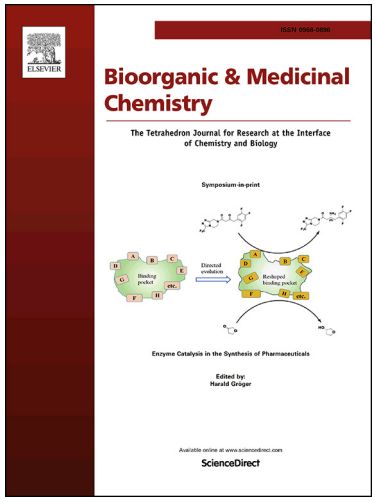

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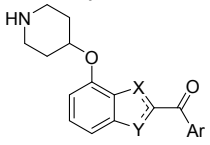

X = C-Me,CH, N-Me, N
Y = NH, N, S
Z = O, NH

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Synthesis of five libraries of 6,5-fused heterocycles to establish the importance of the heterocyclic core for antiplasmodial activity

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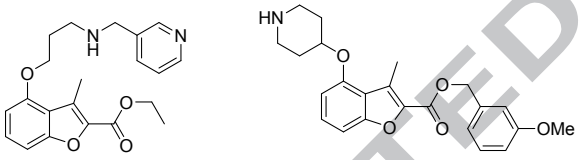
ABSTRACT

Research has indicated that N-myristoyl transferase, an enzyme that catalyzes the addition of a myristate group to the N-terminal glycine residues of proteins, is involved in the myristoylation of more than 100 proteins. Genetic knockdown of the enzyme proved detrimental for the viability of the parasite P. knowlesi. A crystal structure of P. vivax N-myristoyl transferase (pvNMT), containing a 3-methyl benzofuran ligand has made it possible to assess key amino acid residue-ligand interactions. We synthesized five libraries of 6,5-fused heterocycles to establish the importance of the heterocycles as core scaffolds, as well as introduced various aromatic amides and esters to determine which carbonylic group affects the potency of each heterocyclic antiplasmodial agent.

1. Introduction

Malaria is caused by the parasite belonging to the genus *Plasmodium*, of which *Plasmodium falciparum* is the most deadly and widespread causative agent, second being *Plasmodium vivax*.[1] Currently there are five species that infect the human population, *P. falciparum*, *P vivax*, *P. ovale*, *P. malariae* and *P. knowlesi*. [1-2] It has been postulated that malaria is the cause for half of all deaths in human history.[3] According to the WHO 2016 report, an estimated 212 million cases of malaria exist globally and that according to the CDC, 3.2 billion people are still at risk of contracting malaria.[4] 90% of the reported cases of malaria are situated in Africa with more than half of the infected population residing in Sub-Saharan Africa.[5] Regrettably children under five suffer the greatest mortality rate, accounting for approximately 70% of all malaria related deaths, making malaria the third biggest killer of children after pneumonia and diarrhea.[6] Although malaria infection still affects many lives, the number of deaths have been on the decline in recent years due to the effective use of insecticide-treated bed nets (ITN) as a preventative measure and the use of artemisinin combination therapy (ACT) for the treatment of infection.[5] As a result, between 2000 and 2015 it was estimated that there was a 42% decline in incidents of infection and a 66% decline in the number of deaths in Africa.[5] One major cause for concern is the increasing occurence of resistance towards multiple prescribed antimalarials on the market. One of the earliest synthetic antimalarials, chloroquine (CQ) made massive strides in combating malarial infection, however resistance towards CQ, primarily due to its use as a monotherapy, has sparked the urgent need to develop newer antimalarial drugs.[7] Efforts such as Roll Back Malaria and the contribution of the Bill and Melinda Gates Foundation were a response to this dire need. It has been discovered that resistance to drugs like CQ and amodiaquine (AQ) is attributed to polymorphism in the gene *pfcrt* that codes for *P. falciparum* chloroquine resistance transporter protein (pfCRT).[8] The development of multiple drug resistance as a result of monotherapy resulted in the use of ACTs, the administration of artemisinin derivatives together with other antimalarial drugs such as AQ, mefloquine and lumefantrine. The use of ACTs today is the recommended chemotherapeutic treatment of malaria and has a high success rate in the treatment of uncomplicated and severe malaria. However, resistance towards artemisinin discovered in South-

East Asia poses an imminent problem.[9] Therefore, the search for new antiplasmodial targets and chemotherapeutic agents continues to be essential in the effort to effectively combat the disease. *N*-Myristoyl transferase (NMT) is an important enzyme that is ubiquitous in all eukaryotic cells. Using Myr-CoA as a myristate source, it catalyzes the irreversible addition of a myristate group to the *N*-terminal glycine residues of proteins, post- and co-translationally.[10] Research by Wright *et al.* has proven that *N*-myristoylation is essential for the viability of the rodent malaria parasite *P. berghei*, and partial knockdown of NMT expression resulted in reduction of parasitemia in vivo. Effective inhibition of NMT resulted in the inhibition of the parasite's ability to assemble the inner membrane complex, a critical subcellular organelle.[10] Yu *et al*. [11] identified an active inhibitor for *P. vivax* NMT, which shares an 81% sequence identity to *P. falciparum* NMT (pfNMT). This inhibitor, **RO-09-4609**, **(Figure 1)** was developed by Roche[12] in a campaign to develop inhibitors for *Candida albicans* NMT (CaNMT) and *Trypanasoma brucei* NMT (TbNMT), and was later identified via a "piggyback" approach as an inhibitor for pvNMT with an IC_{50} of 51 µM. **RO-09-4609** was further derivatized by introducing a piperidinyl ether group at the C4-position and various benzylic, phenethyl and 1-methylenenaphthyl amides and esters at the C2-position. These efforts lead to the discovery of a 3-methoxy benzoate 3-methyl benzofuran derivative, ***26***, with an improved pvNMT inhibition of 0.60 µM (Figure 1).



RO-09-4609
IC_{50} (pvNMT) 51 µM

26
IC_{50} (pvNMT) 0.60 µM

Figure 1. The 3-methyl benzofuran compound developed by Roche, **RO-09-4609b**, and the structurally modified 3-methoxy benzoate derivative ***26*** developed by Yu *et al*.[11]

A co-crystallized structure of ***26*** and pvNMT (PDB code 4B14) was obtained indicating key chemical interactions with nearby residues at the active site. This co-crystallized structure showed that the introduction of the 3-methoxy benzoate moiety resulted in π-π interactions with a nearby phenylalanine while the piperidine exhibited a cation-dipole interaction with a nearby tyrosine residue as well as ion-pair interaction with a *C*-terminal leucine residue. These additional interactions would account for the improved activity. Our research aim was to replace the 3-methyl benzofuran scaffold with various isostructural and 6,5-fused heterocycles to gain insight into the importance of the heterocyclic core as well as the importance of the methyl at the C3-position with regards to efficacy. Each heterocycle would subsequently be derivatized to specific benzylic, phenethyl and 1-methylenenaphthyl amides and esters as a short SAR study. Figure 2 illustrates the indole, 3-methyl indole, 1-methyl benzimidazole, benzoxazole and benzothiophene heterocycles intended to replace the benzofuran scaffold, as well as the aromatic ester and amides at the C2-position.

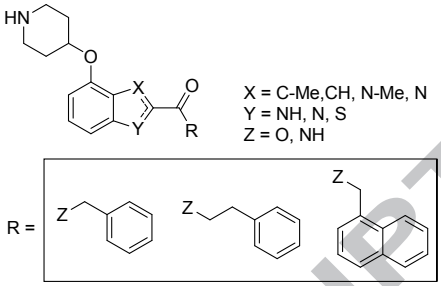
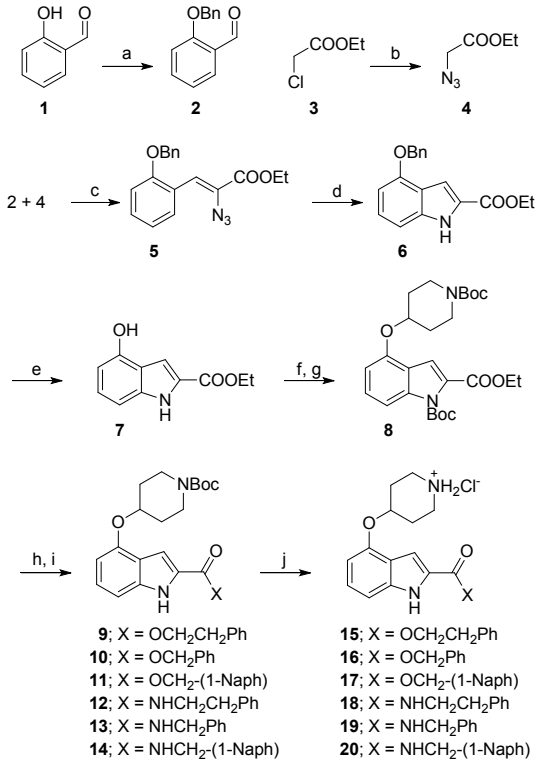


Figure 2. Generalized structure of the indole, 3-methyl indole, 1-methyl benzimidazole, benzoxazole and benzothiophene heterocycles indicating the various aromatic amide and ester groups at the C2-position.

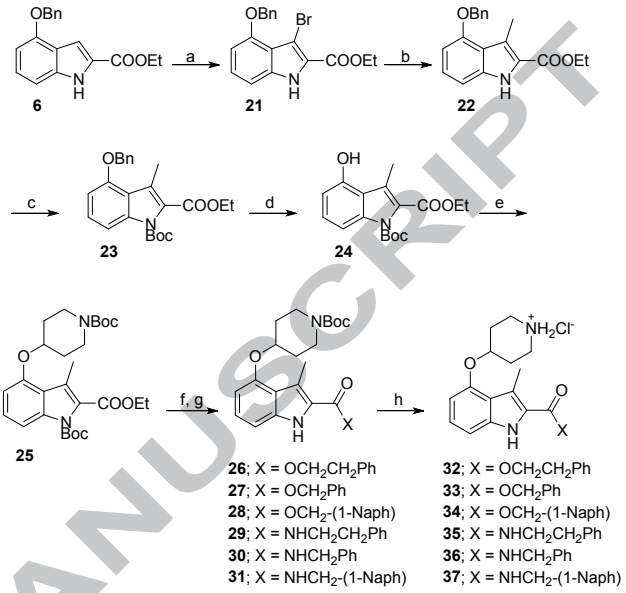
2. Chemistry

Scheme 1 shows the steps involved in the synthesis of the indole scaffold. **1** was benzylated with benzylbromide in DMF to produce aldehyde **2** in a 94% yield, while the reaction of sodium azide and **3** produced azide **4** in a 91% yield after purification. The Knoevenagel-condensation reaction between **2** and **4** was carried out in anhydrous ethanol with sodium ethoxide, and ethyl trifluoroacetate acting as a sacrificial electrophile. The aromatic vinyl azide **5** was isolated in a 55% yield. The subsequent Hemetsberger-Knittel indolization reaction was carried out by the addition of **5** to 1,3-dichlorobenzene at 160 °C, producing the desired indole precursor **6** in a 90% yield. Debenzylation of the indole was achieved with 10% Pd/C and H_2, affording phenol **7** in a 91% yield. This was followed by a Mitsunobu coupling with 4-hydroxy *N*-Boc piperidine which resulted in full conversion of **7** when the reaction was monitored my means of thin layer chromatography. Purification of the coupled product proved difficult as it co-eluted alongside the by-products of the Mitsunobu reaction. To overcome this issue the indole nitrogen was Boc-protected to decrease the polarity in relation to the Mitsunobu by-products, enabling effective separation to provide **8**. Subsequent reactions involved transesterifications between **8** and 2-phenylethanol, benzyl alcohol and 1-naphthalenemethanol as well as amidation reactions between **8** and 2-phenylethylamine, benzyl amine and 1-naphthylmethylamine. Transesterification was achieved by using the corresponding alcohol as solvent and K_3PO_4 as base to facilitate the transesterification reaction, affording compounds **9** and **10** in a 39% and 45% yield respectively. The transesterification between 1-naphthalenemethanol and **8** to yield the desired product **11** presented purification difficulties and as a result was taken crude to the subsequent, Boc-deprotection step to yield the desired product **17**. Deprotection of the piperidine ring was achieved with 4 M HCl in dioxane providing **17** in a 23% yield over two steps.



