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Homogeneous Catalysis

Copper Catalyzed Assembly of *N*-Aryloxazolidinones: Synthesis of Linezolid, Tedizolid, and Rivaroxaban

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Abstract: The total synthesis of oxazolidinone-based pharmaceuticals, linezolid, tedizolid and rivaroxaban is reported. They are synthesized using a recently reported copper-catalyzed one-pot cyclization and arylation as the key step to construct the *N*-aryloxazolidinone core. Active pharmaceutical ingredients (API) were synthesized from a common synthetic pool of a simple protected amino alcohol in 22 %, 61 % and 40 % total synthesis yields, respectively.

Introduction

Over recent decades, the synthesis and modification of the *N*-aryloxazolidinone motif has received great attention due its prevalence in a variety of modern pharmaceuticals.[1] DuPont found that these structures possess potent activity as antibacterial agents through a unique mechanism of action. This family of antibiotics function by selectively inhibiting protein synthesis in bacteria cells. Linezolid, the first of these pharmaceuticals, was approved by the FDA in 2000 to treat severe Gram-positive bacterial infections such as MRSA and VRE.[2] Due to its unique mechanism of action little cross resistance was found with other common antibacterials. Despite this, resistance against linezolid itself has been found, and the second generation analogue, tedizolid, has been shown to have wide spread potency against linezolid-resistant gram positive bacteria.[3] Rivaroxaban is the first available orally active direct factor Xa inhibitor and is used post-surgery to prevent blood clots and in cases of people suffering from non-valvular atrial fibrillation.[4] The chemical structure of these three drug compounds can be seen to possess a similar common core, making up of three rings (Figure 1); (A) a 5-substituted oxazolidinone ring, (B) 1,4-substituted aryl ring where a small group *meta* to the nitrogen is also predominant and (C) the most structurally diverse ring, allowing for varied analogues.

We have previously reported a copper-catalyzed one-pot cyclization and arylation used in synthesis of the *N*-aryloxazolidinone motif (Scheme 1).[5] This reaction methodology was applied to the synthesis of the reversible and selective monoamine oxidase (MAO) inhibitor, Toloxatone, which has been used in the treatment of depression.[6] This reaction protocol was

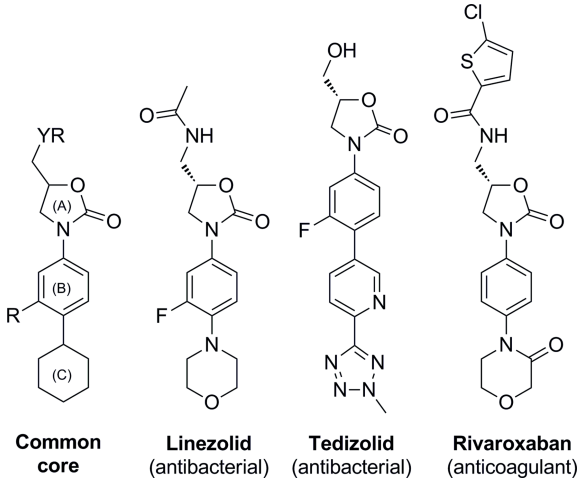

Figure 1. Oxazolidinone-based API's synthesized in this study.

shown to permit access to a wide range of highly decorated pharmaceutically relevant oxazolidinone motifs. This transformation was also shown to possess a vast functional group tolerance with a wide range of reactive functionality for further derivation. This report describes the application of these initial studies in the total syntheses of linezolid, tedizolid and rivaroxaban. The racemates of these drugs were synthesized as a proof of concept.

Retrosynthetic analysis of the common core could envisage going back to one universal starting material for each of the drugs, 3-amino-1,2-propanediol (Scheme 2). From this, the forward route would begin with the construction of the *N*-ethyl carbamate protected structure primed for the key copper-catalyzed one-pot cyclization and arylation step. This step would introduce the (A) and (B) rings. Following this, cross coupling could be used to install the (C) ring. Subsequent late stage FGI('s) would be used to leave the desired functionality in the 5-position of the (A) ring to give the fully furnished drug molecules.

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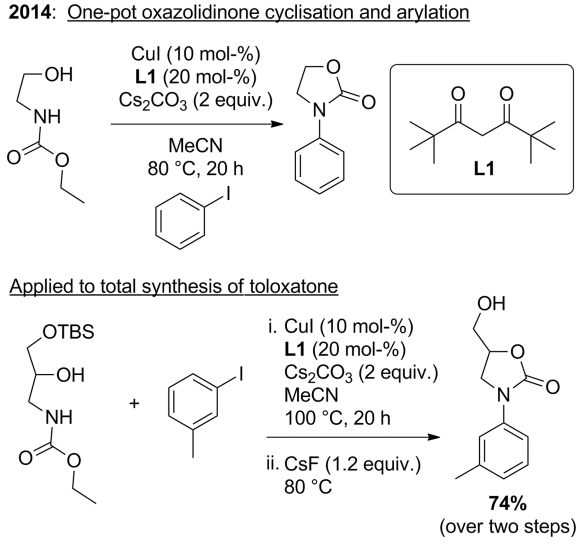
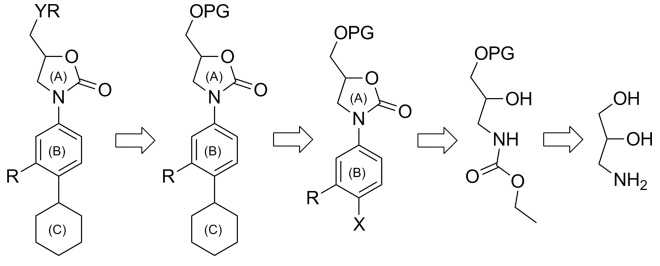


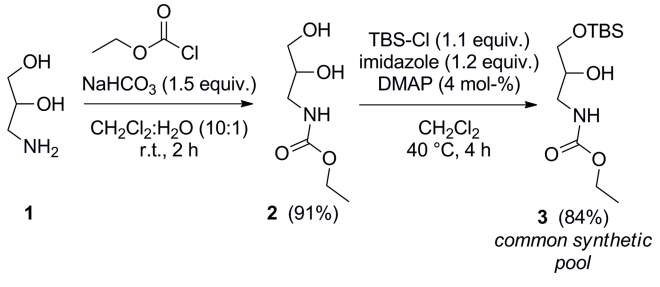
Scheme 1. Copper-catalyzed construction of the *N*-aryloxazolidinone core and the application to the total synthesis of Toloxatone.



Scheme 2. Retrosynthetic analysis of common core to universal amino alcohol starting material.

Results and Discussion

The total synthesis of all three drugs was envisioned to stem from a *N*,*O*-protected amino alcohol (Scheme 3) which is to be used as a common synthetic pool for this work. This was obtained by selective *N*-protection using ethyl chloroformate and then a selective primary alcohol silyl protection governed by protecting group choice.

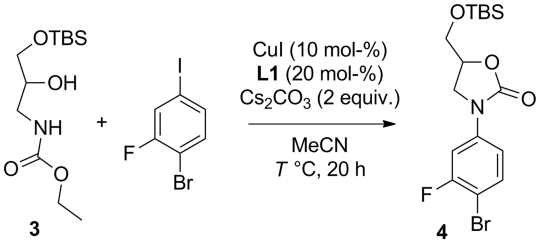


Scheme 3. Synthesis of di-protected amino alcohol used as a synthetic pool in pharmaceutical synthesis.

For the synthesis of linezolid and tedizolid it was of paramount importance install a di-halogenated aromatic motif. To introduce the *meta*-fluoro substituent at this time was important as late stage fluorinations could lead to selectivity issues and waste of high value intermediates. The installation of a *para*-substituted halogen is also necessary to allow addition of (C) ring via cross coupling methodology.

The copper-catalyzed cyclization and arylation protocol was initially tested. However this only gave conversion to product in poor yields. From this, further investigation was needed in attempt to determine more bespoke conditions for this transformation. Low yields were deduced to be due to potential saponification of the oxazolidinone product and subsequent potential *N*-/*O*-arylations. Varying the quantity of aryl iodide, temperature and the presence of any additives were tested under the reaction conditions (Table 1). *t*BuOH and HFIP were added in order to attempt to suppress saponification. Unfortunately the isolated yields for any of these variations remained uniformly poor. As such, it was proposed that this was a non-viable route towards the high value linezolid and tedizolid intermediate.

