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Pd/PTABS: An Efficient Catalytic System for the Aminocarbonylation of a Sugar-Protected Nucleoside

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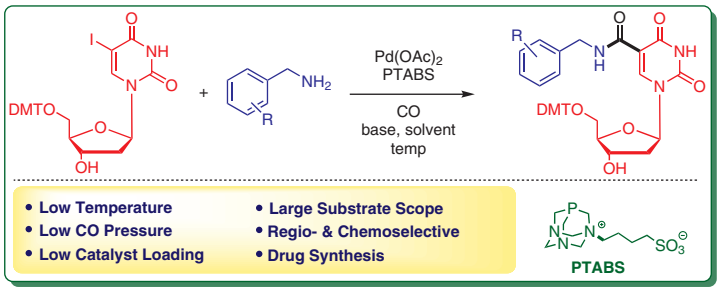

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Abstract A highly efficient and mild protocol for the aminocarbonylation of a nucleoside is developed by employing palladium/(1,3,5-triaza-7-phosphaadamantan-1-ium-1-yl)butane-1-sulfonate (Pd/PTABS) as the catalytic system. The developed aminocarbonylation methodology employs CO gas at a relatively low temperature of 60 °C and is suitable for a wide range of amines, including (heteroaryl)benzylic, aliphatic acyclic, alicyclic and secondary amines. This protocol is also utilized for the synthesis of a sangivamycin precursor by carrying out the Pd-catalyzed amination and aminocarbonylation simultaneously. The utility of this protocol is further demonstrated by the synthesis of the drugs moclobemide and nikethamide.

Key words palladium, PTABS, aminocarbonylation, nucleoside, sangivamycin

The diversity of palladium-catalyzed coupling systems is exemplified by the many named reactions, viz., Heck–Mizoroki, Suzuki–Miyaura, Sonogashira, Stille, Kumada, Negishi, Buchwald–Hartwig, and others that have found numerous applications in academia and industry in the past decades.[1,2] However, the scope of palladium catalysis is not limited to these coupling processes but goes well beyond, with carbonylation[3] offering a range of options for generating a variety of functional groups capable of further elaboration.[4] The original reaction conditions defined by Heck over 30 years ago have undergone tremendous change through the identification of a broader range of catalyst precursors allowing the reaction to be conducted under mild reaction conditions.[5] On a similar note, the meteoric rise in reports involving palladium-catalyzed carbonylation chemistry has allowed the direct synthesis of carbonyl compounds using readily available feedstocks such as carbon monoxide (CO),[6] thus enabling atom economic[5] as well as step-economic approaches to synthesis.[7–9]

Aminocarbonylation or amidation, employing an amine as a nucleophile, is an important variant of the carbonylation reaction,[10,11] although in comparison to alkoxycarbonylation,[12] it has received much less attention. This comes in spite of the fact that aminocarbonylation has been identified as one of the most sought-after processes in the pharmaceutical industry,[13] proving to be both valuable and simple in terms of the involved process parameters. A testament to the growing importance of aminocarbonylation[14] can be visualized in the form of the several well-known amide-cored compounds that have been identified in several commercially important molecules, natural products, and biologically active motifs in a variety of drug molecules (Figure 1).[15–20]

Amongst the molecules of synthetic and biological relevance that have been highlighted above, echiguanine[16] A and sangivamycin[15] are particularly important due to the presence of a privileged nucleoside scaffold. In past decades, significant progress has been made on nucleoside chemistry,[21] ranging from their synthesis, modification and photophysical examination, leading to their potential exploration in the field of medicines.[22] For the construction of such macromolecular biologically relevant motifs/devices and for the installation of important functionalities such as amides (as seen in Figure 1), the role of smaller building blocks (such as carbon monoxide) is crucial and significant[23] as they offer elegant synthetic pathways for molecules[24] of high commercial and biological relevance.[25,26]

The amide functionality in nucleoside chemistry has proved useful due to the restricted rotation of the amide bond[27,28] and its ability to serve as both a hydrogen bond acceptor and donor,[29] thus providing an attractive prospect for the assessment of new H-bonding contacts with different protein targets and eventually helping in DNA stabilization.[30,31] Furthermore, keeping in mind the requirement for the minimization of the number of rotatable bonds be-

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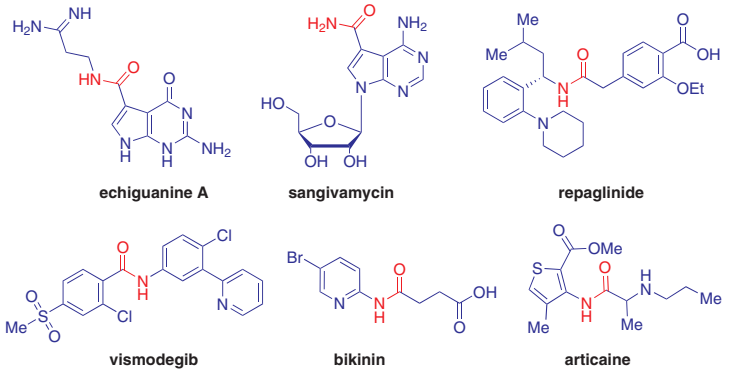


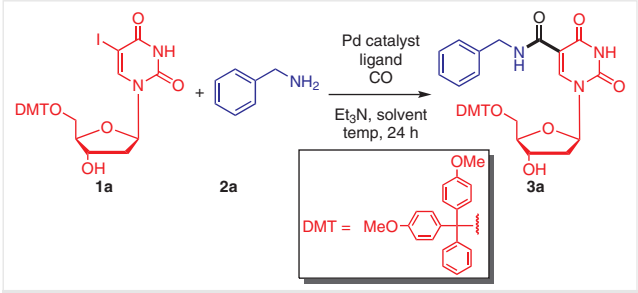
Figure 1 Examples of drugs containing an amide linkage

tween the nucleobase and the pendant modification for precise orientation at the aptamer protein interface also makes the amide functionality an ideal candidate for installation onto the nucleoside backbone. Moreover, modified 2′-deoxyuridine nucleotides, exhibiting an N-substituted carboxamide group at the 5-position, have been demonstrated as important tools for expanding the *in vitro* selection of protein-binding aptamers (SELEX process) and for post-SELEX optimization of the binding and pharmacokinetic properties of the selected aptamers.[32,33]