Scheme 1. Reagents and conditions: a) BnBr, Na_2CO_3, DMF, 94%; b) NaN_3, acetone, H_2O, 85%; c) NaOEt, EtOH, ethyl trifluoroacetate, -10 °C – r.t., 55%; d) 1,3-dichlorobenzene, 160 °C, 90%; e) 10% Pd/C, H_2, MeOH, 90%; f) PPh_3, DBAD, THF, 1-Boc-4-hydroxypiperidine, partial product purification; g) Boc_2O, Et_3N, DCM, 95% over two steps; h) aromatic alcohol (30 eq), K_3PO_4, 80 °C; i) aromatic amine (10 eq), DBU, ACN, 140 °C; j) 4 M HCl in dioxane, DCM, 0 °C

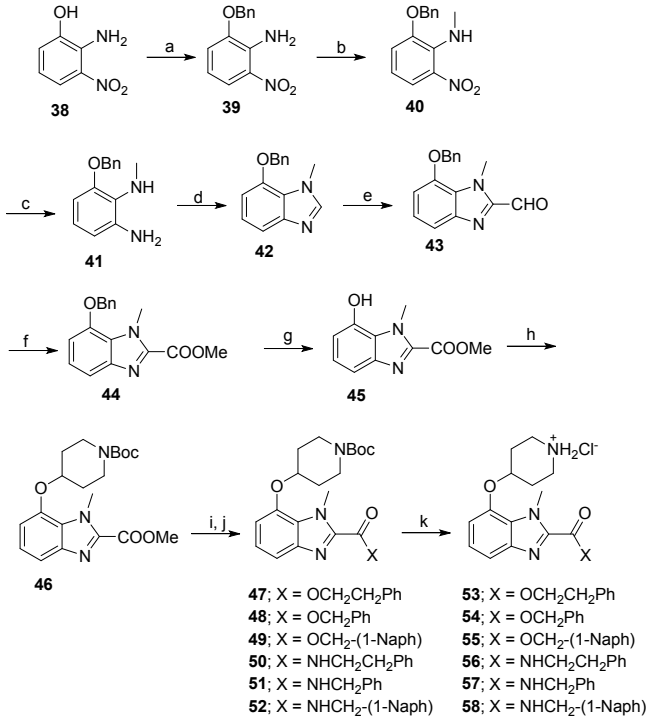
For the amidation reactions, **8** and the corresponding aromatic amine were taken up in acetonitrile in the presence of DBU and the reaction was heated to 140 °C for 10 – 20 hours, affording **12** – **14** in a 53 – 64% yield. In both transesterification and amidation steps, the Boc-group at the indole *N*1-position were thermally labile and were subsequently cleaved. Compounds **15**, **16** and **18** – **20** were obtained after Boc-deprotection of the 4-piperidinyloxy group using 4 M HCl in dioxane. The yields obtained for this step ranged between 79 – 97%. In Scheme 2 the synthesis of the 3-methyl indole scaffold is shown. **6** was regioselectively brominated with NBS in DMF to produce **21** in an 80% yield. A Suzuki-coupling of **21** and trimethylboroxine (TMB) produced the desired 3-methyl indole scaffold **22** in an 87% yield. Due to the purification difficulties faced for the Mitsunobu-coupling between **7** and 4-hydroxy *N*-Boc piperidine (Scheme 1), we pre-emptively decided to Boc-protect the 3-methyl indole nitrogen prior to the Mitsunobu-coupling affording **23** in a 99% yield. Subsequent debenzylation produced the 4-hydroxy indole **24** in a 36% yield. The low yield could be attributed to hydrogenation of the indole aryl ring, leading to the conversion of **23** to a 4-indolone by-product. The Mitsunobu-coupling between **24** and 4-hydroxy *N*-Boc piperidine afforded **25** in a 94% yield. Transesterification between **25** and benzyl alcohol yielded compound **27** in a 38% yield. Transesterifications yielding compounds **26** and **28** presented purification difficulties and were taken crude to the Boc-deprotection step to produce compounds **32** and **34** in a 38% and 49% yield respectively over two steps. Compounds **27** and **29** – **31** were Boc-deprotected to produce **33** and **35** – **37** in yields ranging between 38% and 73%.



Scheme 2. Reagents and conditions: a) NBS, DMF, 0 °C, 80%; b) $Pd(PPh_3)_4$, TMB, K_2CO_3, Dioxane, 110 °C, 87%; c) Boc_2O, Et_3N, DCM, 99%; d) 10% Pd/C, H_2, EtOH, 36%; e) PPh_3, DBAD, THF, 1-Boc-4-hydroxypiperidine, 94%; f) aromatic alcohol (30 eq), K_3PO_4, 80 °C; g) aromatic amine (30 eq), 140 °C; h) 4 M HCl in dioxane, DCM, 0 °C

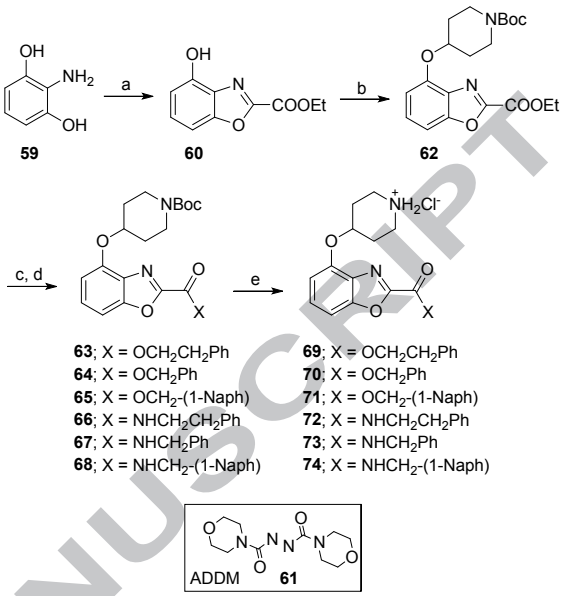
The synthesis of the benzimidazole scaffold is illustrated in Scheme 3. 2-Amino-3-nitrophenol **38** was benzylated to produce **39** in a 98% yield, this was followed by methylation of the amine to produce **40** in a 97% yield. The reduction of the nitro group produced phenylene diamine **41** in a 72% yield, which subsequently underwent cyclisation with trimethylorthoformate under neat conditions to produce the benzimidazole precursor **42** in a 97% yield. The C2-position of **42** was formylated using *n*-BuLi and DMF in a Bouveault type aldehyde synthesis[13] to produce aldehyde **43** in a 76% yield. Oxidative esterification of the aldehyde to the methyl ester yielded ester **44** in a 79% yield. Subsequent debenzylation to produce **45** and coupling with 4-hydroxy *N*-Boc piperidine produced **46** in a 76% yield. Transesterification of the carbomethoxy proved difficult at first as product degradation was observed when treated with the desired alcohol and K_3PO_4 at elevated temperatures. However, it was noticed that the ester was significantly more electrophilic than the indole counterpart and transesterification of **46** proceeded at room temperature providing **47** – **49** in yields ranging between 50% and 57%. Amidation also proceeded at room temperature affording compounds **50** – **52** in yields between 81% and 92%. Boc-deprotection of compounds **47** – **52** afforded the benzimidazole salts **53** – **58** in yields ranging between 83% – 95%. Scheme 5 illustrates the synthesis of the benzoxazole scaffold. The syntheses of oxazoles and benzoxazoles by way of an intramolecular cyclodehydration of 2-

hydroxyanilide derivatives under Mitsunobu reaction conditions have been well documented in the literature.[14,15]



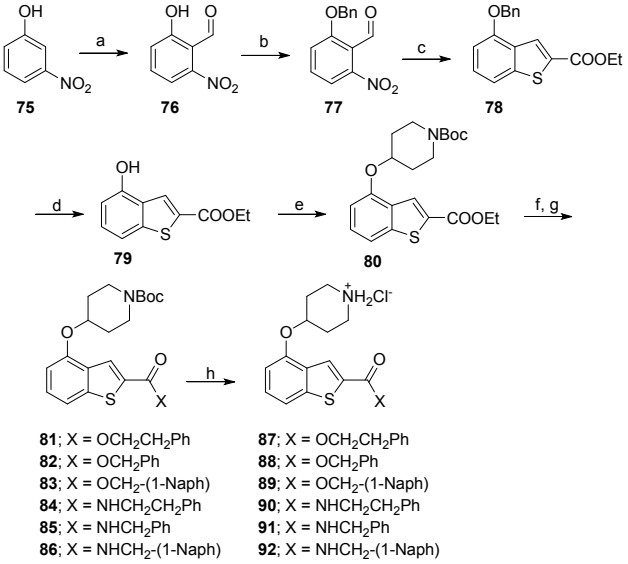
Scheme 3. Reagents and conditions: a) BnBr, K_2CO_3, DMF, 0 °C, 98%; b) NaH, MeI, THF, 0 °C, 97%, c) Fe, AcOH, EtOH, H_2O, sonication, 72%; d) trimethylorthoformate, *p*TsOH, 100 °C, 97%; e) *n*BuLi, THF, -78 °C then DMF, -78 – 0 °C, 76%; f) MeOH, KOH, I_2, 0 °C – r.t, 79%; g) 10% Pd/C, H_2, MeOH, 92%; h) PPh_3, DBAD, THF, 1-Boc-4-hydroxypiperidine, 76%; i) aromatic alcohol (20 – 30 eq), K_3PO_4, r.t; j) aromatic amine (10 eq), r.t; k) 4 M HCl in dioxane, DCM, 0 °C

With this in mind we envisaged synthesizing the desired benzoxazole intermediate with the ester group at the C2-position already installed using a one-pot conversion of 2-aminoresorcinol **59** to the substituted benzoxazole. **59** was chemoselectively acylated with ethyl chloro oxoacetate in THF. The reaction was monitored by TLC to determine that the resorcinol had been completely acylated after which dilution of the reaction mixture with THF and the addition of PPh_3 and DEAD lead to the formation of the cyclo-dehydrated product **60** in an 84% yield. The Mitsunobu coupling between **60** and 4-hydroxy *N*-Boc piperidine in the presence of DBAD as the Mitsunobu reagent, resulted in purification difficulties. This was overcome through the use of azodicarbonyl dimorpholide (ADDM) as the Mitsunobu reagent. Transesterification and amidation of **62** proved to be similar in nature to that of **46** whereby the transformation was achieved at room temperature. **63** – **65** were isolated in yields ranging between 24% and 53%, whereas **66** – **68** ranged between 86% – 96%. Boc-deprotection of **63** – **68** afforded compounds **69** – **74** in yields ranging between 69% – 97%. Scheme 4 illustrates the synthesis of the benzothiophene scaffold. 3-Nitrophenol **75** was formylated through a Duff reaction[14] using TFA and HMTA to produce aldehyde **76** in a 29% yield and was subsequently benzylated yielding compound **77**. The substitution/ condensation reaction between **77** and ethyl mercaptoacetate in the presence of K_2CO_3 in DMF produced the benzothiophene heterocycle **78** in a 95% yield over 2 days.



Scheme 5. Reagents and conditions: a) $ClCOCO_2Et$, Et_3N, THF, then PPh_3, DEAD, THF, 84%; b) ADDM, THF, DCM, PPh_3, 79%; c) aromatic alcohol (20 – 30 eq), K_3PO_4, r.t; d) aromatic amine (10 eq), THF, r.t; e) 4 M HCl in dioxane, DCM, 0 °C

Subsequent debenzylation produced **79** and a Mitsunobu coupling between **79** and 4-hydroxy *N*-Boc piperidine produced the coupled product **80** in a 99% yield. Transesterification was achieved at 70 °C producing **81** – **83** with yields between 51% and 88%. Amidation of **80** was produced **84** – **86** in yields between 50% – 77%, and final Boc-deprotection afforded compounds **87** – **92** in yields between 87% – 98%

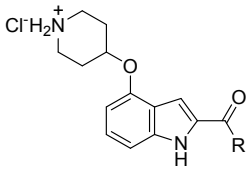
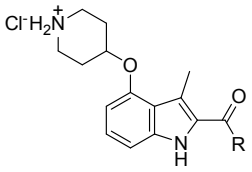
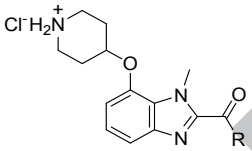
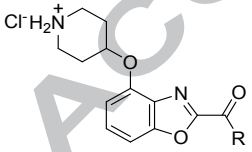
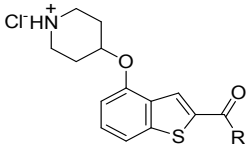


Scheme 6 Reagents and conditions: a) HMTA, TFA, 90 °C, 29%; b) BnBr, K_2CO_3, DMF, quant.; c) ethyl mercaptoacetate, K_2CO_3, DMF, 50 °C, 95%; d) 10% Pd/C, H_2, MeOH, 68%; e) PPh_3, DBAD, THF, 1-Boc-4-hydroxypiperidine, 76%; f) aromatic alcohol (26 eq), K_3PO_4, 70 °C; g) aromatic amine (20 eq), 145 °C; h) 4 M HCl in dioxane, DCM, 0 °C.

3. Results and discussion

The compounds of each heterocyclic series were tested against the chloroquine sensitive (CQS) NF54 strain of *P. falciparum*. The EC_{50} values corresponding to each compound are summarized in Table 1. We began with the whole cell assay rather than the enzymic assay for the simple reason that a compound which has high efficacy against the enzyme but has little impact on the whole cell is not a useful antiplasmodial agent. Thus the standards chloroquine and artemisinin were chosen these are well known and allow relatively easy interpretation of the whole cell data even thought neither is structurally equivalent to the fused heterocycles we synthesised.

