), 7.38–7.51 (m, 7H), 7.65–7.70 (m, 1H), 7.83 (d, J=8.2 Hz, 1H), 7.89–7.94 (m, 1H); ^{13}C NMR (100 MHz, MeOD-d_4) δ 36.4, 57.9, 72.7, 98.8, 109.7, 124.2, 126.0, 126.2, 126.7, 127.7, 127.8, 128.0, 128.9, 129.0, 131.3, 131.8, 133.3, 133.8, 135.1, 154.9, 156.0, 158.4, 169.8.

4.16. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-8-cyclopropyl-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-lithium carboxylate 13e

LiBr (69 mg, 0.79 mmol) and TEA (33 μL, 0.24 mmol) were added to a stirred solution of **12b** (30 mg, 0.08 mmol) in MeCN (0.4 mL) containing 2 v/v % H_2O. The reaction mixture was allowed to stir for 2 h at room temperature and was then diluted with EtOAc and washed with 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried, concentrated, and further purified by centrifugal chromatography. This product was lyophilized from H_2O to yield carboxylic acid **13e** (21 mg, 73%). $[\alpha]_D^{23}$ 34 (*c* 0.1, $CHCl_3$); IR λ 1656, 1513, 1209, 1174; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.57–0.73 (m, 2H), 0.78–0.87 (m, 2H), 1.46–1.55 (m, 1H), 4.39 (d, J=17.3 Hz, 1H), 4.48 (d, J=17.3 Hz, 1H), 4.72 (dd, J_1=3.6 Hz, J_2=8.8 Hz, 1H), 4.80–4.86 (m, 1H), 4.92 (dd, J_1=3.6 Hz, J_2=9.1 Hz, 1H), 5.13 (s, 1H), 7.36 (d, J=6.9 Hz, 1H), 7.47–7.57 (m, 3H), 7.84–7.99 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 6.7, 7.0, 7.2, 36.1, 57.6, 72.5, 96.8, 109.6, 124.5, 126.1, 126.3, 126.8, 127.7, 127.9, 129.1, 132.1, 133.9, 135.2, 155.5, 158.5, 159.1, 170.1.

4.17. Preparation of (3*S*)-7-(naphthalen-1-ylmethyl)-5-oxo-2,3-dihydro-5*H*-oxazolo[3,2-*a*]pyridine-3-lithium carboxylate 13f

LiBr (142 mg, 1.64 mmol) and TEA (68 μL, 0.49 mmol) were added to a stirred solution of **12c** (55 mg, 0.16 mmol) in MeCN (1 mL) containing 2 v/v % H_2O. The reaction mixture was allowed to stir for 5 h at room temperature and was then diluted with EtOAc and washed with 2 M HCl. The aqueous layer was extracted with EtOAc. The combined organic layers were dried, concentrated, and further purified by chromatography and then lyophilized from H_2O to yield carboxylic acid **13f** (44 mg, 83%). $[\alpha]_D^{23}$ −4 (*c* 0.5, $CHCl_3$); IR λ 1660, 1525, 1396, 1220; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.24 (s, 2H), 4.68 (dd, J_1=3.6 Hz, J_2=8.8 Hz, 1H), 4.77–4.84 (m, 1H), 4.95 (dd, J_1=3.6 Hz, J_2=9.3 Hz, 1H), 5.58 (s, 1H), 5.68 (s, 1H), 7.43–7.63 (m, 4H), 7.81–8.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 58.8, 70.4, 88.8, 108.6, 123.7, 125.5, 125.9, 126.5, 128.0, 128.2, 128.9, 131.8, 133.0, 134.0, 156.9, 161.2, 162.1, 167.3.

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Supplementary data

Electronic Supplementary Information (ESI) available: ^{13}C NMR spectra of compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.015.

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