For the installation of the amide functionality on the nucleoside substructure, it is therefore necessary to identify environmentally benign and sustainable synthetic protocols (such as aminocarbonylation *via* CO insertion). Eaton et al.[31] were the first to report the palladium-catalyzed aminocarbonylation of 5′-*O*-(4,4′-dimethoxytrityl)-5-iodo-2′-deoxyuridine (5′-*O*-DMT-5-IdU) (**1a**) (see Scheme 1) by utilizing CO gas as a C1 source (for the installation of a carbonyl group) and an aromatic amine hydrochloride as the amine source. Matsuda and co-workers[34] have reported a useful palladium-catalyzed transamidation protocol for the aminocarbonylation of various nucleoside analogs. More recently, Fitzwater et al.[32] disclosed a carboxyamidation reaction over the nucleosidic backbone.

Although useful, most of these methods have continued with the classical carbonylative amidation process conditions for nucleosides, which involve high catalyst loadings, long reaction times, high CO pressures, lower yields and limited substrate scope.[29,31,32,35] To address and overcome the above described limitations, we describe herein a sustainable catalytic solution that employs a low-temperature, low-pressure, palladium-catalyzed carbonylative amidation protocol with nucleoside **1a**, utilizing a simple phosphatriazene ligand [PTABS: (1,3,5-triaza-7-phosphaadamantan-1-ium-1-yl)butane-1-sulfonate].[36] We also intend to expand the repertoire of available reagents for *in vitro* selection,[29] enabling the incorporation of a second modified base into randomized DNA libraries in the SELEX process.[32] The present method exhibits a substantial substrate scope (22 examples), and utilizes a low CO pressure (<3 bar), a low temperature (60 °C) and a low palladium loading (2 mol%), whilst affording high yields of the desired products.

At the outset of our studies, the influence of the reaction parameters including solvent, palladium precursor, base, temperature, and the pressure of carbon monoxide was examined, and the results are discussed below (Scheme 1 and Table 1).



Scheme 1 The aminocarbonylation of **1a**

The catalytic aminocarbonylation protocol was tested with nucleoside **1a** and benzylamine (**2a**) as the model substrates in the presence of 5 mol% of $Pd(PhCN)_2Cl_2$, as reported by Gait et al.,[37] providing a 76% yield of the desired amide (Table 1, entry 1). Likewise, we tried several precatalyst systems such as $Pd(PhCN)_2Br_2$ and $Pd(PPh_3)_4$ (entries 2 and 3), and also $Pd(PhCN)_2Cl_2$ with PTABS as the ligand (entry 26), albeit without much further improvement in the yield. Our recent work on the modification of nucleosides was based on the development of a water-soluble $Pd(Sacc)_2(PTA)_2$ complex,[38] which was used in an attempt to the improve the of yield of the aminocarbonylation reaction (entry 4). However, this well-defined catalyst failed to furnish the desired product in a good yield. Therefore, we turned our attention to our recently developed 1,3,5-triaza-7-phosphaadamantane (PTA) variant, PTABS, which has allowed the development of highly efficient protocols for the modification of nucleosides via palladium-catalyzed cross-

coupling reactions such as Heck, Suzuki–Miyaura and Sonogashira reactions,[36] as well as room-temperature amination,[39,40] low-temperature etherification[41] and C–H bond functionalization of 1,3,4-oxadiazoles.[42]

Table 1 Optimization Studies of the Aminocarbonylation of **1a**[a]

Entry	Pd catalyst , (mol%)	Ligand (mol%)	Solvent	Temp (°C)	CO (psi)	Yield (%)[b]
1	$Pd(PhCN)_2Cl_2$ (5 mol%)	–	MeCN	70	60	76
2	$Pd(PhCN)_2Br_2$ (5 mol%)	–	MeCN	70	60	75
3	$Pd(PPh_3)_4$ (5 mol%)	–	MeCN	70	60	65
4	$Pd(Sacc)_2(PTA)_2$ (5 mol%)	–	MeCN	70	60	20
5	$Pd(OAc)_2$ (5 mol%)	PTABS (10 mol%)	MeCN	70	60	80
6	$Pd(OAc)_2$ (5 mol%)	PTAPS (10 mol%)	MeCN	70	60	60
7	$Pd(OAc)_2$ (5 mol%)	PTABS (10 mol%)	H_2O	70	60	65
8	$Pd(OAc)_2$ (5 mol%)	PTABS (10 mol%)	PEG-400	70	60	58
9	$Pd(OAc)_2$ (5 mol%)	PTABS (10 mol%)	DMF	70	60	82
10	$Pd(OAc)_2$ (3 mol%)	PTABS (6 mol%)	DMF	70	60	81
11	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	70	60	85
12	$Pd(OAc)_2$ (1 mol%)	PTABS (2 mol%)	DMF	70	60	75
13	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	70	40	84
14	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	70	20	70
15[c]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	70	14	0
16	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	82
17	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	50	40	64
18	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	30	40	0
19[d]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	45
20[e]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	70
21[f]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	40
22[g]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	55
23[h]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	45
24[i]	$Pd(OAc)_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	75
25	$Pd(OAc)_2$ (2 mol%)	–	DMF	60	40	43
26	$Pd(PhCN)_2Cl_2$ (2 mol%)	PTABS (4 mol%)	DMF	60	40	78
27	$Pd(OAc)_2$ (2 mol%)	XantPhos (4 mol%)	DMF	60	40	55
28	$Pd(OAc)_2$ (2 mol%)	XPhos (4 mol%)	DMF	60	40	61
29	$Pd(OAc)_2$ (2 mol%)	SPhos (4 mol%)	DMF	60	40	64

[a] *Reaction conditions*: 0.5 mmol of **1a**, 1.0 mmol of **2a**, 5.0 mmol of triethylamine (as the base unless otherwise stated), 10 mL of solvent, reaction kept in an autoclave for 24 h.
[b] Yield of isolated product.
[c] Reaction at 1 atm pressure using a CO balloon.
[d] DBU was used instead of triethylamine.
[e] Diisopropylethylamine (DIPEA) was used instead of triethylamine.
[f] K_2CO_3 was used instead of triethylamine.
[g] Cs_2CO_3 was used instead of triethylamine.
[h] The reaction was carried out for 12 h.
[i] The reaction was carried out for 48 h.