Table 1: *In vitro* activity against *P. falciparum* (NF54)

Heterocyclic Series	Compound	NF54 EC_{50} (μM)
	**15**	6.53 ± 0.12
	16	3.39 ± 0.46
	17	0.83 ± 0.12
	18	3.1 ± 0.11
	19	3.74 ± 0.87
	20	0.90 ± 0.08
	**32**	3.90 ± 0.41
	33	0.56 ± 0.08
	34	0.74 ± 0.02
	35	3.4 ± 0.26
	36	6.11 ± 0.19
	37	0.74 ± 0.05
	**53**	11.10 ± 0.21
	54	13.28 ± 2.98
	55	7.37 ± 0.83
	56	8.69 ± 0.79
	57	8.80 ± 1.06
	58	1.15 ± 0.09
	**69**	n.a
	70	n.a
	71	n.a
	72	n.a
	73	n.a
	74	1.96 ± 0.18
	**87**	5.87 ± 0.17
	88	5.69 ± 0.22
	89	1.90 ± 0.09
	90	3.01 ± 0.06
	91	3.48 ± 0.26
	92	0.71 ± 0.02
	Chloroquine	13.0 ± 0.67 nM
	Artesunate	9.41 ± 0.72 nM

All benzoxazole compounds **69** – **73** apart from **74**, were inactive against *P. falciparum* NF54, which eliminated this heterocyclic core as a viable *P. falciparum* antiplasmodial series. When we compared the activity of the 3-methyl indole series with the indole series, no trend could be observed to indicate that one series was more active than the other. This indicated that the methyl at the C3-position in the 3-methyl indole series, which is isostructural to the proof of concept 3-methyl benzofuran scaffold, is not crucial for better whole-cell activity. Comparison of the benzothiophene and indole series proved interesting, as each aromatic ester and amide had comparable activity. This indicated that the heterocyclic scaffold has no significant effect on the activity of each compound and that activity is related to the aromatic ester/amide at the C2-position of each heterocycle. The isostructural benzimidazole series in relation to the 3-methyl indole series proved to be less active. The esters **53** – **55** were significantly less active than the esters **32** – **34**. The decreased activity of amides **56** – **58** relative to the analogous amides **35** – **37** were minor. No significant difference in efficacy was observed between the activity of the esters and the analogous amides in the 3-methyl indole and benzimidazole series with respect to the function of the methyl-group and the effect it would have on potency. However, this assumption could only be verified with a pfNMT assay to determine the significance of the methyl group of both 3-methyl indole and benzimidazole compounds, as the stability of the benzimidazole and 3-methyl indole compounds might be compromised in vitro. The most notable trend is the effect of the aromatic ester and amide substituents on the efficacy of each compound. Compounds containing the naphthylmethyl ester and amide substituent were significantly more effective than the other aromatic ester and amides, (except **55**), whereby **74** also indicated a low EC_{50} of 2.0 μM. The naphthylmethyl amides **20**, **37**, **58**, and **92** indicated that a naphthyl methyl amide was in fact the most preferred substituent for high potency, with a narrow range of activities ranging between 0.71 – 1.1 μM, reiterating the statement that the function of the heterocycle is not as important regarding efficacy as the C2-substituent would be.

From these results we can conclude that the structure of the heterocycle did have some moderate influence on activity. There are several avenues which would usefully be explored in the future. Firstly, to carry out the efficacy tests on the pfNMT enzyme. A correlation between the whole cell assay and the enzymic assay would suggest that our intended target is in fact responsible for the whole cell efficacy. These results with molecular modelling in the active site of the enzyme may shed some light on the moderate variation in efficacy observed for the heterocyclic cores themselves. Secondly, the lack of activity of the benzoxazole may be caused by an unexpected instability of the compound under the experiment conditions, or the compound may not be reaching the required site of action. Both of these possibilities can be explored. Finally, the indoles do appear on average to have the most potent activity. This core

could be taken forward to form new variants including substitution at different positions. It would also be useful to compare the efficacy of these compounds with those compounds already reported.

A data in brief file has been prepared for all compounds. Reported here is the synthesis of one compound in each series.

4. **Experimental***Chemistry*

4.1.1 *General information regarding to synthesis and characterization*

All chemicals used were bought from Merck, Fluka and Aldrich. Tetrahydrofuran (THF) and diethylether (Et_2O) were dried over sodium wire/sand and distilled under nitrogen with benzophenone as an indicator. Dichloromethane (DCM) was distilled over calcium hydride under nitrogen. Other solvents e.g. ethyl acetate, hexane and triethylamine were purified according to standard procedures.[15] The molarity of *n*-BuLi was determined using a method as described in the literature.[16] Reactions requiring anhydrous conditions were performed under an atmosphere of nitrogen or argon. All ^{1}H and ^{13}C nuclear magnetic resonance spectra were obtained using a 300 MHz Varian VNMRS (75 MHz for ^{13}C), a 400 MHz Varian Unity Inova (100 MHz for ^{13}C) or a 600MHz Varian Unity Inova (150 MHz for ^{13}C). *d*-Chloroform was used as standard solvent. Chemical shifts (δ) were recorded using residual chloroform peaks at δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR, and residual DMSO peaks at δ 2.50 in ^{1}H NMR and δ 39.51 in ^{13}C NMR. All chemical shifts are reported in ppm and coupling constants, *J*, are given in Hertz (Hz). All spectra were obtained at 25 °C. All NMR spectroscopy and mass spectrometry was performed by the CAF (Central Analytical Facility) Institute at Stellenbosch University. Infrared spectra were obtained using a Nexus Thermo-Nicolet FT-IR using the ATR. LC-MS purity data were obtained at CAF using a Waters Synapt G2 instrument, ESI positive, using a diode array as detection method. Compounds were detected at a wavelength of 280 nm. All chromatography was performed using either (or a combination of) ethyl acetate, methanol, ethanol, triethylamine, acetone and dichloromethane. Thin layer chromatography (TLC) was carried out on aluminium backed Merck silica gel 60 F254 plates. Visualization was achieved with a UV lamp, iodine vapour or by spraying with a Cerium Ammonium Molybdate solution (CAM), *p*-anisaldehyde or a ninhydrin solution and then heating. All column chromatography was carried out with Merck silica gel 60 (particle size 0.040-0.063 mm).

*4.1.2 Synthesis of compounds **(15)** – **(20)***

4.1.2.1 *2-(benzyloxy)benzaldehyde **(2)**:*

To a solution of salicylaldehyde **(1)** (7.71 g, 63.2 mmol), Na_2CO_3 (9.38 g, 88.5 mmol) in DMF (50 mL) was added 10.5 mL (88.5 mmol) benzyl bromide dropwise at 0 °C under an atmosphere of nitrogen. The mixture was stirred at room temperature for 2 hours, where the initial yellow solution turned milky white. The reaction was monitored until complete consumption of starting material was observed on TLC. The mixture was diluted with EtOAc (150 mL) and washed with water (4 x 50 mL), and then washed with brine. The organic phase was dried over $MgSO_4$, filtered and reduced *in vacuo*. The product was crystallized with EtOAc:hexane to provide the product as a white solid. 11.8 g, 88% yield; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) *δ* ppm 5.21 (s, 2 H), 7.07 (d, *J*=8.2 Hz, 2 H), 7.34 – 7.48 (m, 5 H), 7.1 – 7.58 (m, 1 H), 7.88 (dd, *J*=8.0, 1.8 Hz, 1 H), 10.58 (s, 1 H); HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_{14}H_{13}O_2$: 213.0916; found: 213.0920. Characterization data corresponded with literature values. [17] [18]

4.1.2.2 *Ethyl 2-azidoacetate **(4):***

To a mixture of acetone (75 mL) and water (25 mL) was added sodium azide (8.1 g, 124.3 mmol) and ethyl 2-chloroacetate **(2)** (7 mL, 65.4 mmol) and stirred overnight at room temperature. The heterogeneous mixture was diluted with water (70 mL) and washed with EtOAc (3 x 30 mL). The organic fractions were combined, dried over $MgSO_4$ and the solvent removed *in vacuo* to afford a light yellow liquid. 7.21 g, 85% yield; ^{1}H NMR (400 MHz, CHLOROFORM-*d*) *δ* ppm 1.26 (t, *J*=7.0 Hz, 3 H), 3.81 (s, 2 H), 4.20 (q, *J*=7.0 Hz, 2 H); HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_4H_8N_3O_2$: 130.0572; found: 130.0512. Characterization data corresponded with literature values.[19]

4.1.2.3 *(Z)-Ethyl 2-azido-3-(2-(benzyloxy)phenyl)acrylate **(5):***

To EtOH (60 mL, freshly distilled from Mg/I_2) was added 1.30 g sodium metal (divided in small pieces) under an atmosphere of nitrogen. While stirring, the temperature was kept below 10 °C until the complete dissolution of the sodium metal. 2-(Benzyloxy)benzaldehyde **(2)** (6.00 g, 28.3 mmol) was added to the solution and ethyl trifluoroacetate (6.7 mL, 56.5 mmol) was added via a syringe. The solution was cooled to -10 °C, and ethyl azidoacetate **(4)** (7.00 g, 56.5 mmol) was added dropwise over a period of 5 minutes. The yellow heterogeneous solution started to become more turbid during the addition of the ethyl azidoacetate. The reaction was stirred at -10 °C for 2 hours while the heterogeneous solution becomes slurry like. The precipitate was filtered with the aid of a vacuum pump and dried under vacuum to afford the desired compound in analytically pure form. 5.03 g, 55% yield.^{1}H NMR (300 MHz, CHLOROFORM-*d*) *δ* ppm 1.39 (t, *J*=7.1 Hz, 3 H), 4.36 (q, *J*=7.1 Hz, 2 H), 5.15 (s, 2 H), 6.96 (d, *J*=8.4 Hz, 1 H), 7.03 (t, *J*=7.3 Hz, 1 H), 7.28 – 7.49 (m, 6 H), 7.54 (s, 1 H), 8.24 (dd, *J*=7.8, 1.6 Hz, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) *δ* ppm 14.4, 62.3, 70.6, 112.5, 119.6, 121.0, 122.9, 125.5, 127.1 (2 C), 128.1, 128.8 (2 C), 130.8, 130.9, 137.0, 157.0, 164.0; HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_{18}H_{18}N_3O_3$: 324.1303; found: 324.1348. IR ATR (cm^{-1}): 2118, 1684, 1485, 1242.

4.1.2.4 *Ethyl 4-(benzyloxy)-1H-indole-2-carboxylate **(6):***

1,3-dichlorobenzene (7 mL) was heated to 160 °C to which **(5)** (700 mg, dissolved in 1 mL 1,3-dichlorobenzene) was added dropwise under an atmosphere of nitrogen. The slow addition of **(5)** resulted in the evolution of gas from the heated solution.

The reaction mixture was stirred for an additional 5 minutes and cooled to room temperature, where the desired product crystallized out of solution. The product was filtered off, and the remaining product dissolved in the mother liquor was purified by column chromatography over silica gel (20% EtOAc, 80% hexane) to afford the product as a white solid. Combined yield of 556 mg, 87%, R_f: 0.39 (15% EtOAc, 85% hexane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.42 (t, *J*=7.1 Hz, 3 H), 4.41 (q, *J*=7.1 Hz, 2 H), 5.23 (s, 2 H), 6.60 (d, *J*=7.8 Hz, 1 H), 7.04 (d, *J*=8.6Hz, 1 H), 7.19 – 7.24 (m, 1 H), 7.33 – 7.48 (m, 4 H), 7.52 (d, *J*=8.2 Hz, 2 H), 8.95 (br. s., 1 H); ^{13}C NMR (CHLOROFORM-*d*) δ ppm 14.4, 60.9, 69.9, 101.1, 105.0, 106.5, 119.3, 126.2, 126.3, 127.4, 127.9, 128.5, 137.1, 138.2, 153.7, 162.0; HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_{18}H_{18}NO_3$: 296.1287; found: 296.1283. Mp: 160 – 162 °C; IR ATR (cm^{-1}): 3321, 1682, 1620, 1242, 1195. Characterization data corresponded with literature values.[20]

4.1.2.5 *Ethyl 4-hydroxy-1H-indole-2-carboxylate* ***(7):***

(6) (700 mg, 3.41 mmol) and 70 mg 10% Pd/C was added to MeOH (12 mL) and placed under an atmosphere of H_2 via a balloon. The solution was stirred overnight, after which the solution was filtered through Celite® and the solvent reduced *in vacuo*. The compound was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford the product as a white solid. 87%, 423.1 mg. R_f: 0.23 (20% EtOAc, 80% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.43 (t, *J*=7.0 Hz, 3 H), 4.42 (q, *J*=7.0 Hz, 2 H), 5.23 (s, 1 H), 6.53 (dd, *J*=7.6, 0.7 Hz, 1 H), 7.02 (dt, *J*=8.3, 0.8 Hz, 1 H), 7.18 (dd, *J*=8.3, 7.6 Hz, 1 H), 7.34 (dd, *J*=2.2, 1.0 Hz, 1 H), 8.89 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.4, 61.1, 104.5, 104.7, 105.3, 118.0, 126.4, 138.5, 150.3, 160.5; HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_{11}H_{12}NO_3$: 206.0818; found: 206.0848; Mp: 156 – 158 °C; IR ATR (cm^{-1}): 3313, 1691, 1585, 1238, 1197, 1020. Characterization data corresponded with literature values.[20]

4.1.2.6 *1-tert-Butyl 2-ethyl 4-((1-(tert-butoxycarbonyl) piperidin-4-yl)oxy)-1H-indole-1,2-dicarboxylate* ***(8):***

To a solution of **(7)** (380 mg, 1.85 mmol), PPh_3 (930 mg, 4.62 mmol) and 1-Boc-4-hydroxypiperidine (1,21 g, 4.62 mmol) in THF (8 mL) was added DBAD (851 mg, 4.62 mmol) dissolved in 2 mL THF dropwise at 0 °C under an atmosphere of nitrogen. The solution was stirred overnight, followed by the removal of the solvent *in vacuo*. The crude product was loaded directly onto silica gel and the intermediate product was isolated together with di-*tert*-butyl hydrazine-1,2-dicarboxylate as co-eluent, (EtOAc 15%, hexane 85% an eluent). The fractions containing the intermediate product were collected, and the solvent reduced *in vacuo* to produce a white solid. The mixture was dissolved in DCM (12 mL) to which Et_3N (0.5 mL) was added and Boc_2O (2.83 g, 12.2 mmol, dissolved in 3 mL DCM) was added dropwise at 0 °C under an atmosphere of nitrogen. The reaction was stirred overnight, after which the solvent was reduced *in vacuo*. The compound was purified by column chromatography over silica gel (12% EtOAc, 88% hexane) to afford the product as a colourless semi-solid that solidified into a white solid. 859 mg, 95%. R_f: 0.39 (15% EtOAc, 85% hexane) ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.39 (t, *J*=7.2 Hz, 3 H), 1.48 (s, 9 H), 1.61 (s, 9 H), 1.77 – 1.89 (m, 2 H), 1.89 – 2.00 (m, 2 H), 3.38 – 3.49 (m, 2 H), 3.63 – 3.74 (m, 1 H), 4.37 (q, *J*=7.2 Hz, 2 H), 4.59 – 4.68 (m, 1 H), 6.67 (d, *J*=7.9 Hz, 1 H), 7.24 (d, *J*=0.7 Hz, 1 H), 7.26 – 7.33 (m, 1 H), 7.65 (d, *J*=8.5 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.2, 27.7 (s, 3 C), 28.4 (s, 3 C), 30.3 (s, 2 C), 40.3, 61.2, 72.2, 79.5, 84.4, 105.8, 107.7, 112.2, 119.3, 127.7, 129.3, 139.4, 149.2, 151.3, 154.7, 161.6; HRMS–ESI+: m/z $[M+H]^+$ calculated for $C_{26}H_{37}N_2O_7$: 489.2601; found: 489.2589; Mp: 85 – 89 °C; IR ATR (cm^{-1}): 2974, 1743, 1728, 1689, 1364, 1278, 1145, 1035.