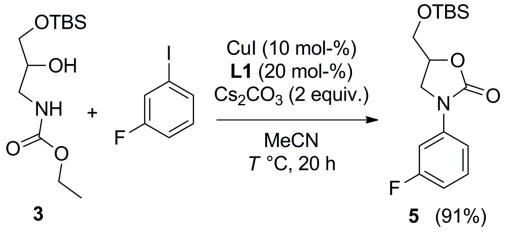
Table 1. Optimisation copper-catalyzed one-pot cyclization and arylation synthesising pharmaceutical intermediate; **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione.



Entry	Ar–I (equiv.)	*T* [°C]	Additive	**4** [%][a]
1	1.0	80	–	34
2	1.4	80	–	33
3	1.8	80	–	44
4	1.8	100	–	35
5	1.8	80	*t*BuOH[b]	28
6	1.8	80	HFIP [b]	0

[a] Isolated yield. [b] 1.5 equiv. hexafluoroisopropanol (HFIP).

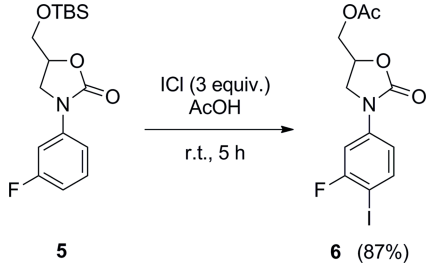
On reflection of reactivity of these systems, it was then anticipated that the same copper-catalyzed transformation could be applied to 3-fluoroiodobenzene, followed by a selective iodination to give a similar intermediate. The introduction of iodide functionality (cf. bromide) also allows access to further copper-catalyzed systems for installation of the (C) ring. The reaction of **3** with the fluorinated aromatic gave the corresponding *N*-aryloxazolidinone cleanly in 91 % yield (Scheme 4).



Scheme 4. Copper-catalyzed cyclization and arylation of *meta*-fluoroiodobenzene. **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione.

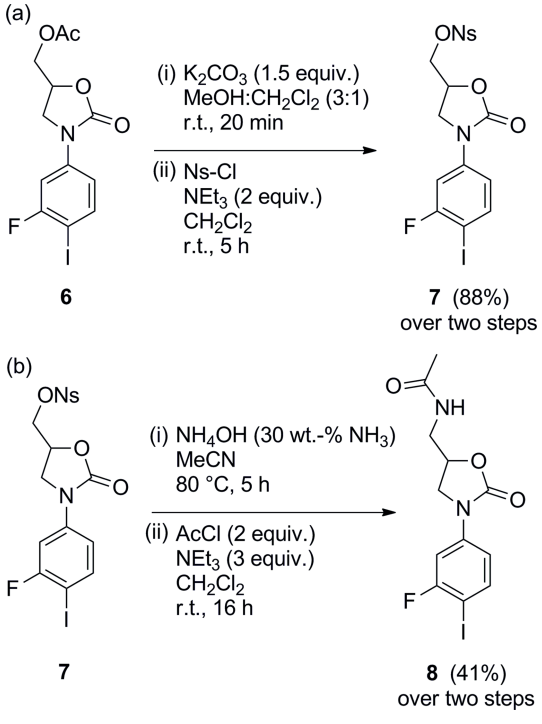
para-Selective electrophilic iodination using Wij's solution facilitated the formation of the di-halogenated aromatic intermediate **6** in excellent yields (Scheme 5). This transformation also

led to an unexpected protecting group exchange where only the acetyl protected alcohol structure was observed. This structure served as the key common intermediate in the synthesis of linezolid and tedizolid. The former will be discussed first.



Scheme 5. *para*-Selective aromatic iodination and protecting group exchange.

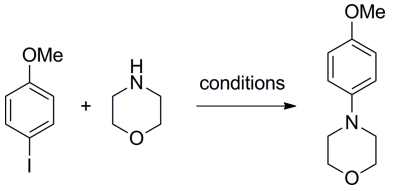
Hydrolysis of the acetyl structure under basic conditions in methanolic dichloromethane gave clean access to the free alcohol structure (Scheme 6, a). Subsequent nosylation gave the activated alcohol primed for nucleophilic substitution in excellent yields. Aqueous ammonium hydroxide was used to generate the primary amine. This was telescoped through to acetylation in a modest yield for a two-step process (Scheme 6, b).[2a]



Scheme 6. Acetyl deprotection and subsequent activation by nosylation; Ns-Cl = 4-nitrobenzenesulfonyl chloride.

Due to the high value of this final intermediate, investigations into the cross coupling of the aryl iodide with morpholine were performed using 4-iodoansiole as an electronic mimic of the electron-donating oxazolidinone heterocycle. Similar reaction conditions from the literature were sought and adapted for this transformation employing both copper and palladium catalysis (Table 2).[7–10]

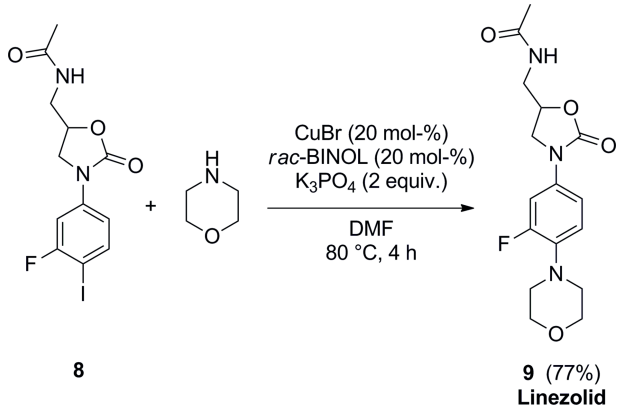
Table 2. Transition metal-catalyzed amination of electron-rich aryl iodide.



Entry	Cross coupling conditions[a]	Conv. [%][b]
1[5]	CuI (10 %), **L1** (20 %), Cs_2CO_3, MeCN, 80 °C, 20 h	0
2[7]	CuI (10 %), **L2** (10 %), K_3PO_4, 1,4-dioxane, 80 °C, 24 h	9
3[8]	CuI (10 %), **L3** (20 %), K_2CO_3, DMSO, 100 °C, 20 h	30
4[9]	CuBr (20 %), L4 (20 %), K_3PO_4, DMF, 80 °C, 4 h	**78**
5[9]	CuI (20 %), **L4** (20 %), K_3PO_4, DMF, 60 °C, 20 h	30[c]
6[10]	$Pd(dba)_2$ (5 %), **L5** (10 %), NaO*t*Bu, PhMe, 100 °C, 20 h	10[c,d]

[a] **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione, **L2** = ethylenediamine, **L3** = proline, **L4** = *rac*-BINOL, **L5** = Xantphos. [b] ^{1}H NM conversion. [c] Modification of literature procedure. [d] Protodehalogenation observed.

Unfortunately the cyclization-arylation conditions were not tolerated in this reaction (entry 1). Pleasingly one set of conditions (entry 4) led to efficient morpholine coupling, however at elevated temperatures cf. literature precedent.[9] Application of these conditions to the pharmaceutical intermediate (**8**) proved successful manifesting comparable efficiency to the test substrate (Scheme 7). This granted access to linezolid in a 77 % yield with a total synthesis yield of 22 % for the final product from ethyl carbamate **3**. This yield is lower than the current synthetic route to linezolid.[2c] Despite this, currently the morpholine structure was introduced in the first step, whereas here it is installed in the final step. Due to this, ease of variation and analogue generation of the (C) ring would be significantly improved using this synthetic strategy.

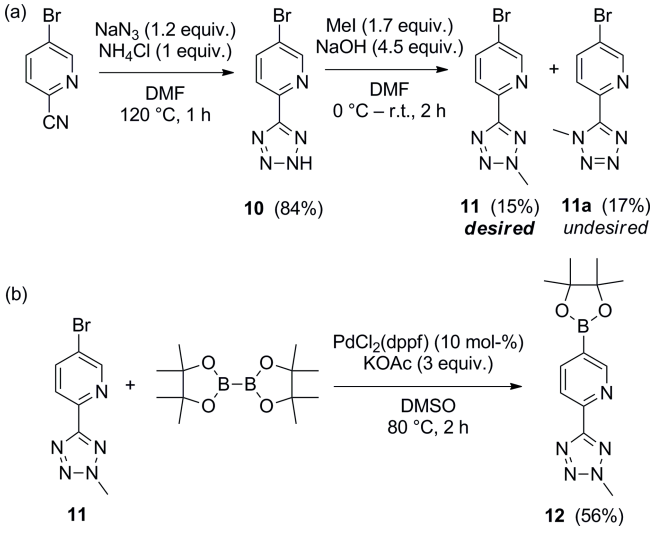


Scheme 7. Copper-catalyzed amination of linezolid intermediate.