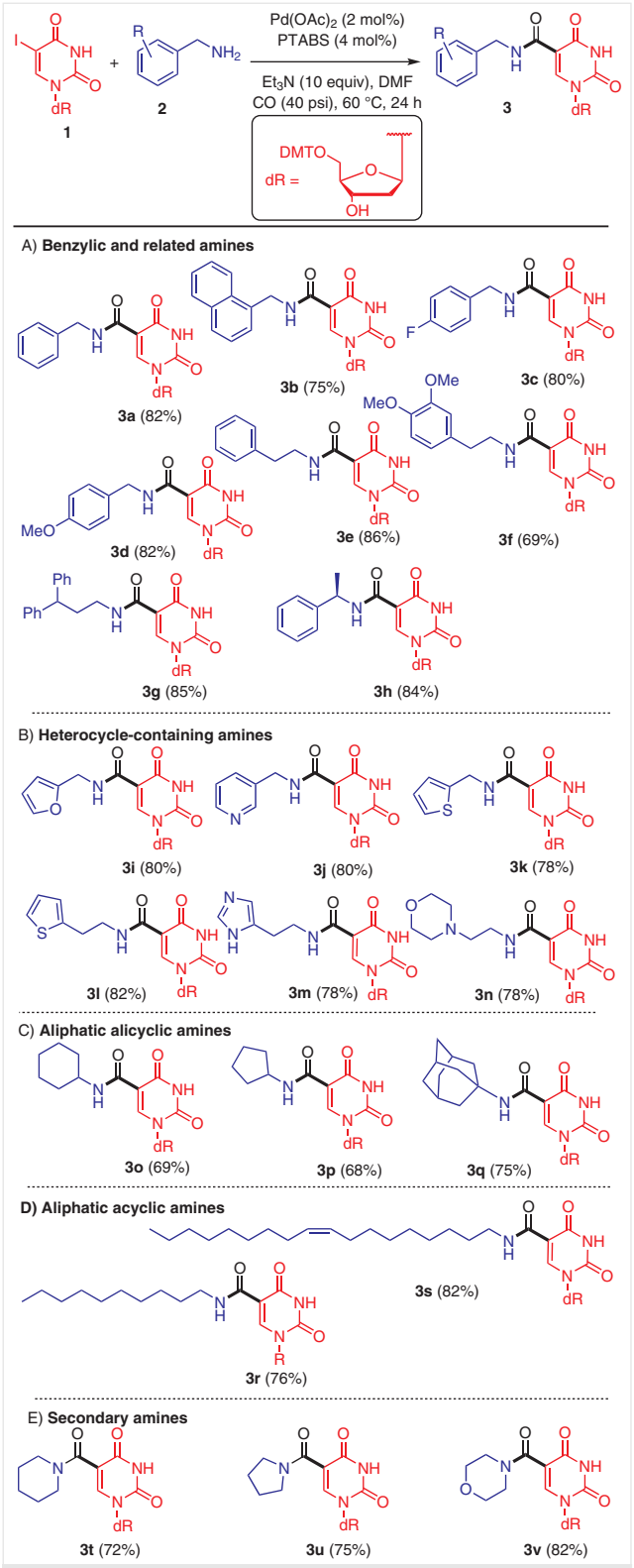
We envisaged the use of $Pd(OAc)_2$ as a catalyst precursor in combination with PTABS for this current protocol, and to our delight, obtained an improved yield (80%) of the amide-derivatized product (Table 1, entry 5). This yield was higher than those obtained using other commercially available monodentate and bidentate ligands (entries 27–29). Having established the catalytic system for the aminocarbonylation, we further screened the reaction solvent with H_2O and PEG-400 giving lower yields of the desired product (entries 7 and 8) in comparison to MeCN. Lastly, we employed DMF (entry 9) instead of MeCN and observed a slight improvement in the yield.

Catalyst concentration is an important parameter in determining the feasibility of the developed protocol for large-scale applications, and in most reports in the literature this has been a critical point that needs to be addressed. Accordingly, the catalytic amidation reaction was performed at different catalyst concentrations (Pd as well as PTABS), with Pd (2 mol%) and PTABS (4 mol%) providing the best result in terms of reactivity (Table 1, entry 11). Another aspect besides catalyst concentration that needs urgent attention is the pressure of CO gas applied for the catalytic amidation process, as in most cases pressures in excess of 100 psi have been applied. Initial studies were performed at 60 psi of CO pressure; however, it was observed that even a CO pressure of 40 psi (entry 13) provided a similar yield to that obtained at 60 psi. Any further reduction in pressure of CO, such as by carrying out the reaction using a CO balloon, resulted into complete loss of activity (entry 15). Having so far carried out all the reactions at 70 °C, we decided to analyze the effect of temperature on the catalytic activity. It was observed that a comparable product yield could be ob-

tained at 60 °C (entry 16) and any further reduction had a detrimental effect on the yield of the amide product (entries17 and 18). Next, we turned our attention towards optimization of the base. A series of catalytic reactions with different bases, namely Et_3N, DIPEA and DBU (organic soluble bases), as well as some inorganic bases, viz. K_2CO_3 and Cs_2CO_3were carried out (entries 19–22). In spite of the wide range of bases analyzed, Et_3N provided the optimum result in terms of yield. It is also worth noting that the addition of excess of base (10 equiv) is required to keep the reaction medium basic and avoid deprotection of the DMT group.[43]