Compounds **(9)** and **(10)** were synthesized from **(8)** via the same transesterification procedure. Compound **(8)**, K_3PO_4 (3 equivalents) and the alcohol used for transesterification (20 – 30 equivalents) were placed in a vial, purged with argon, sealed and heated to 80 °C for 10 – 20 hours. The reaction was monitored via TLC using either (15% EtOAc, 85% hexane) or (5% EtOAc, 95% DCM) as mobile phase to determine whether the starting material had been consumed. The K_3PO_4 was filtered off, and the alcohol removed via heating the solution to 50 °C and streaming compressed air over the solution. After the majority of the solvent volume has been evaporated off, the product was purified by column chromatography over silica gel (5% EtOAc, 95% DCM).

4.1.2.7 *Phenethyl 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1H-indole-2-carboxylate* ***(9):***

(8) (100 mg, 0.205 mmol), 2-phenylethanol (720 µL, 6.15 mmol) and K_3PO_4 (150 mg, 0.701 mmol) was heated to 80 °C. White solid, 37.2 mg, 39% yield, R_f: 0.69 (5% EtOAc, 95% DCM); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.54 (s, 9 H), 1.86 – 2.09 (m, 4 H), 3.15 (t, *J*=7.0 Hz, 2 H), 3.43 – 3.56 (m, 2 H), 3.70 – 3.81 (m, 2 H), 4.61 (t, *J*=7.0 Hz), 4.66 – 4.75 (m, 1 H), 6.58 (d, *J*=7.6 Hz, 1 H), 7.05 (d, *J*=8.2 Hz, 1 H), 7.20 – 7.27 (m, 2 H), 7.28 – 7.43 (m, 6 H), 9.09 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.5 (2 C), 35.3, 40.7, 65.3, 72.0, 79.6, 102.6, 105.0, 106.5, 120.0, 126.0, 126.3, 126.6, 128.5 (2 C), 128.9 (2 C), 137.6, 138.5, 152.0, 154.8, 161.8; HRMS–ESI-: m/z $[M-H]^-$ calculated for $C_{27}H_{31}N_2O_5$: 463.2233; found: 463.2231; Mp: 131 – 134 °C; IR ATR (cm^{-1}): 3314, 2928, 1692, 1666, 1582, 1516, 1355.

4.1.2.8 *Benzyl 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1H-indole-2-carboxylate* ***(10):***

(8) (100 mg, 0.205 mmol), benzyl alcohol (640 µL, 6.15 mmol) and K_3PO_4 (150 mg, 0.701 mmol) was heated to 80 °C. White solid, 41.3 mg, 45 % yield, R_f: 0.36 (15% EtOAc, 85% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.79 – 2.06 (m, 4 H), 3.39 – 3.52 (m, 2 H), 3.65 – 3.79 (m, 2 H), 4.63 – 4.73 (m, 2 H), 5.42 (s, 2 H), 6.55 (d, *J*=7.6 Hz, 1 H), 7.02 (d, *J*=8.2 Hz, 1 H), 7.18 – 7.25 (m, 1 H), 7.34 – 7.57 (m, 6 H), 9.21 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.4 (2 C), 40.7 (2 C), 66.6, 71.9, 79.5, 102.4, 104.9, 106.8, 120.0, 125.8,

126.3, 128.3 (2 C), 128.3, 128.6 (2 C), 135.7, 138.6, 152.0, 154.8, 161.8; HRMS–ESI-: m/z [M-H]$^-$ calculated for $C_{26}H_{29}N_2O_5$: 449.2076; found: 469.2072; Mp: 147 – 149 °C; IR ATR (cm^{-1}): 3318, 2959, 1702, 1686, 1583, 1518, 1392.

Compounds **(12)** – **(14)** were synthesized from **(8)** via the same procedure. Compound **(8)** and the aromatic amine used for the amidation reaction (10 equivalents) were placed in a vial, to which was added acetonitrile (1 mL) and DBU (15 µL). The vial was purged with argon, sealed and heated to 140 °C for 10 – 20 hours. The reaction was monitored via TLC using (50% EtOAc, 50% hexane) as mobile phase to determine whether the starting material has been consumed. The product was purified by column chromatography over silica gel (30% EtOAc, 70% hexane to 100% EtOAc).

Compounds **(15)** – **(20)** with the exception of **(17)** were synthesized from **(9)** – **(14)** via the same procedure. In a small flask was added the Boc-protected compound and DCM (1 mL) followed by the addition of 4M HCl/dioxane (1 mL). The solution was stirred for one to two hours, after which the solvent was reduced *in vacuo*. A small amount of DCM was added followed by the addition of EtOAc which caused the salt to precipitate out of solution. The solvent was reduced *in vacuo* and the product dried under vacuum.

4.1.2.9 *4-((2-(Phenethoxycarbonyl)-1H-indol-4-yl)oxy)piperidin-1-ium chloride* ***(15):***

25.5 mg, 79% yield, white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.91 – 2.02 (m, 2 H), 2.12 – 2.21 (m, 2 H), 3.05 (t, *J*=6.8 Hz, 2 H), 3.07 – 3.15 (m, 2 H), 3.21 – 3.30 (m, 2 H), 4.48 (t, *J*=6.8 Hz, 2 H), 4.78 – 4.85 (m, 1 H), 6.65 (d, *J*=7.8 Hz, 1 H), 7.05 (d, *J*=8.2 Hz, 1 H), 7.13 (d, *J*=1.2 Hz, 1 H), 7.14 – 7.20 (m, 1 H), 7.19 – 7.37 (m, 5 H), 9.24 (br. s., 2 H), 11.92 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 27.0 (2 C), 34.5, 40.2 (2 C), 64.9, 68.8, 102.3, 105.1, 105.9, 118.9, 125.7, 126.0, 126.4, 128.4 (2 C), 128.9 (2 C), 137.9, 139.0, 150.8, 161.0; HRMS-TOF MS ES+: m/z [M+H]$^+$ calculated for $C_{22}H_{25}N_2O_3$: 365.1865; found: 365.1859; Purity: >99%; Mp: 215 – 217 °C; IR ATR (cm^{-1}): 3191, 2927, 1712, 1581, 1526, 1349, 1240, 1189.

4.1.2.10 *4-((2-((Naphthalen-1-ylmethoxy)carbonyl)-1H-indol-4-yl)oxy)piperidin-1-ium chloride* ***(17):***

(8) (100 mg, 0.205 mmol), K_3PO_4 (150 mg, 0.742 mmol) and naphthalen-1-ylmethanol (158 mg, 1.00 mmol) was added to a vial and the mixture stirred at 100 °C overnight where compound (**11)** could be observed by way of TLC. The mixture was dissolved in DCM (3 mL) and the K_3PO_4 filtered off. The solvent was reduced *in vacuo* and the crude product dissolved in DCM (1 mL) to which 4 M HCl/dioxane (1 mL) was added and stirred for 2 hours. The solvent was reduced *in vacuo* and the product was purified by column chromatography over silica gel (100% DCM to 10% MeOH, 90% DCM) to afford the product as a white solid. 20.4 mg, 23% yield over two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 – 1.98 (m, 2 H), 2.06 – 2.18 (m, 2 H), 3.01 – 3.12 (m, 2 H), 3.17 – 3.30 (m, 2 H), 4.75 – 4.83 (m, 1 H), 5.85 (s, 2 H), 6.63 (d, *J*=7.4 Hz, 1 H), 7.04 (d, *J*=8.2 Hz, 1 H), 7.13 – 7.19 (m, 2 H), 7.52 – 7.66 (m, 3 H), 7.71 (d, *J*=7.3 Hz, 1 H), 7.96 – 8.03 (m, 2 H), 8.14 (d, *J*=8.6 Hz, 1 H), 8.77 (br. s, 1 H), 8.98 (br. s, 1 H), 11.96 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 27.1 (2 C), 40.2 (2 C), 64.2, 68.9, 102.3, 105.5, 105.9, 118.9, 123.6, 125.4, 125.8, 125.9, 126.1, 126.7, 127.3, 128.6, 129.0, 131.1, 131.6, 133.3, 139.2, 150.9, 161.0; HRMS-TOF MS ES+: m/z [M+H]$^+$ calculated for $C_{25}H_{25}N_2O_3$: 401.1865; found: 401.1867; Purity: >99%; Mp: 211 – 214 °C; IR ATR (cm^{-1}): 3224, 2929, 1713, 1581, 1514, 1345, 1233, 1186.

4.1.3 Synthesis of compounds ***(32) – (37)***

4.1.3.1 *Ethyl 4-(benzyloxy)-3-bromo-1H-indole-2-carboxylate* ***(21):***

To a solution of **(6)** (1.14 g, 3.87 mmol) in DMF (15 mL) was added NBS (178 mg, 4.25 mmol, dissolved in 2 mL DMF) dropwise and stirred for 1 hour at 0 °C. The reaction mixture was diluted with EtOAc (100 mL), and washed with water (4 x 100 mL), followed by a wash with brine. The organic layer was dried over $MgSO_4$ and reduced *in vacuo*. The compound was purified by column chromatography over silica gel (25% EtOAc, 75% hexane) to afford the product as a white solid. 1.17 g, 80% yield. R_f: 0.44 (25% EtOAc, 75% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δppm 1.46 (t, *J*=7.04 Hz, 3 H), 4.45 (q, *J*=7.19 Hz, 2 H), 5.26 (s, 2 H), 6.61 (dd, *J*=7.78, 0.6 Hz, 1 H), 7.01 (dd, *J*=8.36, 0.7 Hz, 1 H), 7.24 (dd, *J*=8.36, 7.78 Hz, 1 H), 7.30 – 7.45 (m, 3 H), 7.57 – 7.64 (m, 2 H), 8.98 (br. s., 1 H) ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.4, 61.4, 70.2, 95.9, 102.2, 105.2, 118.0, 123.3, 127.1 (2 C), 127.2, 127.7, 128.4 (2 C), 136.9, 137.2, 154.2, 161.1; HRMS–ESI+: m/z [M+H]$^+$ calculated for $C_{18}H_{17}NO_3Br$: 374.0392; found: 374.0398; Mp: 164 – 166 °C; IR ATR (cm^{-1}): 3307, 1676, 1576, 1507, 1249, 1199, 1099.

4.1.3.2 *Ethyl 4-(benzyloxy)-3-methyl-1H-indole-2-carboxylate* ***(22):***

In a flask containing **(21)** (1.00g, 4.74 mmol), K_2CO_3 (1.97 g, 14.2 mmol), $Pd(PPh_3)_4$ (548 mg, 0.474 mmol) and trimethylboroxine (729 µL, 5.21 mmol), was added 24 mL dioxane under an atmosphere of nitrogen and stirred at 110 °C for 6 h followed by stirring at room temperature overnight. The reaction mixture was filtered through a plug of Celite® and the solvent reduced *in vacuo*. The compound was purified by column chromatography over silica gel (15% EtOAc, 85% hexane) to afford the product as a white solid. 725 mg, 87%. R_f: 0.37 (15% EtOAc, 85% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.43 (t, *J*=7.0 Hz, 3 H), 2.84 (s, 3 H), 4.42 (q, *J*=7.0 Hz, 2 H), 5.22 (s, 2 H), 6.54 (d, *J*=7.8 Hz, 1 H), 6.97 (dd, *J*=8.3, 0.7 Hz, 1 H), 7.16 – 7.22 (m, 1 H), 7.33 – 7.46 (m, 3 H), 7.50 – 7.56 (m, 2 H), 8.63 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 12.4, 14.5, 60.6, 69.9, 100.6, 104.9, 119.0, 121.5, 122.3, 126.4, 127.3 (2 C), 127.8, 128.6 (2 C), 137.2, 137.7, 155.7, 162.7; HRMS–ESI+: m/z [M+H]$^+$ calculated for $C_{19}H_{20}NO_3$: 310.1443; found: 310.1445; Mp: 149 – 150 °C; IR ATR (cm^{-1}): 3323 2916, 1661, 1351, 1246, 1198, 1099.