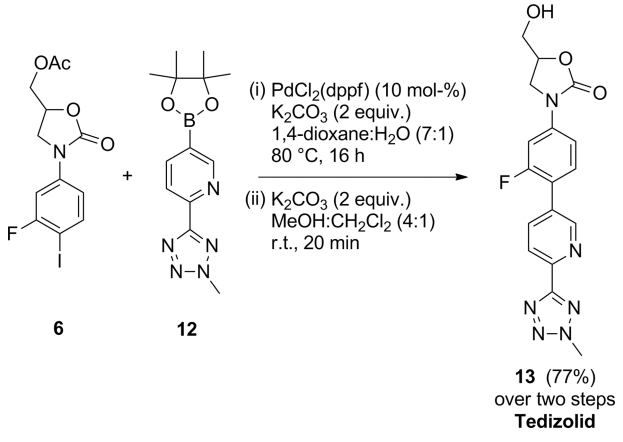
For the synthesis of tedizolid, the pharmaceutical intermediate (**6**) can again be utilized. This shows the high value of late stage catalytic modifications to create different pharmaceutically active motifs. In this case a different coupling strategy must be used to install the pyridyl-tetrazole motif to tedizolid.

The unsubstituted tetrazole ring was furnished using a dipolar cycloaddition reaction under acidic conditions. Unfortunately subsequent selective methylation was not possible and a mixture of isomers was observed (Scheme 8, a).[3b] Despite

this, they were fully separable by standard chromatographic techniques. Following clean isolation of the tetrazole isomer it was decided to install a boronic ester group to prime the structure for cross coupling (Scheme 8, b).[11a] This was carried out using palladium catalysis and afforded the coupling partner in good yield. This was then followed by the palladium-catalyzed Suzuki–Miyaura reaction with the pharmaceutical intermediate **6** (Scheme 9).[11]



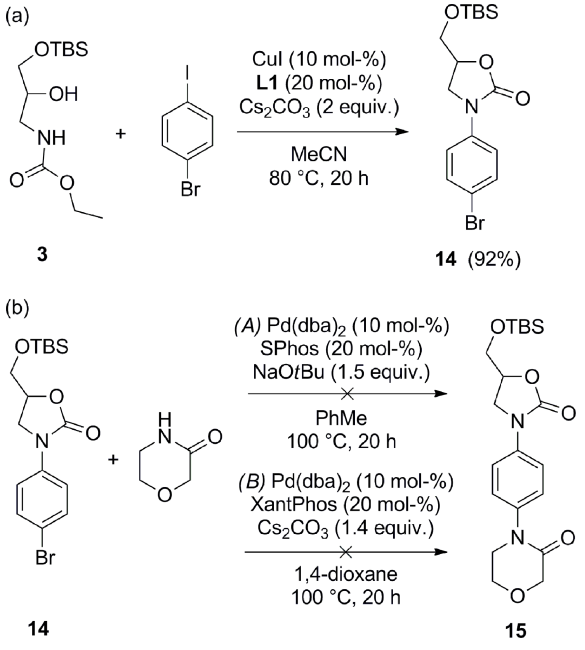
Scheme 8. Formation of pyridyl-tetrazole coupling partner.



Scheme 9. Palladium-catalyzed Suzuki–Miyaura coupling followed by acetyl deprotection to give tedizolid.

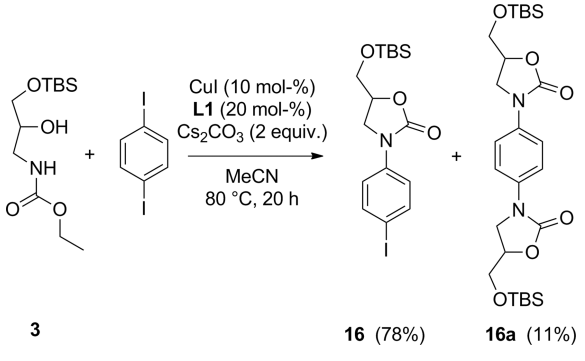
This reaction led to some deprotection of the acetyl protecting group therefore a post-synthetic deprotection was carried out to give the unprotected alcohol structure of tedizolid in a total 77 % yield over two steps. The total yield for this synthesis was 61 % from the synthetic pool of ethyl carbamate **3**. This is significantly higher than the current reported synthesis, primarily due to a much more efficient Suzuki–Miyaura coupling cf. Stille coupling previously reported.[11]

The final target drug molecule to be synthesized was the anticoagulant rivaroxaban. This core structure bears similarities to that previously used however there is no *meta*-fluoro substituent on the (B) ring. Therefore the copper-catalyzed cyclization and arylation was used to construct the *para*-bromo motif. This was achieved in excellent yields with complete selectivity for C–I over C–Br coupling. (Scheme 10, a). It was then proposed that a Buchwald–Hartwig amination would allow coupling of the morpholine-3-one heterocycle to install the (C) ring of rivaroxaban (Scheme 10, b). Despite this, two traditional palladium-catalyzed protocols gave rise to no conversion to product.[10]



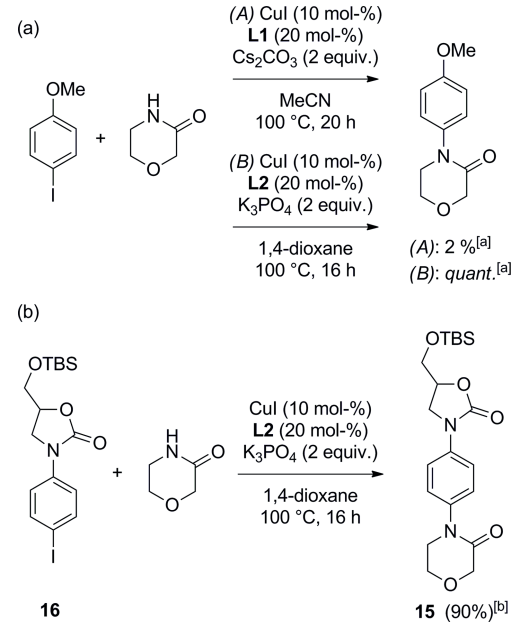
Scheme 10. (a) Copper-catalyzed construction of a *para*-bromo pharmaceutical intermediate. **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione (b) Palladium-catalyzed amidation of intermediate.

Copper-catalyzed cross coupling would be significantly more challenging as the structure would require C–Br activation and the aromatic is electron-rich. Due to this, the *para*-iodo substituted intermediate was investigated as a more amenable intermediate for copper-catalyzed amidations. The cyclization and arylation methodology was carried out with diiodobenzene and fortunately there was only minor oxazolidinone di-arylation observed (Scheme 11). This was rationalized as due to the electron-donating ability of the oxazolidinone, the electron-rich mono-amidated product was less amenable to act as a coupling partner than diiodobenzene.



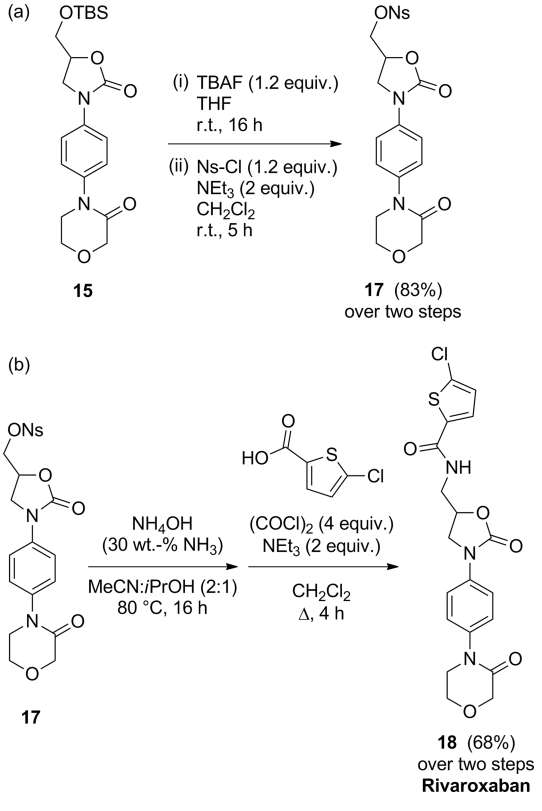
Scheme 11. Copper-catalyzed cyclization and arylation of diiodobenzene. **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione.

Due to the success shown earlier for using 4-iodoanisole as a test substrate for the *para*-substituted oxazolidinone aromatic it was again used in the investigation of copper-catalyzed amidation techniques. The cyclization and arylation conditions were again studied with this coupling partner, however only trace conversion was found using ^{1}H NMR spectroscopy (Scheme 12, a). However the second set of conditions used gave the amidated product in quantitative conversion.[7] These conditions were then applied to the API and pleasingly, an excellent yield of cross coupled product was observed (Scheme 12, b).