With the reaction parameters having been optimized, studies on the scope of the process were undertaken for the synthesis of several nucleoside-based amides by incorporating a variety of different amines. Various benzyl, heteroaryl, acyclic and cyclic alkyl amines were utilized and were proficiently transformed into the desired products **3a–v** in good to excellent yields (Scheme 2). Initially, simple amines such as benzylamine, 1-naphthylmethylamine, 4-fluorobenzylamine, 4-methoxybenzylamine and phenethylamine were utilized, providing access to a variety of amino-carbonylated products (**3a–e**) in excellent yields. Dopamine dimethoxide (used for the treatment of hypotension),[44] 3,3-diphenylpropan-1-amine (used as an internal standard for simultaneous determination of D- and L-modafinil in human plasma using stereospecific high-performance liquid chromatography and which has an antiextensor effect and worsens chronic seizure produced by pentylenetetrazole),[45] and (*R*)-1-phenylethan-1-amine (a human metabolite)[46] were also incorporated onto the nucleoside backbone of **1a** using the developed protocol to afford the corresponding products **3f–h** in excellent yields.

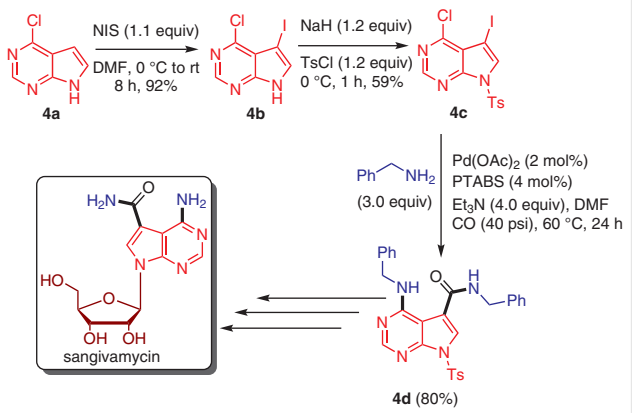
The encouraging results obtained with the benzylamines inspired us to employ heteroaryl methyl- and ethylamine(s), which furnished the carboxyamide products **3i–n** in good to excellent yields, especially that of 2-thiophene ethanamine **3l** (82%). Histamine[47] (a nitrogenous compound involved in local immune responses, as well as regulating physiological function in the gut and acting as a neurotransmitter for the brain, spinal cord, and uterus) was also employed and the corresponding product **3m** was obtained in a good yield of 78%. The amide of histamine is of particular importance as of the 2 competitive N–H groups, only the primary aliphatic amine reacted. Also, the second N–H group may provide an additional H-bonding site.[29] Next, alicyclic amines such as cyclohexyl, cyclopentyl and adamantyl amines were tested, providing the corresponding products **3o–q** in good yields. Aliphatic long-chain amines such as decylamine and oleylamine (a surfactant; coordinates with metal ions, changes the form of metal precursors and affects the formation kinetics of nanoparticles during synthesis)[48] were next to be used as the amine counterparts, providing good yields of the carboamidation products **3r** and **3s**. Lastly, we employed this protocol for the



Scheme 2 *Reaction conditions*: **1a** (1 mmol), amine **2** (2 mmol), $Pd(OAc)_2$ (2 mol%), PTABS (4 1mol%), Et_3N (10 equiv), DMF (10 mL), CO (40 psi), 60 °C, 24 h.

synthesis of amides using secondary amines, namely piperidine, pyrrolidine and morpholine, with the expected products **3t–v** being obtained in good to excellent yields.

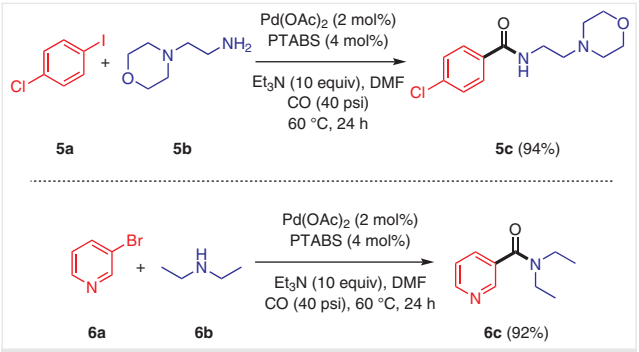
Encouraged by these results, the utility of the present chemistry was highlighted by demonstrating the successful installation of an amide functionality on a purine structural motif towards the synthesis of the precursor of the bioactive molecule sangivamycin,[15] a naturally occurring nucleoside analog that inhibits protein kinase C activity. A recent report also indicated that this compound is currently undergoing third-phase clinical trials.[49] The synthesis of the sangivamycin precursor also exhibits excellent regio- and chemoselectivity between amination of a chloroheteroarene[41] and carbonylative amidation. The synthesis is initiated by the iodination of 6-chloro-7-deazapurine (**4a**) to yield 4-chloro-5-iodo-7*H*-pyrrolo[2,3-d]pyrimidine (**4b**). This was followed by tosylation of **4b** using an *N*-tosylation procedure reported in the literature.[50] The corresponding *N*-tosyl-6-chloro-7-iodo-7-deazapurine (**4c**) was then used for the final step. This involved one-pot amination of the 6-chloro group and amidation of the 7-iodo group using the $Pd(OAc)_2$/PTABS catalytic system, benzylamine as the nucleophile and CO (40 psi) in an autoclave to yield the precursor **4d** in 80% yield (Scheme 3).



Scheme 3 Synthesis of sangivamycin precursor **4d**

Next, to increase the substrate scope, we employed other sugar-protected and unprotected nucleosides such as 5-iodo-2′-deoxycytidine (5-IdC), 8-bromo-2′-deoxyadenosine (8-BrdA), 8-bromo-2′-deoxyguanosine (8-BrdG) and 2′-deoxy-5-iodo-3′,5′-*O*-[1,1,3,3-tetrakis(1-methylethyl)-1,3-disiloxanediyl]uridine (see the Supporting Information). However, positive results were not obtained under the optimized conditions.