4.1.3.3 *1-tert-Butyl 2-ethyl 4-(benzyloxy)-3-methyl-1H-indole-1,2-dicarboxylate* ***(23):***

To a solution of **(22)** (826 mg, 2.67 mmol) and DMAP (20 mg, 0.164 mmol) in DCM (10 mL) was added Boc_2O (680 mg, 3.20 mmol, dissolved in 2 mL DCM) dropwise and stirred for 3 hours. The solvent was reduced *in vacuo* and the product purified by column chromatography over silica gel (10% EtOAc, 90% hexane) to afford the product as a white solid. 1.09 g, 99% yield. R_f: 0.43 (10% EtOAc, 90% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.41 (t, *J*=7.1 Hz, 3 H), 1.64 (s, 9 H), 2.60 (s, 3 H), 4.41 (q, *J*=7.2 Hz, 2 H), 5.19 (s, 2 H), 6.72 (d, *J*=7.9 Hz, 1 H), 7.26 – 7.32 (m, 1 H), 7.32 – 7.53 (m, 5 H), 7.71 (d, *J*=8.4 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.9, 14.2, 27.9 (3 C), 61.1, 70.0, 84.1, 104.6, 107.9, 119.0, 123.6, 125.7, 127.2 (2 C), 127.4, 127.8, 128.5 (2 C), 136.8, 138.3, 149.5, 154.6, 162.7.

4.1.3.4 *Ethyl 4-hydroxy-3-methyl-1H-indole-2-carboxylate* ***(24):***

(23) (1.09 g, 2.66 mmol) and Pd/C (10%, 245 mg, 0229 mmol) was placed in a flask, evacuated and purged with hydrogen from a balloon, to which was added EtOH (10 mL) and stirred overnight at room temperature under an atmosphere of hydrogen. The mixture was filtered through a plug of Celite® and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel (30% EtOAc, 70% hexane) to afford the product as a white solid. 296 mg, 36% yield. R_f: 0.50 (30% EtOAc, 70% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.41 (t, *J*=7.2 Hz, 3 H), 1.62 (s, 9 H), 2.60 (s, 3 H), 4.43 (q, *J*=7.1 Hz, 2 H), 6.58 (dd, *J*=7.8, 0.7 Hz, 1 H), 6.73 (s, 1 H), 7.09 – 7.19 (m, 1 H), 7.58 (dd, *J*=8.4, 0.7 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 11.6, 14.2, 28.0 (3 C), 61.5, 84.3, 107.1, 108.5, 118.0, 124.4, 125.4, 127.7, 138.8, 149.7, 152.2, 163.5.

4.1.3.5 *1-tert-Butyl 2-ethyl 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-3-methyl-1H-indole-1,2-dicarboxylate* ***(25):***

(24) (238 mg, 0.745 mmol), PPh_3 (294 mg, 1.12 mmol) and 1-Boc-4-hydroxypiperdine were dissolved in THF (4.7 mL) after which DBAD (258 mg, 1.12 mmol, dissolved in 1mL THF) was dropwise at 0 °C under an atmosphere of nitrogen, and stirred overnight. The solvent was reduced *in vacuo* and the product purified by column chromatography over silica gel (15% EtOAc, 85% hexane) to afford the product as a semi solid. 352 mg, 94% yield. R_f: 0.44 (15% EtOAc:85% hexane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.38 (t, *J*=7.0 Hz, 3 H), 1.45 (s, 9 H), 1.59 (s, 9 H), 1.79 – 1.90 (m, 2 H), 1.90 – 2.01 (m, 2 H), 2.55 (s, 3 H), 3.43 – 3.53 (m, 2 H), 3.55 – 3.66 (m, 2 H), 4.37 (q, *J*=7.3 Hz, 2 H), 4.61 – 4.69 (m, 1 H), 6.62 (d, *J*=8.2 Hz, 1 H), 7.19 – 7.29 (m, 1 H), 7.64 (d, *J*=8.2 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 12.0, 14.0, 27.7 (3 C), 28.2 (3 C), 30.1 (2 C), 40.1 (2 C), 60.9, 71.4, 79.3, 83.9, 105.0, 107.4, 119.3, 123.2, 125.6, 127.2, 138.4, 149.2, 152.8, 154.5, 162.5; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{27}H_{39}N_2O_7$: 503.2757; found: 503.2758; IR ATR (cm^{-1}): 2978, 1723, 1692, 1592, 1214, 1156, 1096, 1024.

4.1.3.6 *Benzyl 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-3-methyl-1H-indole-2-carboxylate* ***(33):***

(25) (80 mg, 0.159 mmol), K_3PO_4 (119 mg, 0.48 mmol) and benzyl alcohol (500 µL, 4.85 mmol) were added to a vial. The vial was sealed and the mixture stirred at 120 °C for 10 hours. The K_3PO_4 was filtered off, and the alcohol removed via heating the solution to 50 °C and streaming compressed air over the solution. After the majority of the solvent volume had been evaporated off, the product was purified by column chromatography over silica gel (5% EtOAc, 95% DCM) to afford the product as a white solid. 28 mg, 38% yield. R_f: 0.61 (5% EtOAc, 95% DCM) (^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.53 (s, 9 H), 1.85 – 2.06 (m, 4 H), 2.85 (s, 3 H), 3.56 (s, 2 H), 3.59 – 3.70 (m, 2 H), 4.64 – 4.75 (m, 1 H), 5.40 (s, 2 H), 6.45 (d, *J*=8.2 Hz, 1 H), 6.90 (d, *J*=8.2 Hz, 1 H), 7.13 – 7.20 (m, 1 H), 7.28 – 7.52 (m, 5 H), 8.73 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 12.5, 28.4 (3 C), 30.2 (2 C), 40.3 (2 C), 66.3, 71.2, 79.6, 101.1, 104.5, 119.4, 121.9, 121.9, 126.5 (2 C), 126.9, 128.3, 128.6 (2 C), 135.9, 137.9, 154.0, 154.8, 162.2; HRMS-TOF MS ES+: m/z $[M+Na]^+$ calculated for $C_{27}H_{32}N_2O_5Na$: 488.2287; found: 488.2231; Mp: 121 – 124 °C, IR ATR (cm^{-1}): 3337, 2928, 1668, 1580, 1511, 1422, 1248, 1229, 1090.

Compounds **(35)** – **(37)** were synthesized via the same procedure. Compound **(25)** and the aromatic amine used for the amidation reaction (30 equivalents) were placed in a vial. The vial was purged with argon, sealed and heated to 140 °C for 30 hours. The reaction was monitored via TLC using (50% EtOAc, 50% hexane) as mobile phase to determine whether the starting material has been consumed. The product was purified by column chromatography over silica gel (30% EtOAc, 70% hexane to 100% EtOAc).

4.1.3.7 *tert-Butyl 4-((3-methyl-2-(phenethylcarbamoyl)-1H-indol-4-yl)oxy)piperidine-1-carboxylate* ***(35):***

21 mg, 34% yield, yellow solid. R_f: 0.35 (30% EtOAc, 70% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.83 – 1.95 (m, 2 H), 1.95 – 2.07 (m, 2 H), 2.59 (s, 3 H), 2.99 (t, *J*=6.7 Hz, 2 H), 3.41 – 3.54 (m, 2 H), 3.62 – 3.74 (m, 2 H), 3.83 (q, *J*=6.5 Hz, 2 H), 4.64 – 4.72 (m, 1 H), 6.04 (t, *J*=5.3 Hz, 1 H), 6.46 (d, *J*=7.6 Hz, 1 H), 6.97 (d, *J*=7.6 Hz, 1 H), 7.09 – 7.16 (m, 1 H), 7.23 – 7.40 (m, 5 H), 9.29 (br. s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 12.1, 28.4 (3 C), 30.4 (2 C), 35.6, 40.6 (2 C), 40.8, 71.5, 79.6, 101.2, 104.7, 112.5, 119.2, 125.1, 126.4, 126.7 (2 C), 128.5, 128.8 (2 C), 137.1, 138.7, 153.5, 154.8, 162.6; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{28}H_{36}N_3O_4$: 478.2706; found: 478.2710; Mp: 168 – 170 °C, IR ATR (cm^{-1}): 3253, 2929, 1681, 1627, 1545, 1422, 1259, 1098.

Compounds **(33)** and **(35)** – **(37)** were synthesized via the same procedure. In a small flask was added the Boc-protected compounds **(27)** and **(29)** – **(31)** separately dissolved in DCM (1 mL) followed by the addition of 4M HCl/dioxane (1 mL). The solution was stirred for one hour, after which the solvent was reduced *in vacuo*. A small amount of DCM was added followed

by the addition of EtOAc which caused the salt to precipitate out of solution. The solvent was reduced *in vacuo* and the product dried under vacuum.

4.1.3.8 *4-((3-Methyl-2-(phenethoxycarbonyl)-1H-indol-4-yl)oxy)piperidin-1-ium chloride (32):*

In a vial was added **(25)** (80 mg, 0.159 mmol), K_3PO_4 (110 mg, 0.518 mmol) and 2-phenyl ethanol (400 µL, 1.00 mmol) and stirred neat at 100 °C overnight until compound **(26)** was observed by way of TLC. The mixture was dissolved in DCM (3 mL) and the K_3PO_4 filtered of. The solvent was reduced *in vacuo* and the crude residue redissolved in DCM (1 mL) to which 4M HCl/dioxane (1 mL) was added and stirred for 2 hours. The solvent was reduced *in vacuo* and the product was purified by column chromatography over silica gel using gradient elution (100% DCM to 10% MeOH, 90% DCM) to afford the product as a white solid. 12.3 mg, 19% yield over two steps. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.89 – 2.02 (m, 2 H), 2.10 – 2.23 (m, 2 H), 2.67 (s, 3 H), 3.06 (t, *J*=6.8 Hz, 2 H), 3.08 – 3.24 (m, 4 H), 4.50 (t, *J*=6.8 Hz, 2 H), 4.76 – 4.84 (m, 1 H), 6.55 (d, *J*=7.8 Hz, 1 H), 6.97 (d, *J*=8.2 Hz, 1 H), 7.08 – 7.14 (m, 1 H), 7.19 – 7.38 (m, 5 H), 8.87 – 9.20 (m, 2 H), 11.42 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 12.1, 27.0 (2 C), 34.5, 40.3 (2 C), 64.7, 68.6, 101.1, 105.5, 118.4, 119.0, 122.0, 125.8, 126.4, 128.4 (2 C), 128.9 (2 C), 138.1, 138.3, 152.8, 161.8; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{23}H_{27}N_2O_3$: 379.2022; found: 379.2013; Purity: 77.1%; Mp: 188 – 191 °C, IR ATR (cm^{-1}): 3345, 2926, 1681, 1615, 1579, 1453, 1356, 1243, 1087.

4.1.3.9 *4-((3-Methyl-2-((naphthalen-1-ylmethoxy)carbonyl)-1H-indol-4-yl)oxy)piperidin-1-ium chloride **(34):***

In a vial was added **(25)** (57 mg, 0.114 mmol), K_3PO_4 (88.0 mg, 0.426 mmol) and naphthalen-1-yl-methanol (242 mg, 1.53 mmol) and stirred at 100 °C overnight until compound **(28)** was observed by way of TLC. The mixture was dissolved in DCM (3 mL) and the K_3PO_4 filtered off. The solvent was reduced *in vacuo* and the crude dissolved in DCM (1 mL) to which 4M HCl/dioxane (1 mL) was added and stirred for 2 hours. The solvent was reduced *in vacuo* and the product was purified by column chromatography over silica gel using a gradient elution (100% DCM to 10% MeOH,90% DCM) to afford the product as a white solid. 25.1 mg, 49% yield. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 – 2.00 (m, 2 H), 2.07 – 2.20 (m, 2 H), 2.68 (s, 3 H), 3.02 – 3.20 (m, 4 H), 4.73 – 4.84 (m, 1 H), 5.83 (s, 2 H), 6.53 (d, *J*=7.8 Hz, 1 H), 6.96 (d, *J*=8.2 Hz, 1 H), 7.07 – 7.14 (m, 1 H), 7.50 – 7.66 (m, 3 H), 7.71 (d, *J*=6.6 Hz, 1 H), 7.93 – 8.03 (m, 2 H), 8.16 (d, *J*=8.2 Hz, 1 H), 8.96 (br. s, 2 H), 11.45 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 12.6, 27.4 (2 C), 40.7 (2 C), 64.3, 69.0, 101.6, 106.0, 118.9, 120.0, 122.2, 124.1, 125.9, 126.3, 126.5, 127.1, 127.8, 129.0, 129.4, 131.5, 132.2, 133.7, 138.8, 153.2, 162.1; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{26}H_{27}N_2O_3$: 415.2022; found: 415.2010; Purity: > 98%; Mp: 197 – 200 °C, IR ATR (cm^{-1}): 3338, 2927, 1682, 1578, 1509, 1357, 1254, 1086.