Scheme 12. Copper-catalyzed amination of test motif and application to API. **L1** = 2,2,6,6-tetramethyl-3,5-heptanedione, **L2** = ethylenediamine [a] Conversion by ^{1}H NMR spectroscopy. [b] Isolated yield.

Treatment of the silyl ether group with tetrabutylammonium fluoride solution and subsequent synthesis of the activated alcohol structure was achieved in excellent yield of 83 % for a two-step process (Scheme 13, a). Following this displacement of the nosylate with a primary amine was again achieved with aqueous ammonium hydroxide. This amine was again telescoped through to an amide coupling with a preformed acid chloride (Scheme 13, b). This gave rivaroxaban in 68 % over the two steps. The total synthesis yield for rivaroxaban was 40 % from the ethyl carbamate pool which is comparable to the current reported yield of 39 %.[4c]



Scheme 13. Synthesis of Rivaroxaban through late stage FGI's.

Conclusions

Three oxazolidinone-based API's used in the treatment of a wide scope of diseases were synthesized via novel synthetic strategies and constructed primarily utilizing cost-effective and environmentally sustainable copper catalysis. All synthetic routes used the copper-catalyzed one-pot cyclization and arylation methodology as the key synthetic step to construct the core of these drug motifs. Antibacterial linezolid was synthesized in a 22 % overall yield with seven steps from the silyl-protected ethyl carbamate. Second generation antibacterial tedizolid was synthesized in a 61 % overall yield from the silyl protected ethyl carbamate, heavily improving on current literature synthesis of this compound. Anticoagulant rivaroxaban was synthesized in a 40 % overall yield from silyl protected ethyl carbamate.

Experimental Section

General Information: All reactions used solvents and reagents as obtained from commercial sources without further purification. Reactions requiring anhydrous conditions were performed under nitrogen in oven-dried apparatus. Dry solvents were obtained from the SPS system. Solvents were removed under reduced pressure by Büchi rotorvapor apparatus. All temperatures quoted are external. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on a Bruker Advance 300.22 MHz spectrometer or on an Agilent Technologies spectrometer 500 MHz at 303 K. The spectra were recorded in $CDCl_3$ solvent and chemical shifts are reported relative to the residual $CDCl_3$ solvent peak as an internal standard unless otherwise stated. Data are reported as follows: Chemical shift multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), Chemical shifts are reported in parts per million (ppm) and all coupling constants, *J*, are reported in Hertz. Infra-red spectrum were recorded on a PerkinElmer 100 FT-IR spectrometer using a Universal ATR accessory for sampling with only selected absorbencies quoted as $\tilde{\nu}_{max}$ = in cm^{-1}. Mass Spectra were recorded using an electrospray Time-of-Flight MicroTOFTM mass spectrometer with acetonitrile as the solvent. Masses were recorded in either positive or negative mode. Normal phase flash chromatography was performed under medium pressure using Fischer 60 Å silica gel (35–70 μm). Samples were loaded as saturated solutions in an appropriate solvent system. Analytical thin layer chromatography (TLC) was performed using aluminium-

backed plates coated with Alugram® SIL G/UV$_{254}$ purchased from Macherey–Nagel and visualised by UV light (254 nm), and/or $KMnO_4$ staining. Optical rotations were measured using an Optical Activity Ltd. AA-10 automatic polarimeter. Solutions were prepared in 2 mL samples of $CHCl_3$, cell volume 1.5 mL, cell path length 1 dm. Measurements were performed at room temperature, approx. 23 °C.

Ethyl (2,3-Dihydroxypropyl)carbamate (2):[5] A solution of 3-aminopropane-1,2-diol (9.11 g, 100 mmol) in water (20 mL) was prepared in a round-bottomed flask. $NaHCO_3$ (12.6 g, 150 mmol) was added to the solution followed by CH_2Cl_2 (200 mL) to form a biphasic mixture. The mixture was vigorously stirred at room temperature before ethyl chloroformate (11.4 g, 9.9 mL, 105 mmol) was added drop wise. Following complete addition, the reaction mixture was vigorously stirred at room temperature for 2 h. After this time the contents of the reaction vessel were concentrated under reduced pressure. The crude residue was suspended in acetone, filtered and dried ($MgSO_4$). The crude material was then purified by flash silica gel chromatography (eluent: 100 % EtOAc) to give the desired product. Pale yellow oil (91 %, 14.84 g). IR (thin film) $\tilde{\nu}_{max}$ = 3338, 2984, 2936, 1683 (C=O), 1531 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.88 (t, J = 5.7 Hz, 1 H, N*H*), 4.11–4.04 (m, 4 H, O*H*, CH_2CH_3) 3.80–3.68 (m, 1 H, C*H*OH), 3.54 (ddd, J = 17.4, 11.7, 4.9 Hz, 2 H, NHCH_2), 3.35–3.03 (m, 2 H, CH_2OH), 1.21 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.1, 71.2, 63.8, 61.3, 43.2, 14.6 ppm. HRMS (ESI): *m/z* calculated for $C_6H_{13}NO_4$ requires 186.0742 for $[M + Na]^+$: found: 186.0770.

Ethyl {3-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxypropyl}carbamate (3):[5] To a solution of ethyl (2,3-dihydroxypropyl)carbamate (8.159 g, 50 mmol), in CH_2Cl_2 was added triethylamine (8.40 mL, 60 mmol) and DMAP (0.239 g, 1.96 mmol). The solution was cooled to 0 °C in an ice-water bath before the portion wise addition of *tert*-butylchlorodimethylsilane (8.290 g, 55 mmol). The reaction mixture was stirred at 0 °C for 1 h before warming to 40 °C for a further 4 h. After this time the contents of the reaction vessel were concentrated under reduced pressure, suspended with EtOAc (50 mL), filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash silica gel chromatography (eluent: 0–40 % EtOAc/hexanes) The desired fraction were concentrated under reduced pressure to give the title compound as a pale yellow oil (84 %, 11.65 g). IR (thin film): $\tilde{\nu}_{max}$ = 3347, 2953, 2930, 2886, 2858, 1694 (C=O), 1523 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.13 (s, 1 H, N*H*), 4.11 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 3.80–3.69 [m, 1 H, (OH)C*H*], 3.64 (dd, J = 10.1, 4.5 Hz, 1 H, CH_2OSi), 3.53 (dd, J = 10.1, 6.1 Hz, 1 H, CH_2OSi), 3.40 (ddd, J = 13.7, 6.6, 3.5 Hz, 1 H, NCH_2), 3.15 (ddd, J = 13.9, 6.8, 5.2 Hz, 1 H, NCH_2), 1.23 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 0.89 [s, 9 H, SiC(CH_3)$_3$], 0.11–0.01 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.5, 71.2, 64.8, 61.1, 43.7, 25.9, 18.4, 14.7, –5.3 (d, J = 1.1 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{27}NO_4Si$ requires 278.1787 for $[M + H]^+$: found: 278.1772.

5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-(3-fluorophenyl)-oxazolidin-2-one (5): To a solution of ethyl {3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl}carbamate (2.77 g, 10 mmol), 3-fluoroiodobenzene (1.76 mL, 15 mmol) and 2,2,6,6-tetramethylheptane-3,5-dione (0.44 mL, 2 mmol) in MeCN (40 mL) was added cesium carbonate (6.52 g, 20 mmol) and copper iodide (0.190 g, 1 mmol). The reaction mixture was heated to 80 °C for 20 h. After this time, the mixture was cooled to room temperature and was then diluted with EtOAc (50 mL). The resulting suspension was filtered through a short plug of silica (eluent: 100 % EtOAc). The crude filtrate was concentrated under vacuum and the resulting oil was purified by flash silica gel chromatography (eluent: 30 % EtOAc/hexanes) to give the title compound as a white solid (2.66 g, 91 %), m.p. 95–96 °C. IR (thin film): $\tilde{\nu}_{max}$ = 2953, 2928, 2856, 1747 (C=O), 1132, 834 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (dt, J = 11.3, 2.3 Hz, 1 H, Ar*H*), 7.31 (td, J = 8.2, 6.5 Hz, 1 H, Ar*H*), 7.24 (ddd, J = 8.3, 2.2, 0.9 Hz, 1 H, Ar*H*), 6.81 (tdd, J = 8.2, 2.5, 0.9 Hz, 1 H, Ar*H*), 4.67 (dddd, J = 8.9, 5.6, 4.1, 3.3 Hz, 1 H, OC*H*), 4.02 (t, J = 8.7 Hz, 1 H, NCH_2), 3.93 (dd, J = 8.5, 5.6 Hz, 1 H, CH_2OSi), 3.90 (dd, J = 11.4, 4.1 Hz, 1 H, NCH_2), 3.79 (dd, J = 11.3, 3.3 Hz, 1 H, CH_2OSi), 0.84 [s, 9 H, SiC(CH_3)$_3$], 0.07 [s, 6 H, Si(CH_3)$_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.1 (d, J = 244.7 Hz), 154.6, 140.0 (d, J = 10.7 Hz), 130.2 (d, J = 9.3 Hz), 113.2 (d, J = 2.9 Hz), 110.6 (d, J = 21.3 Hz), 105.7 (d, J = 27.0 Hz), 72.5, 63.5, 46.7, 25.8, 18.2, –5.3 (d, J = 7.8 Hz) ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –111.21 (ddd, J = 11.4, 8.2, 6.6 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{16}H_{24}NO_3SiF$ requires 326.1587 for $[M + H]^+$: found: 326.1565.