To showcase the versatility of the developed protocol, moclobemide[51] (**5c**), a reversible monoamine-oxidase-A (RIMA) inhibitor and an antidepressant drug having reactive oxygen and tertiary amine functions, was synthesized by employing the developed aminocarbonylation protocol. Moclobemide was obtained via one step in an excellent 94% yield (Scheme 4). Additionally, the three-component reaction between 3-bromopyridine (**6a**), *N*,*N*′-diethylamine (**6b**) and CO was also successful in producing the corresponding amide, commonly known as nikethamide (**6c**)[52] in 92% yield (Scheme 4). Nikethamide is a stimulant which mainly affects the respiratory cycle and is widely known by its former trade name, coramine, which was used in the mid-twentieth century as a medical countermeasure against tranquilizer overdoses.



Scheme 4 Synthesis of drug molecules: moclobemide and nikethamide

In conclusion, we have demonstrated that the Pd/PTABS catalytic system promotes the efficient carbonylative amidation of nucleoside **1a** with amines at a relatively low temperature. A wide spectrum of amines can be used, including heteroaryl benzyl amines, aliphatic acyclic and alicyclic amines and secondary amines. The synthetic potential of the catalytic system was further explored for the regioselective and chemoselective palladium-catalyzed amination and amidation of **4b** in order to synthesize the precursor of sangivamycin. Finally, the catalytic system was also explored towards the synthesis of two drug molecules, moclobemide and nikethamide. In summary, we have disclosed a mild catalytic system with the potential for generating a library of amide-containing nucleosides, which could be utilized for *in vitro* selection of DNA. This work will be extended to the synthesis of modified oligonucleotides and studies toward this goal are currently in progress.

Unless mentioned otherwise, all materials and solvents were obtained commercially and used without further purification. All experiments were performed under a nitrogen atmosphere. The high-pressure reactions were performed using an autoclave (Amar Equipments made autoclave of 100 mL size) in a fume hood. Column chromatography was performed using Merck silica gel (60–120 mesh size). Optical rotations were measured on a Rudolph AUTOPOL IV polarimeter at 20 °C. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 126 MHz, respectively, on an Agilent 500 MHz instrument. An Elementar Vario MICRO cube was used for the experimental determination of elemental compositions of the final pure products. HPLC anal-

yses were obtained using an Agilent 1260 Infinity instrument. Separation was achieved using a Daicel CHIRALPAK AD-H column, a flow rate of 1 mL/min and hexane/IPA (80:20) as the eluent.

Carbonylative Amidation; General Procedure

5′-*O*-(4,4′-Dimethoxytrityl)-5-iodo-2′-deoxyuridine (5′-*O*-DMT-5-IdU) (**1a**) (1.0 mmol, 656mg), the corresponding amine **2** (2.0 mmol), $Pd(OAc)_2$ (2 mol%), PTABS ligand (4 mol%), Et_3N (10 mmol) and N_2-purged DMF (10 mL) were added to a 100 mL stainless steel autoclave reaction flask at room temperature. The autoclave was closed and flushed with nitrogen gas and then pressurized with CO gas (40 psi). **Caution**! Carbon monoxide (CO) is an odorless, colorless and highly toxic gas. The reactions should be carried out in efficient fume hoods fitted with CO detectors. The reaction mixture was stirred with a mechanical stirrer (500 rpm) and heated at 60 °C for 24 h. The mixture was then allowed to cool to room temperature and the CO was vented carefully in a fume hood by adding $KMnO_4$ solution. The reaction mass was diluted in cold water and subsequently extracted with EtOAc (3 × 25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. A slurry was prepared from the residue using silica gel and the product was isolated by column chromatography (60–120 neutralized silica gel; $CHCl_3$/MeOH/Et_3N, 97.5:2.0:0.5).

N-Benzyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3a)

Yield: 544 mg (82%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.05 (t, *J* = 6.6 Hz, 1 H), 8.43 (s, 1 H), 7.35–7.09 (m, 15 H), 6.83 (d, *J* = 8.7 Hz, 4 H), 6.03 (ddd, *J* = 6.9, 4.0, 1.8 Hz, 1 H), 5.33–5.26 (m, 1 H), 4.46–4.40 (m, 2 H), 4.09–4.02 (m, 1 H), 3.89 (s, 1 H), 3.67 (d, *J* = 1.7 Hz, 6 H), 3.16–3.12 (m, 2 H), 2.24–2.13 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.6, 161.9, 158.4, 149.8, 146.0, 145.2, 139.6, 135.7, 130.1, 130.0, 128.7, 128.2, 127.6, 127.3, 127.0, 113.6, 105.5, 86.4, 86.3, 86.1, 70.7, 64.0, 55.3, 46.1, 42.5.

Anal. Calcd for $C_{38}H_{37}N_3O_8$: C, 68.77; H, 5.62; N, 6.33. Found: C, 68.59; H, 5.52; N, 6.33.

N-(Naphthalen-1-ylmethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3b)

Yield: 534 mg (75%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.14–9.08 (m, 1 H), 8.50 (dd, *J* = 4.7, 2.0 Hz, 1 H), 8.11–8.05 (m, 1 H), 7.96–7.90 (m, 1 H), 7.87–7.81 (m, 1 H), 7.56–7.47 (m, 2 H), 7.47–7.41 (m, 2 H), 7.41–7.34 (m, 2 H), 7.34–7.19 (m, 7 H), 7.19–7.12 (m, 1 H), 6.90–6.81 (m, 4 H), 6.08–6.03 (m, 1 H), 5.40–5.26 (m, 1 H), 4.98–4.90 (m, 2 H), 4.11–4.06 (m, 1 H), 3.95–3.91 (m, 1 H), 3.69–3.64 (m, 6 H), 3.19–3.16 (m, 2 H), 2.31–2.24 (m, 1 H), 2.23–2.16 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.7, 161.7, 158.45, 158.42, 149.8, 146.1, 145.3, 135.8, 135.7, 134.7, 133.7, 131.1, 130.2, 130.1, 129.0, 128.2, 128.1, 128.0, 126.8, 126.3, 125.9, 123.7, 113.6, 105.3, 86.5, 86.3, 86.1, 70.8, 64.0, 55.3, 55.3, 46.1.