*4.1.4 Synthesis of compounds **(53) – (58)***

4.1.4.1 *2-(Benzyloxy)-6-nitroaniline **(39):***

To a solution of 2-amino-3-nitrophenol **(38)** (1.00 g, 6.48 mmol) in DMF (15mL) was added K_2CO_3 (1.34g, 9.72 mmol) at -10 °C, followed by the addition of benzyl bromide (1.00 mL, 8.42 mmol) under an atmosphere of nitrogen. The mixture was stirred at -10 °C for 8 hours to prevent *N*-alkylation. The mixture was added to EtOAc (100mL) and was washed with water (4 x 100 mL) followed by a wash with brine. The organic phase was dried over $MgSO_4$, and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel using a gradient elution (10% EtOAc, 90% hexane to 30% EtOAc, 70% hexane gradient) to afford a red oil. 1.55 g, 98% yield. R_f: 0.55 (20% EtOAc:80% hexane) ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 5.13 (s, 2 H), 6.51 (br. s, 2 H), 6.59 (dd, *J*=8.9, 7.8 Hz, 1 H), 6.97 (dd, *J*=7.8, 0.9 Hz, 1 H), 7.34 – 7.51 (m, 5 H), 7.75 (dd, *J*=8.9, 1.2 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 71.1, 114.4, 114.8, 117.5, 127.6 (2 C), 128.4, 128.7 (2 C), 131.6, 135.7, 137.1, 147.1. Characterization data corresponded with literature values.[21]

4.1.4.2 *2-(Benzyloxy)-N-methyl-6-nitroaniline **(40):***

To a mixture of NaH (144 mg, 60% dispersion in oil, 3.59 mmol) in THF (14 mL) was added **(39)** (800 mg, 3.27 mmol, dissolved in 2 mL THF) dropwise at -10 °C under an atmosphere of nitrogen. The mixture was stirred for 30 minutes to which MeI (224 µL, 3.59 mmol) was added. The mixture was allowed to reach room temperature and left stirring overnight. The mixture was quenched with water (10 mL) and the product was extracted with EtOAc (2 x 60 mL). The organic phase was washed with brine, dried over $MgSO_4$ and the solvent was removed *in vacuo*. The product was purified by column chromatography over silica gel (15% EtOAc, 85% hexane) to afford a red solid. 820 mg, 97% yield. R_f: 0.59 (15% EtOAc, 85% hexane) ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.15 (s, 3 H), 5.07 (s, 2 H), 6.59 (dd, *J*=8.7, 7.8 Hz, 1 H), 6.99 (dd, *J*=7.8, 1.4 Hz, 1 H), 7.35 – 7.49 (m, 5 H), 7.73 (dd, *J*=8.7, 1.4 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 34.0, 71.8, 115.2, 117.5, 118.9, 127.6 (2 C), 128.2, 128.6 (2 C), 134.7, 135.9, 139.6, 149.6, HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{14}H_{15}N_2O_3$: 259.1083; found: 259.1076.

4.1.4.3 *6-(Benzyloxy)-N^1-methylbenzene-1,2-diamine **(41):***

In an open flask was added **(40)** (820 mg, 3.17 mmol), glacial acetic acid (6.6 mL), EtOH (6.6 mL), water (3.3 mL) and iron powder (880 mg, 15.9 mmol). The mixture was subjected to sonication at 30 °C for 3 hours, turning the red solution to dark yellow. The iron powder was removed via a magnet. The mixture was diluted with EtOAc (100 mL) and washed with a 2M KOH solution (2 x 60 mL). The organic phase was dried over $MgSO_4$, and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford a yellow oil. 520 mg, 72% yield. R_f: 0.28

(50% EtOAc, 50% hexane) ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.82 (s, 3 H), 3.98 (s, 3 H), 5.17 (s, 2 H), 6.47 – 6.59 (m, 2 H), 6.93 – 7.04 (m, 1 H), 7.41 – 7.65 (m, 5 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 34.1, 70.1, 102.2, 108.9, 123.3, 125.5, 127.2 (2 C), 127.6, 128.2 (2 C), 137.0, 141.8, 152.1, HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{14}H_{17}N_2O$: 229.1341; found: 229.1345; Characterization data corresponded with literature values.[22]

4.1.4.4 *7-(Benzyloxy)-1-methyl-1H-benzo[d]imidazole* ***(42):***

In an open 10 mL round bottom flask was added **(41)** (956 mg, 4.19 mmol), trimethyl orthoformate (550 µL, 5.02 mmol) and *p*TsOH (20 mg). The mixture was heated to 100 °C for 40 minutes. The solution was diluted with DCM (2 mL) and purified by column chromatography over silica gel (100% EtOAc) to afford a white solid. 967 mg, 97% yield. R_f: 0.56 (100% EtOAc); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 4.04 (s, 3 H), 5.19 (s, 2 H), 6.78 (d, *J*=8.2 Hz, 1 H), 7.12 – 7.18 (m, 1 H), 7.34 – 7.50 (m, 6 H), 7.71 (s, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 33.9, 70.4, 104.6, 113.3, 122.4, 124.4, 127.4 (2 C), 128.0, 128.6 (2 C), 136.7, 143.8, 146.0, 146.6; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{15}H_{15}N_2O$: 239.1184; found: 239.1135; Mp: 114 – 116 °C; IR ATR (cm^{-1}): 3092, 2866, 1620, 1586, 1499, 1378, 1286, 1259, 1077.

4.1.4.5 *7-(Benzyloxy)-1-methyl-1H-benzo[d]imidazole-2-carbaldehyde* ***(43):***

To a solution of **(42)** (600 mg, 2.52 mmol) in THF (12 mL) was added *n*-BuLi (1.6M in hexanes, 1.73 mL, 2.77 mmol) dropwise at -78 °C under an atmosphere of argon, and stirred at -78 °C for 30 minutes, after which DMF (253 µL, 3.28 mmol) was added dropwise, and stirred for 30 minutes, after which the solution was left to reach 0 °C. The reaction was quenched with a solution of aqueous $NaHCO_3$ (5 mL), diluted with water (15 mL) and the product extracted with EtOAc (2 x 30 mL). The organic phase was washed with brine, dried with $MgSO_4$, and reduced *in vacuo*. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford a yellow solid. 460 mg, 69% yield. R_f: 0.73 (50% EtOAc, 50% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 4.40 (s, 3 H), 5.22 (s, 2 H), 6.89 (d, *J*=7.8 Hz, 1 H), 7.22 – 7.29 (m, 1 H), 7.37 – 7.49 (m, 5 H), 7.51 (d, *J*=8.4 Hz, 1 H), 10.09 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 34.0, 70.8, 107.5, 114.8, 124.2, 127.2, 127.4 (2 C), 128.3, 128.7 (2 C), 136.1, 144.6, 146.0, 147.4, 184.8; HRMS-TOF MS ES+: m/z $[M+H+MeOH]^+$ calculated for $C_{17}H_{19}N_2O_3$: 299.1396; found: 229.1344; Mp: 88 – 90 °C; IR ATR (cm^{-1}): 3002, 2362, 1699, 1687, 1581, 1471, 1264, 1195, 1090.

4.1.4.6 *Methyl 7-(Benzyloxy)-1-methyl-1H-benzo[d]imidazole-2-carboxylate* ***(44):***

(43) (42.3 mg, 0.159 mmol) was dissolved in MeOH (2.1 mL) and cooled to 0 °C. KOH (23.0 mg, 0.412 mmol, dissolved in 0.50 mL MeOH) was added to the solution, followed by the dropwise addition of I_2 (52.7 mg, 0.208 mmol, dissolved in 0.50 mL MeOH). The reaction was left to warm up to room temperature and stirred overnight. The mixture was diluted with EtOAc (50 mL) and washed with 2 x 30 mL water. The organic phase was washed with brine, dried with $MgSO_4$, and reduced *in vacuo*. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford a white solid. 37 mg, 79% yield. R_f: 0.55 (50% EtOAc, 50% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 4.03 (s, 3 H), 4.42 (s, 3 H), 5.21 (s, 2 H), 6.86 (d, *J*=7.8 Hz, 1 H), 7.18 – 7.25 (m, 1 H), 7.37 – 7.51 (m, 6 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 34.8, 52.7, 70.8, 106.6, 114.6, 123.8, 126.8, 127.5 (2 C), 128.2, 128.7 (2 C), 136.2, 140.6, 143.5, 147.0, 160.3; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{17}H_{17}N_2O_3$: 297.1239; found: 297.1182; Mp: 78 – 82 °C; IR ATR (cm^{-1}): 3366, 2953, 1713, 1593, 1468, 1247, 1096.

4.1.4.7 *Methyl 7-hydroxy-1-methyl-1H-benzo[d]imidazole-2-carboxylate (45):*

(44) (350 mg, 1.18 mmol) and Pd/C (10%, 22 mg, 0.0206 mmol) was placed in a flask, evacuated and purged with hydrogen from a balloon after which MeOH (6 mL) was added and the reaction was stirred overnight. The mixture was filtered through a plug of Celite® and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel (70% EtOAc, 30% hexane) to afford a white solid. 224 mg, 92% yield. R_f: 0.37 (70% EtOAc, 30% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.87 (s, 3 H), 4.31 (s, 3 H), 6.62 (d, *J*=7.6 Hz, 1 H), 6.88 – 6.97 (m, 1 H), 7.15 (d, *J*=8.2 Hz, 1 H), 9.45 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 34.2, 52.4, 109.4, 111.6, 123.7, 125.8, 140.6, 143.3, 145.5, 160.1; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{10}H_{11}N_2O_3$: 207.0770; found: 207.0727; Mp: 202 – 204 °C; IR ATR (cm-1): 2951, 1723, 1597, 1471, 1281, 1242, 1127, 1072.

4.1.4.8 *Methyl 7-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1-methyl-1H-benzo[d]imidazole-2-carboxylate* ***(46):***

(45) (224 mg, 1.09 mmol), PPh_3 (429 mg, 1.64 mmol) and 1-Boc-4-hydroxypiperidine (329 mg, 1.63 mmol) were dissolved in THF (6mL). The solution was cooled to 0 °C and DBAD (376 mg, 1.63 mmol, dissolved in 1 mL THF) was added dropwise under an atmosphere of nitrogen. The reaction was stirred overnight at room temperature. The solvent was reduced *in vacuo* and the product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford a white solid. 321 mg, 76% yield. R_f: 0.41 (50% EtOAc, 50% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.41 (s, 9 H), 1.72 – 1.87 (m, 2 H), 1.91 – 2.05 (m, 2 H), 3.28 – 3.41 (m, 2 H), 3.59 – 3.68 (m, 2 H), 3.94 (s, 3 H), 4.37 (s, 3 H), 4.56 – 4.65 (m, 1 H), 1 H), 6.69 (d, *J*=7.8 Hz, 1 H), 7.07 – 7.14 (m, 1 H), 7.36 (d, *J*=8.2 Hz, 1 H);^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.2 (3 C), 30.2 (2 C), 34.6, 40.5 (2 C), 52.5, 72.7, 79.6, 107.0, 114.1, 123.5, 127.0, 140.4, 143.5, 145.0, 154.5, 160.1; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{20}H_{28}N_3O_5$: 390.2029; found: 390.1953; Mp: 85 – 88 °C; IR ATR (cm^{-1}): 2948, 1728, 1682, 1583, 1482, 1422, 1231, 1167, 1077, 1022.

Compounds **(47)** – **(49)** were synthesized via the same procedure. Compound **(46)**, K_3PO_4 (3 equivalents) and the aromatic alcohol used for the transesterification reaction (20 – 30 equivalents) were placed in a flask and stirred under nitrogen at room temperature for 12 – 20 hours. The reaction was monitored via TLC using (5% EtOAc, 95% DCM) as mobile phase to determine whether the starting material had been consumed. The K_3PO_4 was filtered off, and the alcohol removed via heating the solution to 50 °C and streaming compressed air over the solution. After the majority of the solvent volume has been evaporated off, the product was purified by column chromatography over silica gel (5% EtOAc, 95% DCM).

4.1.4.9 *Phenethyl-7-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)-1-methyl-1H-benzo[d]imidazole-2-carboxylate* ***(47):***

36 mg, 50% yield, brown semi-solid. R_f: 0.55 (50% EtOAc: 50% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.49 (s, 9 H), 1.81 – 1.95 (m, 2 H), 1.99 – 2.11 (m, 2 H), 3.18 (t, *J*=7.6 Hz, 2 H), 3.36 – 3.48 (m, 2 H), 3.66 – 3.77 (m, 2 H), 4.40 (s, 3 H), 4.60 – 4.74 (m, 3 H), 6.78 (d, *J*=7.6 Hz, 1 H), 7.16 – 7.23 (m, 1 H), 7.23 – 7.35 (m, 5 H), 7.48 (d, *J*=8.2 Hz, 1 H);^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.5 (3 C), 30.5 (2 C), 34.8, 35.1, 40.7 (2 C), 66.4, 72.9, 79.9, 107.3, 114.5, 123.7, 126.8, 127.3, 128.6 (2 C), 129.0 (2 C), 137.1, 141.0, 143.8, 145.3, 154.7, 159.9; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{27}H_{34}N_3O_5$: 480.2498; found: 480.2515; IR ATR (cm^{-1}): 2961, 2926, 1718, 1688, 1585, 1465, 1422, 1229, 1084, 1023.