[3-(3-Fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl Acetate (6): To a solution of 5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-(3-fluorophenyl)oxazolidin-2-one (3.95 g, 12.14 mmol) in acetic acid (50 mL) was added iodine monochloride (1.82 mL, 36.42 mmol). The reaction mixture was stirred at room temperature for 5 h. After this time the reaction mixture was concentrated under reduced pressure. The crude oil was quenched with satd. $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (200 mL). The organics were washed with satd. sodium thiosulfate solution (2 × 50 mL), and the organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting crude solid was purified by flash silica gel chromatography (eluent: 50 % EtOAc/hexanes) to give the title compound as a white solid (3.76 g, 82 %), m.p. 118–120 °C. IR (thin film): $\tilde{\nu}_{max}$ = 2970, 1742 (C=O), 1481, 1224 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.70 (dd, J = 8.7, 7.1 Hz, 1 H, Ar*H*), 7.47 (dd, J = 10.2, 2.6 Hz, 1 H, Ar*H*), 7.06 (dd, J = 8.7, 2.5 Hz, 1 H, Ar*H*), 4.88 (dddd, J = 8.9, 6.2, 4.8, 4.0 Hz, 1 H, OC*H*), 4.37 (dd, J = 12.3, 3.9 Hz, 1 H, AcCH_2), 4.30 (dd, J = 12.3, 4.9 Hz, 1 H, AcCH_2), 4.10 (t, J = 9.0 Hz, 1 H, NCH_2), 3.80 (dd, J = 8.9, 6.3 Hz, 1 H, NCH_2), 2.09 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 162.0 (d, J = 244.6 Hz), 153.7, 139.9 (d, J = 9.9 Hz), 139.4 (d, J = 3.0 Hz), 115.0 (d, J = 3.3 Hz), 106.0 (d, J = 29.7 Hz), 74.4 (d, J = 25.8 Hz), 70.2, 64.0, 46.9, 20.7 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –91.44 (dd, J = 10.1, 7.2 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{11}NO_4FI$ requires 379.9795 for $[M + H]^+$: found: 379.9774.

[3-(3-Fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl 4-Nitrobenzenesulfonate (7): To a suspension of potassium carbonate (0.829 g, 6 mmol) in 3:1 MeOH/CH_2Cl_2 (45 mL) was added [3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl acetate (1.504 g, 4 mmol). The reaction mixture was stirred at room temperature for 25 min. The reaction mixture was neutralised with AcOH (0.5 mL) and water (26 mL). MeOH was removed under reduced pressure and the aqueous solution was extracted with CH_2Cl_2 (2 × 100 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated to give a crude glassy product. The crude material was purified by flash silica gel chromatography (eluent: 100 % EtOAc) to give the free alcohol structure. (1.23 g, 91 %), m.p. 116–117 °C (ref.[12] 116–117 °C). IR (thin film): $\tilde{\nu}_{max}$ = 3439, 2971, 1740 (C=O), 1480, 1228 cm^{-1}. ^{1}H NMR [500 MHz, $(CD_3)_2SO$]: δ = 7.82 (dd, J = 8.6, 7.6 Hz, 1 H, Ar*H*), 7.58 (dd, J = 11.0, 2.5 Hz, 1 H, Ar*H*), 7.22 (dd, J = 8.7, 2.4 Hz, 1 H, Ar*H*), 5.21 (t, J = 5.5 Hz, 1 H, O*H*), 4.72 (dq, J = 6.3, 3.7 Hz, 1 H, OC*H*), 4.07 (t, J = 9.0 Hz, 1 H, NCH_2), 3.82 (dd, J = 8.9, 6.2 Hz, 1 H, NCH_2), 3.67 (ddd, J = 12.3, 5.2, 3.4 Hz, 1 H, CH_2OH), 3.55 (ddd, J = 12.3, 5.4, 4.2 Hz, 1 H, CH_2OH) ppm. ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 161.1 (d, J = 240.2 Hz), 154.2, 140.5 (d, J = 10.3 Hz), 139.0 (d, J = 3.4 Hz), 115.4 (d, J = 3.0 Hz), 105.1 (d, J = 29.8 Hz), 73.8 (d, J = 26.1 Hz), 73.3, 61.5, 45.9 ppm. ^{19}F NMR [470 MHz, $(CD_3)_2SO$]: δ = –93.88 (dd, J = 10.9, 7.5 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{10}H_9NO_3FI$ requires 337.9689 for $[M + H]^+$: found:

337.9671. To a solution the above solid (1.14 g, 3.4 mmol) in triethylamine (0.95 mL, 6.8 mmol) and CH_2Cl_2 (50 mL) was added 4-nitrobenzenesulfonyl chloride (0.909 g, 4.1 mmol) portion-wise at room temperature. The reaction mixture was stirred for 5 h. The reaction mixture was then quenched with water (50 mL) and diluted with CH_2Cl_2 (150 mL). The organics were then washed with water (2 × 20 mL). The organics were then dried ($MgSO_4$), filtered and concentrated to give a crude yellow solid. The yellow solid was then triturated with Et_2O/Hexane (20 mL) to give the title compound as a pale yellow solid (1.73 g, 97 %), m.p. 149–151 °C. IR (thin film): $\tilde{\nu}_{max}$ = 1743 (C=O), 1527, 1417, 123 cm^{-1}. ^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.44 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 8.19 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.85–7.76 (m, 1 H, Ar*H*), 7.48 (dd, *J* = 10.8, 2.3 Hz, 1 H, Ar*H*), 7.12 (dd, *J* = 8.7, 2.3 Hz, 1 H, Ar*H*), 4.96 (td, *J* = 9.1, 5.5 Hz, 1 H, OC*H*), 4.56–4.44 (m, 2 H, NsOCH_2), 4.11 (t, *J* = 9.4 Hz, 1 H, NCH_2), 3.70 (dd, *J* = 9.3, 6.1 Hz, 1 H, NCH_2) ppm. ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 161.1 (d, *J* = 240.4 Hz), 154.3, 153.2, 150.7, 139.9 (d, *J* = 10.3 Hz), 139.0 (d, *J* = 3.4 Hz), 129.4, 124.9, 115.5 (d, *J* = 3.1 Hz), 105.3 (d, *J* = 29.9 Hz), 74.4 (d, *J* = 26.1 Hz), 71.3, 69.9, 45.6 ppm. ^{19}F NMR [470 MHz, $(CD_3)_2SO$]: δ = –93.39 (dd, *J* = 10.7, 7.5 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{16}H_{12}N_2O_7SFI$ requires 544.9291 for $[M + Na]^+$: found: 544.9305.