Anal. Calcd for $C_{42}H_{39}N_3O_8$: C, 70.67; H, 5.51; N, 5.89. Found: C, 70.67; H, 5.31; N, 5.63.

N-(4-Fluorobenzyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3c)

Yield: 544 mg (80%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.97 (s, 1 H), 9.07 (d, *J* = 5.5 Hz, 1 H), 8.45 (d, *J* = 2.4 Hz, 1 H), 7.39–7.04 (m, 13 H), 6.90–6.79 (m, 4 H), 6.05 (t, *J* = 5.9 Hz, 1 H), 5.38–5.34 (m, 1 H), 4.41 (d, *J* = 13.2 Hz, 2 H), 4.07 (d, *J* = 5.3 Hz, 1 H), 3.94–3.89 (m, 1 H), 3.75–3.62 (m, 6 H), 3.14 (dd, *J* = 9.3, 8.1 Hz, 2 H), 2.27 (dd, *J* = 15.2, 4.0 Hz, 1 H), 2.23–2.17 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.3, 161.7, 161.4 (d, *J* = 243.1 Hz), 158.2, 149.6, 145.8, 145.0, 135.6, 135.5, 129.9, 129.8, 129.5 (d, *J* = 8.1 Hz), 127.9 (d, *J* = 21.4 Hz), 126.8, 115.3, 115.1, 113.4, 105.3, 86.2, 86.1, 85.9, 70.6, 63.8, 55.1, 41.6.

^{19}F NMR (471 MHz, DMSO-d_6): δ = –116.0.

Anal. Calcd for $C_{38}H_{36}FN_3O_8$: C, 66.95; H, 5.32; N, 6.16. Found: C, 66.75; H, 5.22; N, 6.10.

N-(4-Methoxybenzyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3d)

Yield: 568 mg (82%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.99 (d, *J* = 6.0 Hz, 1 H), 8.47 (s, 1 H), 7.35 (d, *J* = 7.7 Hz, 2 H), 7.28–7.15 (m, 10 H), 6.85 (t, *J* = 8.5 Hz, 6 H), 6.06 (t, *J* = 6.4 Hz, 1 H), 5.35 (d, *J* = 4.6 Hz, 1 H), 4.41–4.35 (m, 2 H), 4.08 (dt, *J* = 9.1, 4.5 Hz, 1 H), 3.92 (dd, *J* = 8.7, 4.4 Hz, 1 H), 3.70 (s, 9 H), 3.17 (d, *J* = 4.4 Hz, 2 H), 2.28–2.18 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.6, 162.7, 161.7, 158.7, 158.4, 149.8, 146.0, 145.3, 135.8, 135.7, 131.5, 130.1, 129.1, 128.2, 127.0, 114.2, 113.6, 105.5, 86.4, 86.3, 86.1, 70.7, 64.0, 55.4, 42.0, 36.2.

Anal. Calcd for $C_{39}H_{39}N_3O_9$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.41; H, 5.52; N, 5.98.

N-Phenethyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3e)

Yield: 582 mg (86%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.93 (s, 1 H), 8.72 (t, *J* = 5.7 Hz, 1 H), 8.44 (s, 1 H), 7.35 (d, *J* = 7.4 Hz, 2 H), 7.27 (d, *J* = 7.9 Hz, 3 H), 7.26–7.16 (m, 9 H), 6.87 (d, *J* = 8.4 Hz, 4 H), 6.05 (t, *J* = 6.4 Hz, 1 H), 5.35 (d, *J* = 4.6 Hz, 1 H), 4.08 (td, *J* = 8.9, 4.4 Hz, 1 H), 3.91 (dd, *J* = 8.8, 4.4 Hz, 1 H), 3.70 (d, *J* = 1.1 Hz, 6 H), 3.50–3.44 (m, 2 H), 3.20–3.14 (m, 2 H), 2.76 (t, *J* = 7.2 Hz, 2 H), 2.28–2.24 (m, 1 H), 2.20 (dd, *J* = 13.4, 6.7 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.5, 161.7, 158.4, 149.8, 145.8, 145.3, 139.6, 135.9, 135.7, 130.1, 129.0, 128.8, 128.2, 127.0, 126.6, 113.6, 105.5, 86.3, 86.2, 86.1, 70.7, 63.9, 55.3, 40.6, 35.6.

Anal. Calcd for $C_{39}H_{39}N_3O_8$: C, 69.11; H, 5.80; N, 6.20. Found: C, 69.19; H, 5.63; N, 6.03.

N-(3,4-Dimethoxyphenethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3f)

Yield: 589 mg (69%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.71 (t, *J* = 5.6 Hz, 1 H), 8.44 (s, 1 H), 7.35 (d, *J* = 7.4 Hz, 2 H), 7.29–7.21 (m, 6 H), 7.18 (t, *J* = 7.3 Hz, 1 H), 6.87 (d, *J* = 8.1 Hz, 4 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.81 (d, *J* = 1.8 Hz, 1 H), 6.71 (dd, *J* = 8.1, 1.8 Hz, 1 H), 6.05 (t, *J* = 6.4 Hz, 1 H), 5.35 (s, 1 H), 4.08 (s, 1 H), 3.93–3.90 (m, 1 H), 3.71 (t, *J* = 3.4 Hz, 6 H), 3.69 (d, *J* = 2.1 Hz, 6 H), 3.18–3.15 (m, 2 H), 2.69 (t, *J* = 7.0 Hz, 2 H), 2.64 (dd, *J* = 14.2, 7.1 Hz, 2 H), 2.28–2.24 (m, 1 H), 2.20 (dd, *J* = 13.3, 6.6 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.5, 161.7, 158.4, 149.8, 149.0, 147.6, 145.8, 145.2, 135.9, 132.1, 130.2, 128.2, 127.0, 120.8, 113.6, 112.9, 112.3, 105.6, 86.3, 86.2, 86.1, 70.7, 63.9, 55.9, 55.7, 55.4, 46.1, 40.8, 35.16, 11.0.