Compounds **(50)** – (**52)** were synthesized via the same procedure. Compound **(46)** and the aromatic amine used for the amidation reaction (10 equivalents) were dissolved in THF (1 mL) and stirred under nitrogen at room temperature for 12 – 20 hours. The reaction was monitored via TLC using (50% EtOAc, 50% hexane) mobile phase to determine whether the starting material had been consumed. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane – 100% EtOAc).

4.1.4.10 *tert-Butyl 4-((1-methyl-2-(phenethylcarbamoyl)-1H-benzo[d]imidazol-7-yl)oxy)piperidine-1-carboxylate* ***(50):***

47 mg, 81% yield, yellow solid. R_f: 0.53 (40% EtOAc: 60% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.50 (s, 9 H), 1.81 – 1.96 (m, 2 H), 1.99 – 2.11 (m, 2 H), 2.96 (t, *J*=7.3 Hz, 2 H), 3.39 – 3.50 (m, 2 H), 3.66 – 3.78 (m, 4 H), 4.52 (s, 3 H), 4.63 – 4.74 (m, 1 H), 6.76 (d, *J*=7.6 Hz, 1 H), 7.14 – 7.21 (m, 1 H), 7.21 – 7.38 (m, 6 H), 7.88 (t, *J*=5.9 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.5 (3 C), 30.5 (2 C), 34.9, 35.9, 40.6 (2 C), 40.8, 72.9, 79.8, 106.7, 113.2, 123.5, 126.5, 127.4, 128.6 (2 C), 128.8 (2 C), 138.7, 143.1, 143.4, 145.5, 154.7, 159.8; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{27}H_{35}N_4O_4$: 479.2658; found: 479.2668; Mp: 84 – 86 °C, IR ATR (cm^{-1}): 2930, 2865, 1671, 1529, 1422, 1231, 1166, 1085, 1023.

Compounds **(53)** – **(58)** were synthesized via the same procedure. In a small flask was added the Boc-protected compounds **(47)** – **(52)** separately dissolved in DCM (1 mL) followed by the addition of 4M HCl/dioxane (1 mL). The solution was stirred for one hour, after which the solvent was reduced *in vacuo*. A small amount of DCM was added followed by the addition of EtOAc which caused the salt to precipitate out of solution. The solvent was reduced *in vacuo* and the product dried under vacuum.

4.1.4.11 *4-((1-Methyl-2-(phenethoxycarbonyl)-1H-benzo[d]imidazol-7-yl)oxy)piperidin-1-ium chloride* ***(53):***

26 mg, 83% yield, yellow solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.97 – 2.07 (m, 2 H), 2.18 – 2.27 (m, 2 H), 3.05 – 3.16 (m, 4 H), 3.21 (br. s., 2 H), 4.30 (s, 3 H), 4.59 (t, *J*=6.7 Hz, 2 H), 4.90 (br. s., 1 H), 7.07 (d, *J*=7.6 Hz, 1 H), 7.20 – 7.39 (m, 7 H), 9.25 (br. s., 1 H), 9.44 (br. s., 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 26.7 (2 C), 34.1, 34.8, 40.2 (2 C), 66.3, 70.2, 108.2, 112.6, 124.6, 126.0, 126.5, 128.4 (2 C), 128.9 (2 C), 137.6, 140.4, 141.3, 144.9, 158.5; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{22}H_{26}N_3O_3$: 380.1974; found: 380.1966; Purity: 98.6%; Mp: 179 – 182 °C, IR ATR (cm^{-1}): 2960, 2568, 1749, 1614, 1491, 1257, 1098, 1022.

4.1.5 Synthesis of compounds ***(69)*** *–* ***(74)***

4.1.5.1 *Ethyl 4-hydroxybenzo[d]oxazole-2-carboxylate* ***(60):***

This method is a modified literature procedure.[23] To a solution of 2-amino resorcinol **(59)** (783 mg, 6.26 mmol) in THF (30 mL) and Et_3N (12.5 mmol, 1.75 mL) was added ethyl chlorooxoacetate (770 µL, 6.89 mmol) at -10 °C. The mixture was stirred and allowed to warm to room temperature. The reaction was monitored by TLC and was completed in 2 hours. *N*-acylated product R_f: 0.75 (60% EtOAc: 40% hexane). The resulting dark brown solution was cooled down to 0 °C followed by the addition of THF (50 mL) and PPh_3 (4.38 g, 16.7 mmol). DEAD (1070 µL, 6.88 mmol) was added dropwise, and the solution turned yellow. The reaction was monitored by TLC and was completed in 3 hours. The solvent was reduced *in vacuo*, and the product was purified by column chromatography over silica gel (40% EtOAc, 60% hexane) to afford a white solid. 1.02 g, 84% yield over two steps. R_f: 0.52 (40% EtOAc, 60% hexane); ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.37 (t, *J*=7.1 Hz, 3 H), 4.43 (q, *J*=7.1 Hz, 2 H), 6.84 (d, *J*=8.1 Hz, 1 H), 7.25 (d, *J*=8.1 Hz, 1 H), 7.34 – 7.42 (m, 1 H), 10.80 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 13.9, 62.5, 101.9, 110.9, 129.1, 129.4, 150.8, 151.0, 151.8, 155.8; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{10}H_{10}NO_4$: 208.0610; found: 208.0616; Mp 131 – 134 °C; IR ATR (cm^{-1}): 3440, 2916, 1717, 1686, 1551, 1375, 1270, 1159, 1017.

4.1.5.2 *(ADDM) Azodicarbonyldimorpholide* ***(61):***

To a solution of diethyl ether (30 mL) and morpholine (2.50 mL, 2.87 mmol) was added diethylazodicarboxylate (1.79 ml, 11.5 mmol) dropwise at 0 °C, and stirred for 30 minutes, after which a light orange precipitate fell out of solution. The precipitate was filtered, washed with diethyl ether and dried under vacuum to afford the product as a light orange solid. 2.63 g, 89% yield. ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 3.58 – 3.66 (m, 4 H),

3.68 – 3.80 (m, 8 H), 3.81 – 3.86 (m, 4 H); ^{13}C NMR; (75 MHz, CHLOROFORM-*d*) δ ppm 43.7, 45.2, 66.4, 66.5, 110.0, 159.7. Characterization data corresponded with available literature values.[23]

4.1.5.3 *Ethyl 4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy) benzo[d]oxazole-2-carboxylate* ***(62):***

To a solution of **(60)** (217 mg, 1.05 mmol), PPh_3 (466 mg, 1.78 mmol) and 1-Boc 4-hydroxypiperidine (358 mg, 1.78 mmol) in THF (6 mL) was added azodicarbonyldimorpholide (ADDM) **(61)** (456 mg, 1.78 mmol, dissolved in 1 mL DCM) dropwise at 0 °C under an atmosphere of nitrogen. The solution was taken off the ice and stirred at room temperature overnight. The solvent was reduced *in vacuo*, and the product was purified by column chromatography over silica gel (40% EtOAc, 60% hexane) to afford a white solid. 323 mg, 79% yield. R_f: 0.62 (40% EtOAc, 60% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.45 – 1.51 (m, 12 H), 1.78 – 1.93 (m, 2 H), 1.96 – 2.08 (m, 2 H), 3.26 – 3.37 (m, 2 H), 3.77 – 3.89 (m, 2 H), 4.55 (q, *J*=7.1 Hz, 2 H), 4.95 – 5.05 (m, 1 H), 6.89 (d, *J*=7.6 Hz, 1 H), 7.22 – 7.26 (m, 1 H), 7.37 – 7.45 (m, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 28.4 (3 C), 30.6 (2 C), 40.7 (2 C), 63.1, 74.1, 79.6, 104.1, 110.5, 128.8, 131.2, 150.6, 151.4, 152.5, 154.8, 156.4; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{20}H_{27}N_2O_6$: 391.1869; found: 391.1868; Mp: 112 – 114 °C; IR ATR (cm^{-1}): 2936, 1739, 1545, 1418, 1269, 1159, 1081.

Compounds **(63)** – **(65)** were synthesized via the same procedure. Compound **(62)**, K_3PO_4 (3 equivalents) and the aromatic alcohol used for the transesterification reaction (20 – 30 equivalents) were placed in a flask and stirred under nitrogen at room temperature for 12 – 20 hours. The reaction was monitored via TLC using (5% EtOAc, 95% DCM) as mobile phase to determine whether the starting material had been consumed. The K_3PO_4 was filtered off, and the alcohol removed via heating the solution to 50 °C and streaming compressed air over the solution. After the majority of the solvent volume had been evaporated off, the product was purified by column chromatography over silica gel (5% EtOAc, 95% DCM).

4.1.5.4 *Phenethyl4-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)benzo[d]oxazole-2-carboxylate* ***(63):***

44 mg, 45% yield, white solid. R_f: 0.56 (30% EtOAc, 70% hexane); ^{1}H-NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.47 (s, 9 H), 1.79 – 1.94 (m, 2 H), 1.98 – 2.12 (m, 2 H), 3.15 (t, *J*=7.3 Hz, 2 H), 3.28– 3.41 (m, 2 H), 3.78 – 3.92 (m, 2 H), 4.66 (t, *J*=7.3 Hz, 2 H), 5.00 – 5.09 (m, 1 H), 6.92 (d, *J*=7.6 Hz, 1 H), 7.20 – 7.38 (m, 6 H), 7.39 – 7.46 (m, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.6 (2 C), 34.9, 40.9 (2 C), 67.2, 74.2, 79.6, 104.1, 110.8, 126.8, 128.6 (2 C), 128.8, 128.9 (2 C), 131.1, 136.8, 150.6, 151.2, 152.5, 154.8, 156.3; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{26}H_{31}N_2O_6$: 467.2182; found: 467.2170; Mp: 114 – 117 °C, IR ATR (cm^{-1}): 2970, 1734, 1685, 1614, 1409, 1324, 1149, 1081, 1026.

Compounds **(66)** – **(68)** were synthesized via the same procedure. Compound **(62)** and the respected amine (10 equivalents) were dissolved in THF (1 mL) and stirred under nitrogen at room temperature for 12 – 20 hours. The reaction was monitored via TLC using (50% EtOAc, 50% hexane) mobile phase to determine whether the starting material had been consumed. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane – 100% EtOAc)

4.1.5.5 *tert-Butyl 4-((2-(phenethylcarbamoyl)benzo[d]oxazol-4-yl)oxy) piperidine-1-carboxylate* ***(66):***

51 mg, 91% yield, yellow solid. R_f: 0.71 (50% EtOAc, 50% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.44 – 1.56 (m, 9 H), 1.76 – 1.92 (m, 2 H), 1.95 – 2.10 (m, 2 H), 2.98 (t, *J*=7.3 Hz, 2 H), 3.25 – 3.38 (m, 2 H), 3.72 – 3.89 (m, 4 H), 4.86 – 4.95 (m, 1 H), 6.90 (d, *J*=8.2 Hz, 1 H), 7.19 – 7.43 (m, 8 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.6 (2 C), 35.5, 40.7 (2 C), 40.9, 74.1, 79.6, 104.5, 110.6, 126.7, 127.9, 128.7 (4 C), 130.6, 138.2, 149.9, 152.8, 154.1, 154.7, 155.5; Missing carbon signal, suspected to be merged with signal located at 128.7 ppm; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{26}H_{32}N_3O_5$: 466.2342; found: 466.2338; Mp: 71 – 73 °C, IR ATR (cm^{-1}): 3313, 2930, 1681, 1617, 1553, 1496, 1423, 1364, 1265, 1165, 1067, 1022.

Compounds **(69)** – **(74)** were synthesized via the same procedure. In a small flask was added the Boc-protected compound **(63)** – **(68)** separately and DCM (1 mL) followed by the addition of 4M HCl/dioxane (1 mL). The solution was stirred for one hour, after which the solvent was reduced *in vacuo*. A small amount of DCM was added followed by the addition of EtOAc which caused the salt to precipitate out of solution. The solvent was reduced *in vacuo* and the product dried under vacuum.

4.1.5.6 *4-((2-(phenethoxycarbonyl)benzo[d]oxazol-4-yl)oxy) piperidin-1-ium chloride* ***(69):***

37 mg, 98% yield, white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.92 – 2.02 (m, 2 H), 2.15 – 2.29 (m, 2 H), 3.05 – 3.14 (m, 4 H), 3.23 – 3.30 (m, 2 H), 4.61 (t, *J*=7.0 Hz, 2 H), 5.02 – 5.07 (m, 1 H), 7.16 (d, *J*=8.2 Hz, 1 H), 7.20 – 7.36 (m, 5 H), 7.45 (d, *J*=8.2 Hz, 1 H), 7.49 – 7.57 (m, 1 H), 9.24 (br. s., 1 H); ^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 27.1 (2 C), 34.1, 40.4 (2 C), 66.7, 70.8, 104.5, 110.3, 126.6, 128.4 (2 C), 128.9 (2 C), 129.2, 130.5, 137.4, 149.6, 151.2, 151.8, 155.6; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{21}H_{23}N2O_4$: 367.1658; found: 367.1663; Purity: >95%; Mp: 184– 186 °C, IR ATR (cm^{-1}): 2958, 2731, 1740, 1609, 1494, 1263, 1142, 1084.