***N*-{[3-(3-Fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl}-acetamide (8):** [3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]-methyl 4-nitrobenzenesulfonate (1.73 g, 3.31 mmol) was partially dissolved in MeCN (15 mL) in a 100 mL pear-shaped Schlenk flask. NH_4OH (30 wt.-% NH_3) solution (20 mL) was added and the vessel was sealed and heated to 80 °C for 5 h. The reaction mixture was cooled to room temperature and the pressure from the vessel was released. The contents of the flask were then concentrated under reduced pressure to dryness to give a crude yellow solid. The crude amine was dissolved in dry CH_2Cl_2 (50 mL) and cooled in an ice-water bath to 0 °C. Triethylamine (1.38 mL, 9.93 mmol) was added followed by the portion wise addition of acetyl chloride (0.47 mL, 6.62 mmol). The reaction mixture was warmed to room temperature and left to stir overnight. After this time the reaction mixture was concentrated under reduced pressure and dissolved in 1:1 MeOH/CH_2Cl_2 and absorbed on to silica. The crude reaction mixture was purified by flash silica gel chromatography (eluent: 90:10 EtOAc/MeOH) to give the title compound as a white solid (0.507 g, 41 %), m.p. 153–154 °C. IR (thin film): $\tilde{\nu}_{max}$ = 3326, 2971, 1741 (C=O), 1655 (C=O), 1374, 1217 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67 (dd, *J* = 8.7, 7.1 Hz, 1 H, Ar*H*), 7.45 (dd, *J* = 10.2, 2.5 Hz, 1 H, Ar*H*), 6.98 (dd, *J* = 8.7, 2.5 Hz, 1 H, Ar*H*), 6.40 (t, *J* = 5.7 Hz, 1 H, N*H*), 4.79 (ddt, *J* = 8.8, 6.7, 4.4 Hz, 1 H, OC*H*), 4.02 [t, *J* = 9.0 Hz, 1 H, CH_2N(O)], 3.77 [dd, *J* = 9.1, 6.8 Hz, 1 H, CH_2N(O)], 3.65 (dd, *J* = 7.7, 3.6 Hz, 2 H, NCH_2), 2.01 [s, 3 H, N(O)CH_3] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.3, 162.0 (d, *J* = 244.6 Hz), 154.1, 139.8 (d, *J* = 9.9 Hz), 139.4 (d, *J* = 2.9 Hz), 115.1 (d, *J* = 3.3 Hz), 106.1 (d, *J* = 29.7 Hz), 74.5 (d, *J* = 26.0 Hz), 72.2, 47.4, 41.9, 23.1 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –91.43 (dd, *J* = 10.2, 7.2 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{12}H_{12}N_2O_3FI$ requires 378.9954 for $[M + H]^+$: found: 378.9936.

***N*-{[3-(3-Fluoro-4-morpholinophenyl)-2-oxooxazolidin-5-yl]-methyl}acetamide (Linezolid) (9):**[13] A carousel tube was charged with *N*-{[3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl}-acetamide (0.378 g, 1 mmol), CuBr (0.029 g, 0.2 mmol), BINOL (0.057 g, 0.2 mmol) and K_3PO_4 (0.425 g, 2.0 mmol). The tube was flushed with argon before DMF (1 mL) and morpholine (0.131 g, 0.13 mL, 1.5 mmol) was charged in to the tube via syringe. The reaction mixture was heated to 80 °C for 4 h. After this time the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (200 mL). The organics were washed with brine (2 × 50 mL) and water (50 mL). The aqueous washes were combined with washed with EtOAc (150 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated to give a crude oil. The oil was purified by flash silica gel chromatography (eluent: 5–30 % acetone/CH_2Cl_2) to give the title compound as a white solid (0.260 g, 77 %), m.p. 187–189 °C. IR (thin film): $\tilde{\nu}_{max}$ = 3280, 2855, 1739 (C=O), 1732 (C=O), 1516, 1231 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.43 (dd, *J* = 14.3, 2.6 Hz, 1 H, Ar*H*), 7.07 (ddd, *J* = 8.8, 2.6, 1.1 Hz, 1 H, Ar*H*), 6.91 (t, *J* = 9.1 Hz, 1 H, Ar*H*), 6.27 (t, *J* = 6.1 Hz, 1 H, N*H*), 4.76 (dddd, *J* = 8.9, 6.7, 5.8, 3.3 Hz, 1 H, OC*H*), 4.01 (t, *J* = 9.0 Hz, 1 H, 1 H, NHCH_2), 3.89–3.84 (m, 4 H, 4 H, OCH_2), 3.75 (dd, *J* = 9.1, 6.7 Hz, 1 H, 1 H, NHCH_2), 3.68 (ddd, *J* = 14.7, 6.1, 3.3 Hz, 1 H, 1 H, ArNCH_2), 3.64–3.57 (m, 1 H, 1 H, ArNCH_2), 3.07–3.01 (m, 4 H, 4 H, NCH_2), 2.01 [s, 3 H, N(O)CH_3] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.2, 155.6 (d, *J* = 246.7 Hz), 154.4, 136.7 (d, *J* = 8.8 Hz), 133.0 (d, *J* = 10.4 Hz), 118.9 (d, *J* = 4.2 Hz), 114.0 (d, *J* = 3.4 Hz), 107.6 (d, *J* = 26.4 Hz), 72.0, 67.0, 51.1 (d, *J* = 3.2 Hz), 47.8, 42.1, 23.2 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –120.13 (dd, *J* = 14.3, 9.5 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{16}H_{70}N_3O_4F$ requires 338.1516 for $[M + H]^+$: found: 338.1493.

5-Bromo-2-(2*H*-tetrazol-5-yl)pyridine (10): A mixture of 5-bromopicolinonitrile (0.366 g, 2.0 mmol), sodium azide (0.156 g, 2.4 mmol) and ammonium chloride (0.106 g, 2.0 mmol) was heated in DMF (4 mL) at 120 °C for 1 h. The reaction mixture was cooled to room temperature before being diluted with EtOAc (20 mL). The resulting suspension was filtered under reduced pressure, the solids were washed with EtOAc and dried to give the title compound as a brown solid (0.380 g, 84 %). ^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.69 (d, *J* = 2.1 Hz, 1 H, Ar*H*), 8.09 (dd, *J* = 8.5, 2.4 Hz, 1 H, Ar*H*), 7.99 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.30 (s, 1 H, N*H*) ppm. Crude compound **10** was used in later steps without further purification.

5-Bromo-2-(1-methyl-1*H*-tetrazol-5-yl)pyridine (11a) and 5-Bromo-2-(2-methyl-2*H*-tetrazol-5-yl)pyridine (11):[3b] A solution of 5-bromo-2-(2*H*-tetrazol-5-yl)pyridine (1.71 g, 7.6 mmol) and NaOH (1.36 g, 34 mmol) in dry DMF (15 mL) were stirred at room temperature for 3 h. The reaction mixture was concentrated to dryness and the solids were re-dissolved in dry DMF (12 mL). The suspension was treated with MeI (0.811 mL, 13 mmol) dropwise at 0 °C. The reaction mixture was warmed to room temperature for 2 h. The reaction mixture was then partitioned between water and EtOAc. The organics were washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was then purified by flash silica gel chromatography (eluent 40 % EtOAc/hexanes) to give the two regio-isomers.

11a: White solid (0.294 g, 17 %), m.p. 168–170 °C. IR (thin film): $\tilde{\nu}_{max}$ = 2970, 1446, 1379 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 2.3 Hz, 1 H, Ar*H*), 8.26 (dd, *J* = 8.5, 0.6 Hz, 1 H, Ar*H*), 8.05 (dd, *J* = 8.4, 2.3 Hz, 1 H, Ar*H*), 4.48 (s, 3 H, NCH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.6, 150.8, 143.4, 140.3, 125.6, 123.1, 37.1 ppm. HRMS (ESI): *m/z* calculated for $C_7H_6BrN_5$ requires 239.9884 for $[M + H]^+$: found: 239.9863.

11: White solid (0.282 g, 15 %), m.p. 163–165 °C. IR (thin film) $\tilde{\nu}_{max}$ = 2991, 1454, 1380 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.82 (s, 1 H, Ar*H*), 8.13 (d, *J* = 8.4 Hz, 1 H, Ar*H*), 7.99 (dd, *J* = 8.4, 2.3 Hz, 1 H, Ar*H*), 4.44 (s, 3 H, NCH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.3, 151.5, 145.2, 139.9, 123.5, 122.3, 39.8 ppm. HRMS (ESI): *m/z* calculated for $C_7H_6BrN_5$ requires 261.9704 for $[M + Na]^+$: found: 261.9685.

2-(2-Methyl-2*H*-tetrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (12): To an oven dried carousel tube was added 5-bromo-2-(2-methyl-2*H*-tetrazol-5-yl)pyridine (0.240 g, 1 mmol), bis(pinacolato)diboron (0.508 g, 2.0 mmol), KOAc (0.294 g, 3.0 mmol) and $PdCl_2$(dppf) (0.073 g, 0.1 mmol). The solids were purged with argon before DMSO was added via septum. The solution was further purged with argon before heating at 80 °C for 2 h.

The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with brine (2 × 50 mL), dried (Na_2SO_4), filterd and concentrated under reduced pressure to give a brown solid. The solid was triturated with Et_2O, decanted and the residual solid dried under reduced pressure to give the title compound as a grey solid (160 mg, 56 %). IR (thin film): $\tilde{\nu}_{max}$ = 2978, 1600, 1356, 1224, 1097 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 9.08 (s, 1 H, Ar*H*), 8.23 (s, 2 H, Ar*H*), 4.46 (s, 3 H, NCH_3), 1.38 [s, 12 H, 12 H, $C(CH_3)_2$] ppm. ^{11}B NMR (160 MHz, $CDCl_3$): δ = –5.5 ppm. HRMS (ESI): *m/z* calculated for $C_{13}H_{17}N_5O_2B$ requires 288.1631 for $[M + H]^+$: found: 288.1601.