Anal. Calcd for $C_{41}H_{43}N_3O_{10}$: C, 66.75; H, 5.87; N, 5.70. Found: C, 66.63; H, 5.63; N, 5.53.

***N*-(3,3-Diphenylpropyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3g)**

Yield: 650 mg (85%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.69 (s, 1 H), 8.39 (s, 1 H), 7.45–6.99 (m, 20 H), 6.89–6.78 (m, 4 H), 6.07–6.02 (m, 1 H), 5.39–5.31 (m, 1 H), 4.10–4.05 (m, 1 H), 3.95–3.89 (m, 2 H), 3.64 (s, 6 H), 3.14 (d, *J* = 3.2 Hz, 2 H), 2.98–2.90 (m, 4 H), 2.24–2.19 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.6, 161.7, 158.4, 149.8, 145.7, 145.2, 145.2, 144.9, 135.8 (2 C), 130.1 (2 C), 128.8, 128.0 (2 C), 127.0, 126.5, 113.6, 105.6, 86.3, 86.2, 86.1, 70.8, 63.9, 55.3, 48.6, 40.4, 37.8, 34.9.

Anal. Calcd for $C_{46}H_{45}N_3O_8$: C, 71.95; H, 5.91; N, 5.47. Found: C, 71.73; H, 5.86; N, 5.37.

***N*-[(*R*)-1-Phenylethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3h)**

Yield: 568 mg (84%); off-white solid; $[\alpha]_D^{20}$ +8.088 (*c* 1.0, MeOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.11 (d, *J* = 7.8 Hz, 1 H), 8.39 (s, 1 H), 7.42–7.27 (m, 7 H), 7.26–7.20 (m, 7 H), 7.15 (dd, *J* = 10.4, 4.2 Hz, 1 H), 6.87–6.82 (m, 4 H), 6.07 (t, *J* = 6.4 Hz, 1 H), 5.44–5.30 (m, 1 H), 5.07 (dd, *J* = 14.4, 7.1 Hz, 1 H), 4.08 (dd, *J* = 10.6, 4.4 Hz, 1 H), 3.91 (dd, *J* = 9.3, 4.3 Hz, 1 H), 3.69 (s, 6 H), 3.18–3.11 (m, 2 H), 2.25 (ddd, *J* = 13.5, 6.3, 4.4 Hz, 1 H), 2.18 (dt, *J* = 13.4, 6.5 Hz, 1 H), 1.43 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.9, 161.0, 158.4, 149.9, 145.9, 145.3, 144.4, 135.9, 135.7, 130.2, 128.8, 128.2, 127.3, 127.0, 126.2, 113.6, 105.4, 86.3, 86.2, 86.1, 70.7, 64.0, 55.3, 48.4, 22.9.

Anal. Calcd for $C_{39}H_{39}N_3O_8$: C, 69.11; H, 5.80; N, 6.20. Found: C, 69.01; H, 5.80; N, 6.10.

Chiral HPLC analysis [CHIRALPAK AD-H, hexane/IPA (80:20), flow rate 1 mL min^{-1}, 250 nm, 25 °C]: t_R = 19.68 min; ee 100%.

***N*-(Furan-2-ylmethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3i)**

Yield: 522 mg (80%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.94 (s, 1 H), 8.98–8.93 (m, 1 H), 8.43 (s, 1 H), 7.54 (s, 1 H), 7.33 (d, *J* = 7.4 Hz, 2 H), 7.28–7.19 (m, 6 H), 7.18–7.14 (m, 1 H), 6.90–6.80 (m, 4 H), 6.38–6.33 (m, 1 H), 6.22 (t, *J* = 4.5 Hz, 1 H), 6.04 (q, *J* = 5.8 Hz, 1 H), 5.30 (q, *J* = 6.1 Hz, 1 H), 4.48–4.41 (m, 2 H), 4.08 (td, *J* = 6.3, 4.0 Hz, 1 H), 3.93–3.87 (m, 1 H), 3.69 (s, 6 H), 3.20–3.10 (m, 2 H), 2.26–2.14 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.6, 161.7, 158.4, 152.3, 149.8, 146.1, 145.3, 142.7, 135.8, 130.2, 128.2, 128.0, 127.0, 113.6, 110.9, 107.4, 105.2, 86.4, 86.2, 86.1, 70.7, 64.0, 55.4, 55.3, 35.8.

Anal. Calcd for $C_{36}H_{35}N_3O_9$: C, 66.15; H, 5.40; N, 6.43. Found: C, 65.95; H, 5.26; N, 6.33.

***N*-(Pyridin-3-ylmethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3j)**

Yield: 530 mg (80%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.98 (s, 1 H), 9.15 (t, *J* = 6.1 Hz, 1 H), 8.51 (d, *J* = 1.7 Hz, 1 H), 8.46 (s, 1 H), 8.43 (dd, *J* = 4.7, 1.3 Hz, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.34 (d, *J* = 7.5 Hz, 2 H), 7.29 (dd, *J* = 7.8, 4.8 Hz, 1 H), 7.27–7.21 (m, 6 H), 7.16 (t, *J* = 7.3 Hz, 1 H), 6.86 (s, 2 H), 6.84 (s, 2 H), 6.06 (t, *J* = 6.4 Hz, 1 H), 5.35 (d, *J* = 4.4 Hz, 1 H), 4.51–4.45 (m, 2 H), 4.08 (dt, *J* = 8.4, 4.2 Hz, 1 H), 3.92 (q, *J* = 4.4 Hz, 1 H), 3.69 (d, *J* = 2.4 Hz, 6 H), 3.16 (d, *J* = 4.6 Hz, 2 H), 2.27 (ddd, *J* = 10.4, 6.3, 4.4 Hz, 1 H), 2.23–2.17 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.5, 162.1, 158.4, 149.8, 149.2, 148.4, 146.1, 145.2, 135.8, 135.7, 135.6, 135.3, 130.1, 128.2, 127.0, 123.9, 113.6, 105.4, 86.4, 86.3, 86.1, 70.8, 64.0, 55.4, 46.0, 15.6, 9.0.