4.1.6 Synthesis of compounds ***(87) – (92)***

4.1.6.1 *2-Hydroxy-6-nitrobenzaldehyde* ***(76):***

3-nitrophenol **(75)** (1.00 g 7.19 mmol) was placed in a vial and combined with hexamethylenetetramine (1.21 g, 8.59 mmol) and 5.00 mL trifluoroacetic acid. The vial was flushed with argon, sealed, and the solution was stirred at 90 °C for 12 hours. The

reaction mixture was poured onto 50 mL ice-water and extracted with 2 x 50 mL EtOAc. The organic fractions were combined, washed with brine, dried over $MgSO_4$, and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel (20% EtOAc, 80% hexane) to afford the product as a yellow solid. 354 mg, 29% yield. R_f: 0.59 (20% EtOAc, 80% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.28 – 7.34 (m, 1 H), 7.54 – 7.60 (m, 1 H), 7.60 – 7.67 (m, 1 H), 10.33 (s, 1 H), 12.11 (br. s., 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 112.3, 116.0, 124.2, 135.9, 163.1, 163.3, 193.8; Characterization data corresponded with available literature values.[24]

4.1.6.2 *2-(Benzyloxy)-6-nitrobenzaldehyde **(77):***

In DMF (4 mL) was added (**76)** (354 mg, 2.12 mmol), benzyl bromide (0.760 mL, 6.36 mmol) and K_2CO_3 (440 mg, 3.18 mmol) at 0 °C under an atmosphere of nitrogen. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was dissolved in EtOAc (60 mL), and washed with water (4 x 50 mL) followed by a wash with brine. The organic layer was dried over $MgSO_4$, filtered and reduced *in vacuo*. The product was purified by column chromatography over silica gel (50% EtOAc, 50% hexane) to afford the product as a yellow solid. Quantitative, 557 mg. R_f: 0.23 (20% EtOAc, 80% hexane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 5.23 (s, 2 H), 7.29 (d, *J*=8.2 Hz, 1 H), 7.34 – 7.43 (m, 5 H), 7.45 (d, *J*=8.2 Hz, 1 H), 7.54 – 7.60 (m, 1 H), 10.45 (s, 1 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 71.5, 115.8, 117.6, 121.1, 127.2 (2 C), 128.6, 128.9 (2 C), 133.4, 135.0, 148.7, 158.8, 187.6; Characterization data corresponded with available literature values.[24]

4.1.6.3 *Ethyl 4-(benzyloxy)benzo[b]thiophene-2-carboxylate **(78):***

To a Schlenk flask was added **(77)** (557 mg, 2.17 mmol), K_2CO_3 (361 mg, 2.61 mmol) and DMF (4.5 mL). Ethyl thioglycolate (250 µL, 2.27 mmol) was added dropwise at 0 °C under an atmosphere of nitrogen, upon which the initial yellow solution turned light yellow. The mixture was stirred at 0 °C for 30 minutes, then heated to 50 °C for 48 hours. The mixture was diluted with EtOAc (60 mL), and washed with water (4 x 50 mL) followed by a wash with brine. The organic fraction was dried over $MgSO_4$, and the solvent reduced *in vacuo*. The product was purified by column chromatography over silica gel (5% EtOAc, 95% hexane) to afford the product as a yellow solid. 644 mg, 95% yield. R_f: 0.45 (5% EtOAc, 95% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.43 (t, *J*=7.0 Hz, 3 H), 4.42 (q, *J*=7.0 Hz, 2 H), 5.22 (s, 2 H), 6.82 (d, *J*=7.0 Hz, 1 H), 7.32 – 7.55 (m, 7 H), 8.31 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 61.4, 70.0, 105.3, 115.0, 127.3 (2 C), 127.4, 128.0, 128.1, 128.5 (2 C), 130.1, 132.1, 136.4, 143.7, 155.2, 162.7; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{18}H_{17}O_3S$: 313.0898; found: 313.0888; IR ATR (cm^{-1}): 2926, 1704, 1564, 1519, 1285, 1233, 1151, 1021.

4.1.6.4 *Ethyl 4-hydroxybenzo[b]thiophene-2-carboxylate **(79):***

To a solution of **(78)** (630 mg, 2.02 mmol) in MeOH (6 mL) was added Pd/C (10%, 170 mg, 0.159 mmol), after which the flask was purged with hydrogen from a balloon, stirred under an atmosphere of hydrogen for 12 hours. The mixture was filtered through a plug of Celite® and the solvent removed *in vacuo*. The product was purified by column chromatography over silica gel (30% EtOAc, 70% hexane) to afford the product as a yellow solid. 314 mg, 68% yield. R_f: 0.43 (30% EtOAc, 70% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.43 (t, *J*=7.0 Hz, 3 H), 4.43 (q, *J*=7.0 Hz, 2 H), 5.73 (s, 1 H), 6.77 (d, *J*=7.0 Hz, 1 H), 7.29 – 7.36 (m, 1 H), 7.43 (d, *J*=8.2 Hz, 1 H), 8.32 (d, *J*=1.2 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.3, 61.7, 109.2, 110.0, 115.2, 126.9, 128.3, 132.1, 144.1, 152.3, 163.1; HRMS-TOF MS ES+: m/z $[M+Na]^+$ calculated for $C_{11}H_{10}O_3SNa$: 245.0249; found: 245.0254; Mp: 154 – 156 °C; IR ATR (cm^{-1}): 3376, 1692, 1564, 1527, 1332, 1279, 1218, 1149.

4.1.6.5 *tert-butyl 4-((2-(ethoxycarbonyl)benzo[b]thiophen-4-yl)oxy) piperidine-1-carboxylate **(80):***

(79) (314 mg, 1.41 mmol), PPh_3 (629 mg, 2.40 mmol) and 1-Boc-4-hydroxypiperidine (483 mg, 2.40 mmol) were dissolved in THF (9 mL) under an atmosphere of nitrogen. To this solution was added DBAD (553 mg, 2.4 mmol, dissolved in 1 mL THF) dropwise at 0 °C. The solution was stirred overnight at room temperature, after which the solvent was removed *in vacuo*, and the product was purified by column chromatography over silica gel (20% EtOAc, 80% hexane) to afford the product as a colorless semisolid that solidified over time into a white solid. 571 mg, 99% yield. R_f: 0.48 (20% EtOAc, 80% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.36 (t, *J*=7.0 Hz, 3 H), 1.44 (s, 9 H), 1.74 – 1.87 (m, 2 H), 1.87 – 1.97 (m, 2 H), 3.34 – 3.45 (m, 2 H), 3.61 – 3.72 (m, 2 H), 4.34 (q, *J*=7.0 Hz, 2 H), 4.56 – 4.66 (m, 1 H), 6.70 (d, *J*=7.0 Hz, 1 H), 7.24 – 7.31 (m, 1 H), 7.34 (d, *J*=8.2 Hz, 1 H), 8.14 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 14.1, 28.2 (3 C), 30.1 (2 C), 40.3 (2 C), 61.2, 72.0, 79.3, 106.2, 114.7, 127.0, 127.9, 130.6, 131.9, 143.7, 153.5, 154.5, 162.5; HRMS-TOF MS ES+: m/z $[M+Na]^+$ calculated for $C_{21}H_{27}NO_5SNa$: 428.1508; found: 428.1515; Mp: 64 – 67 °C; IR ATR (cm^{-1}): 2947, 1716, 1696, 1681, 1562, 1416, 1253, 1230, 1150, 1023.

Compounds **(81)** – **(83)** were synthesized via the same procedure. Compound **(80)**, K_3PO_4 (3 equivalents) and the aromatic alcohol used for the transesterification reaction (26 equivalents) were placed in a flask and stirred under nitrogen at 70 °C for 12 – 20 hours. The reaction was monitored via TLC using 5% EtOAc, 95% DCM as mobile phase to determine whether the starting material had been consumed. The K_3PO_4 was filtered off, and the alcohol removed via heating the solution to 50 °C and streaming compressed air over the solution. After the majority of the solvent volume had been evaporated off, the product was purified by column chromatography over silica gel (5% EtOAc, 95% DCM).

4.1.6.6 *tert-Butyl 4-((2-(phenethoxycarbonyl)benzo[b]thiophen -4-yl)oxy) piperidine-1-carboxylate* ***(81):***

53 mg, 88% yield, clear semi-solid. R_f: 0.50 (20% EtOAc, 80% hexane); ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.50 (s, 9 H), 1.84 – 1.94 (m, 2 H), 1.94 – 2.04 (m, 2 H), 3.11 (t, *J*=7.0 Hz, 2 H), 3.43– 3.52 (m, 2 H), 3.65 – 3.74 (m, 2 H), 4.56 (t, *J*=7.2 Hz, 2 H), 4.65 – 4.74 (m, 1 H), 6.78 (d, *J*=7.4 Hz, 1 H), 7.23 – 7.35 (m, 5 H), 7.35 – 7.40 (m, 1 H), 7.41 – 7.44 (m, 1 H), 8.19 (d, *J*=0.8 Hz, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.3 (2 C), 35.2, 40.3 (2 C), 65.9, 72.2, 79.7, 106.4, 115.0, 126.6, 127.5, 128.2, 128.5 (2 C), 129.0 (2 C), 130.9, 131.8, 137.6, 144.0, 153.7, 154.8, 162.6; HRMS-TOF MS ES+: m/z $[M+Na]^+$ calculated for $C_{27}H_{31}NO_5SNa$: 504.1821; found: 504.1829; IR ATR (cm^{-1}): 2930, 1691, 1564, 1454, 1231, 1152, 1028.

Compounds **(84)** – **(86)** were synthesized via the same procedure. Compound **(80)** and the respected amine (20 equivalents) were stirred under nitrogen at 145 °C for 12 – 20 hours. The reaction was monitored via TLC using (50% EtOAc, 50% hexane) mobile phase to determine whether the starting material had been consumed. The product was purified by column chromatography over silica gel using a gradient elution (50% EtOAc, 50% hexane – 100% EtOAc)

4.1.6.7 *tert-Butyl 4-((2-(phenethylcarbamoyl)benzo[b]thiophen -4-yl)oxy) piperidine-1-carboxylate* ***(84):***

55 mg, 77% yield, white solid. R_f: 0.53 (35% EtOAc, 65% hexane); ^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H), 1.80–1.92 (m, 2 H), 1.92 – 2.04 (m, 2 H), 2.97 (t, *J*=7.0 Hz, 2 H), 3.40 – 3.53 (m, 2 H), 3.65 – 3.78 (m, 4 H), 4.63 – 4.72 (m, 1 H), 6.36 (t, *J*=5.9 Hz, 1 H), 6.78 (d, *J*=7.6 Hz, 1 H), 7.23 – 7.39 (m, 6 H), 7.42 (d, *J*=7.6 Hz, 1 H), 7.85 (s, 1 H); ^{13}C NMR (75 MHz, CHLOROFORM-*d*) δ ppm 28.4 (3 C), 30.3 (2 C), 35.7, 40.4 (2 C), 41.3, 72.1, 79.7, 106.5, 115.0, 121.6, 126.6, 127.4, 128.7 (2 C), 128.8 (2 C), 131.1, 137.1, 138.7, 142.6, 153.2, 154.8, 162.2; HRMS-TOF MS ES+: m/z $[M+Na]^+$ calculated for $C_{27}H_{32}N_2O_4SNa$: 503.1981; found: 503.1989; Mp: 75 – 78 °C, IR ATR (cm^{-1}): 3309, 2930, 1668, 1630, 1497, 1422, 1256, 1164, 1027.

Compounds **(87)** – **(92)** were synthesized via the same procedure. In a small flask was added the Boc-protected compound **(81)** – **(86)** separately and DCM (1 mL) followed by the addition of 4M HCl/dioxane (1 mL). The solution was stirred for one hour, after which the solvent was reduced *in vacuo*. A small amount of DCM was added followed by the addition of EtOAc which caused the salt to precipitate out of solution. The solvent was reduced *in vacuo* and the product dried under vacuum.

4.1.6.8 *4-((2-(Phenethoxycarbonyl)benzo[b]thiophen-4-yl)oxy) piperidin-1-ium chloride* ***(87):***

41 mg, 89% yield, white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.94 – 2.05 (m, 2 H), 2.15 – 2.26 (m, 2 H), 3.04 (t, *J*=6.8 Hz, 2 H), 3.08 – 3.16 (m, 2 H), 3.23 – 3.32 (m, 2 H), 4.50 (t, *J*=6.8 Hz, 2 H), 4.85 – 4.95 (m, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 7.24 (dq, *J*=8.5, 4.2 Hz, 1 H), 7.31 (d, *J*=4.3 Hz, 4 H), 7.44 – 7.50 (m, 1 H), 7.61 (d, *J*=8.2 Hz, 1 H), 8.09 (s, 1 H), 9.28 (br. s., 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 26.8 (2 C), 34.4, 65.8, 69.4, 107.2, 115.3, 126.5, 126.9, 128.4 (2 C), 129.0 (2 C), 129.8, 131.3, 137.8, 142.9, 153.0, 161.7; Missing carbon signal, suspected to be merged with DMSO-d_6 solvent signal located at 40.2 ppm; HRMS-TOF MS ES+: m/z $[M+H]^+$ calculated for $C_{22}H_{24}NO_3S$: 382.1477; found: 382.1477; Purity: >99%; Mp: 226 – 228 °C, IR ATR (cm^{-1}): 2938, 2712, 1705, 1584, 1456, 1234, 1062, 989.

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