3-{3-Fluoro-4-[6-(2-methyl-2*H*-tetrazol-5-yl)pyridin-3-yl]phenyl}-5-(hydroxymethyl)oxazolidin-2-one [Tedizolid (13)]:[3b] An oven-dried Schlenk tube was charged with 2-(2-methyl-2*H*-tetrazol-5-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.160 g, 0.56 mmol), [3-(3-fluoro-4-iodophenyl)-2-oxooxazolidin-5-yl]methyl acetate (0.193 g, 0.51 mmol), K_2CO_3 (0.155 g, 1.12 mmol) and $PdCl_2$(dppf) (0.037 g, 0.0504 mmol). The solids were degassed with argon before the addition of dioxane/water (7:1) (8 mL). The reaction mixture was degassed a further time before heating to 80 °C overnight. The reaction mixture was cooled to room temperature, diluted with CH_2Cl_2 (200 mL) and washed with water (2 × 20 mL). The organics were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash silica gel chromatography (100 % EtOAc) to give the acetyl protected alcohol as a white solid (0.105 g, 50 %). IR (thin film): $\tilde{\nu}_{max}$ = 1745, 1730 cm^{-1}. ^1H NMR [500 MHz, $(CD_3)_2SO/CD_3OD/CDCl_3$, 80:5:15]: δ = 8.93 (s, 1 H, Ar*H*), 8.31 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 8.05 (d, *J* = 8.2 Hz, 1 H, Ar*H*), 7.62 (dd, *J* = 12.8, 2.2 Hz, 1 H, Ar*H*), 7.53 (t, *J* = 8.6 Hz, 1 H, Ar*H*), 7.39 (dd, *J* = 8.5, 2.2 Hz, 1 H, Ar*H*), 4.97–4.88 (m, 1 H, OC*H*), 4.47 (s, 3 H, NCH_3), 4.41 (dd, *J* = 12.3, 3.9 Hz, 1 H, $AcCH_2$), 4.34 (dd, *J* = 12.3, 4.9 Hz, 1 H, $AcCH_2$), 4.18 (t, *J* = 9.0 Hz, 1 H, NCH_2), 3.88 (dd, *J* = 8.9, 6.3 Hz, 1 H, NCH_2), 2.12 (s, 3 H, CO_2CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.6, 164.8, 160.2 (d, *J* = 249.1 Hz), 153.8, 149.9 (d, *J* = 3.5 Hz), 145.6, 139.9 (d, *J* = 10.9 Hz), 137.2 (d, *J* = 3.8 Hz), 132.3, 130.7 (d, *J* = 4.4 Hz), 122.1, 120.5 (d, *J* = 13.9 Hz), 113.9 (d, *J* = 3.3 Hz), 106.5 (d, *J* = 28.5 Hz), 70.2, 64.0, 47.0, 39.8, 20.7 ppm. ^{19}F NMR (470 MHz, $CDCl_3$): δ = –114.37 (dd, *J* = 12.5, 8.7 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{19}H_{17}N_6O_4F$ requires 435.1193 for $[M + Na]^+$: found: 435.1242. To solution of the above solid (105 mg, 0.28 mmol) in CH_2Cl_2 (1 mL) and MeOH (4 mL) was added K_2CO_3 (0.057 g, 0.42 mmol). The reaction mixture was stirred at room temperature for 1 h. After this time the reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed with water (2 × 20 mL). The organics were separated and diluted with MeOH (15 mL), dried ($MgSO_4$), filtered and concentrated to give the title compound as a white solid, (0.090 g, 96 %), no m.p., decomp. > 180 °C. (ref.[3b] 201 °C). IR (thin film) $\tilde{\nu}_{max}$ = 3371, 1741 (C=O), 1625, 1409 cm^{-1}. ^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.82 (s, 1 H, Ar*H*), 8.19 (d, *J* = 8.1 Hz, 1 H, Ar*H*), 8.00 (d, *J* = 8.4 Hz, 1 H, Ar*H*), 7.65–7.60 (m, 1 H, Ar*H*), 7.47 (t, *J* = 8.6 Hz, 1 H, Ar*H*), 7.33 (dd, *J* = 8.6, 2.0 Hz, 1 H, Ar*H*), 4.68 (td, *J* = 9.8, 3.7 Hz, 1 H, OC*H*), 4.39 (s, 3 H, NCH_3), 4.04 [t, *J* = 8.9 Hz, 1 H, $(HO)CH_2$], 3.94 [dd, *J* = 8.6, 6.4, (HO Hz, 1 H)CH_2], 3.77 (dd, *J* = 12.4, 3.6 Hz, 1 H, NCH_2), 3.62 (dd, *J* = 12.4, 3.7 Hz, 1 H, NCH_2) ppm. ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 163.8, 159.3 (d, *J* = 245.6 Hz), 154.3, 149.4 (d, *J* = 3.9 Hz), 145.0, 140.5 (d, *J* = 11.4 Hz), 137.1 (d, *J* = 3.4 Hz), 131.6 (d, *J* = 1.8 Hz), 130.9 (d, *J* = 4.3 Hz), 122.0, 118.5 (d, *J* = 13.4 Hz), 114.0 (d, *J* = 2.2 Hz), 105.3 (d, *J* = 28.5 Hz), 73.4, 61.5, 45.9, 39.3 ppm. ^{19}F NMR [470 MHz, $(CD_3)_2SO$]: δ = –115.49 (dd, *J* = 12.9, 9.0 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{17}H_{15}N_6O_3F$ requires 371.1267 for $[M + H]^+$: found: 371.1254.

5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-3-(4-iodophenyl)oxazolidin-2-one (16): To a solution of ethyl {3-[(*tert*-butyldimethylsilyl)oxy]-2-hydroxypropyl}carbamate (2.77 g, 10 mmol), 1,4-diiodobenzene (4.95 g, 15 mmol) and 2,2,6,6-tetramethylheptane-3,5-dione (0.44 mL, 2 mmol) in MeCN (40 mL) was added cesium carbonate (6.52 g, 20 mmol) and copper iodide (0.190 g, 1 mmol). The reaction mixture was heated to 80 °C for 20 h. After this time the reaction mixture was cooled to room temperature and was diluted with EtOAc (50 mL). Analysis of the crude reaction mixture by ^1H NMR showed total consumption of the free-*N* oxazolidinone, where a 13:1 mixture of mono:di arylated species were present. The resulting suspension was filtered through a short plug of silica (eluent: 100 % EtOAc). The crude filtrate was concentrated under vacuum and the resulting oil was purified by flash silica gel chromatography (eluent: 30 % EtOAc/hexanes) to give the title compound as an off white solid (3.043 g, 78 %), m.p. 84–86 °C. IR (thin film): $\tilde{\nu}_{max}$ = 1504 (C=O), 1460 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.67–7.63 (m, 2 H, Ar*H*), 7.36–7.30 (m, 2 H, Ar*H*), 4.69–4.64 (m, 1 H, OC*H*), 4.00 [t, *J* = 8.7 Hz, 1 H, $(TBSO)CH_2$], 3.91 (ddd, *J* = 15.5, 8.5, 3.9 Hz, 2 H, NCH_2), 3.78 [dd, *J* = 11.3, 3.2 Hz, 1 H, $(TBSO)CH_2$], 0.84 [s, 9 H, $SiC(CH_3)_3$], 0.07 [s, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.6, 138.3, 138.0, 119.9, 87.3, 72.5, 63.5, 46.5, 25.83 (d, *J* = 3.1 Hz), 18.2, –5.30 (d, *J* = 6.9 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{16}H_{24}NO_3ISi$ requires 434.0648 for $[M + H]^+$: found: 434.0660.

4-[4-(5-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-oxooxazolidin-3-yl)phenyl]morpholin-3-one (15): To a solution of 5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-3-(4-iodophenyl)oxazolidin-2-one (0.433 g, 1 mmol), morpholine-3-one (0.121 g, 1.2 mmol) and ethylenediamine (6 mg, 0.1 mmol) in dioxane (3 mL) was added potassium phosphate tribasic (0.424 g, 2 mmol) and copper iodide (19 mg, 0.1 mmol). The reaction mixture was heated to 100 °C for 16 h. After this time the reaction mixture was cooled to room temperature and filtered through a short plug of celite (eluent: 100 % EtOAc). The filtrate was concentrated under vacuum and the crude reaction mixture was purified by flash silica gel chromatography (eluent: 60 % EtOAc/hexanes) to give the title compound as a white solid (364 mg, 90 %), m.p. 141–143 °C. IR (thin film): $\tilde{\nu}_{max}$ = 2953, 2929, 2857, 1744 (C=O), 1662 (C=O), 1515, 1226, 1127 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 7.34 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 4.67 (dq, *J* = 5.6, 4.0 Hz, 1 H, OC*H*), 4.34 [s, 2 H, $OCH_2C(O)$], 4.04 (dd, *J* = 9.6, 6.0 Hz, 3 H, 3 H, CH_2OSi, OCH_2), 3.96 (dd, *J* = 8.5, 5.8 Hz, 1 H, CH_2OSi), 3.90 (dd, *J* = 11.3, 4.2 Hz, 1 H, NCH_2), 3.80 (dd, *J* = 11.3, 3.3 Hz, 1 H, NCH_2), 3.77–3.73 (m, 2 H, NCH_2), 0.85 [s, 9 H, $SiC(CH_3)_3$], 0.08 [d, *J* = 1.8 Hz, 6 H, $Si(CH_3)_2$] ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 154.8, 137.2, 137.0, 126.2, 119.0, 72.5, 68.7, 64.2, 63.5, 49.8, 46.8, 25.8, 18.3, –5.28 (d, *J* = 8.4 Hz) ppm. HRMS (ESI): *m/z* calculated for $C_{20}H_{30}N_2O_5Si$ requires 407.2002 for $[M + H]^+$: found: 407.2001.

{2-Oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl 4-Nitrobenzenesulfonate (17): A solution of 4-[4-(5-{[(*tert*-butyldimethylsilyl)oxy]methyl}-2-oxooxazolidin-3-yl)phenyl]-morpholin-3-one (2.39 g, 5.9 mmol) in THF (55 mL) was treated with tetra-*N*-butylammonium fluoride 1.0 M solution in THF (7.1 mL, 7.1 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was then concentrated and the crude mixture was purified by flash silica gel chromatography (eluent: 6 % $MeOH/CH_2Cl_2$) to give the free alcohol compound as a white solid (1.582 g, 92 %), m.p. 159–161 °C. IR (thin film): $\tilde{\nu}_{max}$ = 3377, 1737 (C=O), 1644 (C=O), 1228 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.35 (d, *J* = 8.9 Hz, 2 H, Ar*H*), 4.74 (ddd, *J* = 12.5, 7.1, 3.7 Hz, 1 H, OC*H*), 4.34 [s, 2 H, $OCH_2C(O)$], 4.06–3.92 (m, 6 H, 6 H), 3.79–3.71 (m, 3 H, 3 H), 1.81 (s, 1 H, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 167.0, 154.7, 137.2, 137.0, 126.3, 119.1, 72.9, 68.7, 64.2, 62.9, 49.8, 46.5 ppm. HRMS (ESI): *m/z* calculated for $C_{14}H_{16}N_2O_5$ requires 293.1137 for $[M + H]^+$: found:

293.1110. To a suspension of the above solid (1.582 g, 5.4 mmol) and triethylamine (1.51 mL, 10.8 mmol) in dry CH_2Cl_2 (50 mL) was added portion wise at room temperature 4-nitrobenzenesulfonyl chloride (1.44 g, 6.5 mmol). The reaction mixture was left to stir at room temperature overnight. After this time the reaction mixture was concentrated under reduced pressure and diluted in the minimum volume of 50:50 MeOH/CH_2Cl_2. The crude reaction mixture was then absorbed on to silica and concentrated to dryness. The reaction mixture was then purified by flash silica gel chromatography (eluent: 10 % MeOH/CH_2Cl_2). The desired fractions were combined, concentrated and the resulting crude solid was washed with water. The solids were then dried in a 80 °C oven overnight to give the title compound as a white solid (2.33 g, 90 %), no m.p., decomp. 197 °C. IR (thin film) $\tilde{\nu}_{max}$ = 3101, 2970, 1735 (C=O), 1654 (C=O), 1518, 1368, 1189 cm^{-1}. ^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.49–8.41 (m, 2 H, Ar*H*), 8.23–8.15 (m, 2 H, Ar*H*), 7.56–7.46 (m, 2 H, Ar*H*), 7.43–7.37 (m, 2 H, Ar*H*), 4.95 (dtd, *J* = 9.0, 5.8, 2.9 Hz, 1 H, OC*H*), 4.50 (qd, *J* = 11.4, 4.1 Hz, 2 H, 2 H), 4.19 [s, 2 H, OCH_2C(O)], 4.14 (t, *J* = 9.4 Hz, 1 H, 1 H), 3.97 (dd, *J* = 5.8, 4.3 Hz, 2 H, 2 H), 3.78–3.67 (m, 3 H, 3 H) ppm. ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 165.9, 153.5, 150.7, 140.1, 137.1, 136.1, 129.4, 125.9, 124.9, 118.3, 71.4, 69.6, 67.7, 63.4, 48.9, 45.7 ppm. HRMS (ESI): *m/z* calculated for $C_{20}H_{19}N_3O_9S$ requires 478.0920 for $[M + H]^+$: found: 478.0927.

5-Chloro-*N*-({2-oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)thiophene-2-carboxamide [Rivaroxaban (18)]:[14] {2-Oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl 4-nitrobenzenesulfonate (2.31 g, 4.84 mmol) was partially dissolved in 2:1 MeCN/*i*PrOH (30 mL) in a 100 mL pear-shaped Schlenk flask. NH_4OH (30 wt.-% NH_3) solution (25 mL) was added and the vessel was sealed and heated to 80 °C overnight. The reaction mixture was cooled to room temperature and the pressure from the vessel was released. The contents of the flask were then concentrated under reduced pressure to dryness to give a crude yellow solid. In a separate vial 5-chlorothiophene-2-carboxylic acid (1.63 g, 10 mmol), oxalyl chloride (1.72 mL, 20 mmol), DMF (0.25 mL) and dry CH_2Cl_2 (70 mL) were heated to reflux overnight. The reaction mixture was concentrated under reduced pressure and dissolved in dry CH_2Cl_2 (30 mL). The crude amine was dissolved in dry CH_2Cl_2 (50 mL) and cooled in an ice-water bath to 0 °C. Triethylamine (1.53 mL, 9.68 mmol) was added followed by the portion wise addition of the acid chloride solution. The reaction mixture was warmed to reflux for 4 h. After this time the reaction mixture was concentrated under reduced pressure and dissolved in 1:1 MeOH/CH_2Cl_2 and absorbed on to silica. The crude reaction mixture was purified by flash silica gel chromatography (eluent: 80:10:10 EtOAc/MeOH/CH_2Cl_2) to give the title compound as an off white solid (1.43 g, 68 %), m.p. 227–228 °C. IR (thin film): $\tilde{\nu}_{max}$ = 2970, (br) 1738 cm^{-1}. ^1H NMR [500 MHz, $(CD_3)_2SO$]: δ = 8.97 (t, *J* = 5.8 Hz, 1 H, N*H*), 7.69 (d, *J* = 4.1 Hz, 1 H, Ar*H*), 7.56 (d, *J* = 9.1 Hz, 2 H, Ar*H*), 7.40 (d, *J* = 9.0 Hz, 2 H, Ar*H*), 7.19 (d, *J* = 4.0 Hz, 1 H, Ar*H*), 4.84 (dq, *J* = 8.9, 5.6 Hz, 1 H, OC*H*), 4.22–4.14 [m, 3 H, O(CH_2)C(O), thiopheneC(O)NHCH_2], 3.97 (dd, *J* = 5.8, 4.3 Hz, 2 H, ArNCH_2), 3.85 [dd, *J* = 9.2, 6.1 Hz, 1 H, thiopheneC(O)NHCH_2], 3.71 (dd, *J* = 5.7, 4.4 Hz, 2 H, NCH_2), 3.60 (t, *J* = 5.7 Hz, 2 H, OCH_2) ppm. ^{13}C NMR [126 MHz, $(CD_3)_2SO$]: δ = 165.9, 160.7, 154.0, 138.4, 137.0, 136.4, 133.2, 128.4, 128.1, 125.9, 118.3, 71.3, 67.7, 63.4, 49.0, 47.4, 42.2 ppm. HRMS (ESI): *m/z* calculated for $C_{19}H_{18}N_3O_5SCl$ requires 436.0733 for $[M + H]^+$: found: 436.0719.

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