Anal. Calcd for $C_{37}H_{36}N_4O_8$: C, 66.86; H, 5.46; N, 8.43. Found: C, 66.65; H, 5.29; N, 8.12.

***N*-(Thiophen-2-ylmethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3k)**

Yield: 521 mg (78%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.11–9.04 (m, 1 H), 8.45 (s, 1 H), 7.38–7.31 (m, 3 H), 7.28–7.14 (m, 8 H), 7.00–6.89 (m, 2 H), 6.85 (d, *J* = 8.7 Hz, 4 H), 6.04 (t, *J* = 6.1 Hz, 1 H), 5.35–5.28 (m, 1 H), 4.59 (t, *J* = 7.6 Hz, 2 H), 4.12–4.04 (m, 1 H), 3.95–3.86 (m, 1 H), 3.69 (s, 6 H), 3.23–3.10 (m, 2 H), 2.29–2.09 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.5, 161.7, 158.4, 149.7, 146.1, 145.2, 142.3, 135.9, 130.2, 128.2, 128.1, 127.1, 127.0, 126.1, 125.6, 113.6, 105.3, 86.6, 86.3, 85.1, 70.7, 64.0, 55.4, 46.1, 37.5.

Anal. Calcd for $C_{36}H_{35}N_3O_8S$: C, 64.56; H, 5.27; N, 6.27; S, 4.79. Found: C, 64.43; H, 5.37; N, 6.17; S, 4.58.

***N*-[2-(Thiophen-2-yl)ethyl]-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3l)**

Yield: 560 mg (82%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.93 (s, 1 H), 8.81 (t, *J* = 5.9 Hz, 1 H), 8.44 (s, 1 H), 7.36–7.33 (m, 2 H), 7.31 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.29–7.21 (m, 6 H), 7.20–7.16 (m, 1 H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1 H), 6.86 (dd, *J* = 6.6, 1.8 Hz, 5 H), 6.05 (t, *J* = 6.4 Hz, 1 H), 5.34 (d, *J* = 4.6 Hz, 1 H), 4.07 (dq, *J* = 6.4, 4.4 Hz, 1 H), 3.91 (q, *J* = 4.5 Hz, 1 H), 3.70 (s, 6 H), 3.52–3.46 (m, 2 H), 3.16 (d, *J* = 4.5 Hz, 2 H), 2.98 (t, *J* = 7.0 Hz, 2 H), 2.28–2.23 (m, 1 H), 2.20 (dd, *J* = 13.5, 6.7 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.4, 161.8, 158.4, 149.8, 145.9, 145.3, 141.7, 135.9, 130.2, 128.2, 128.0, 127.4,, 127.0, 125.6, 124.5, 113.6, 105.5, 86.4, 86.2, 86.1, 70.7, 64.0, 55.3, 40.7, 36.2, 29.7.

Anal. Calcd for C, 64.99; H, 5.45; N, 6.15; S, 4.69. Found: C, 64.78; H, 5.32; N, 6.10; S, 4.51.

***N*-[2-(1*H*-Imidazol-5-yl)ethyl]-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3m)**

Yield: 520 mg (78%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.60 (d, *J* = 0.6 Hz, 1 H), 7.74 (s, 1 H), 7.35 (d, *J* = 7.3 Hz, 2 H), 7.31–7.16 (m, 8 H), 6.86 (d, *J* = 8.0 Hz, 4 H), 6.12 (t, *J* = 5.9 Hz, 1 H), 5.36 (s, 1 H), 4.27 (s, 1 H), 3.90 (s, 1 H), 3.71 (s, 6 H), 3.23–3.19 (m, 1 H), 3.06 (d, *J* = 8.0 Hz, 1 H), 2.73 (d, *J* = 9.8 Hz, 6 H), 2.22 (s, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 164.0, 160.6, 158.4, 150.2, 145.1, 140.3, 136.0, 135.7, 130.0, 128.3, 128.0, 127.1, 127.0, 113.6, 112.5, 86.2, 86.1, 85.3, 70.9, 64.1, 55.5, 46.1, 38.2, 34.9, 9.0.

Anal. Calcd for $C_{36}H_{37}N_5O_8$: C, 64.76; H, 5.59; N, 10.49. Found: C, 64.64; H, 5.45; N, 10.52.

***N*-(2-Morpholinoethyl)-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3n)**

Yield: 535 mg (78%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.99–11.88 (m, 1 H), 8.86 (t, *J* = 5.3 Hz, 1 H), 8.43 (s, 1 H), 7.34 (dd, *J* = 8.4, 1.0 Hz, 2 H), 7.24 (ddd, *J* = 10.8, 8.7, 4.8 Hz, 6 H), 7.20–7.16 (m, 1 H), 6.86 (dd, *J* = 8.9, 1.4 Hz, 4 H), 6.06 (t, *J* = 6.4 Hz, 1 H), 5.36 (d, *J* = 4.5 Hz, 1 H), 4.08 (dt, *J* = 8.9, 4.3

Hz, 1 H), 3.91 (dd, *J* = 8.6, 4.4 Hz, 1 H), 3.71 (d, *J* = 1.1 Hz, 6 H), 3.54 (s, 4 H), 3.18–3.13 (m, 2 H), 2.52–2.46 (m, 2 H), 2.46–2.29 (m, 6 H), 2.29–2.24 (m, 1 H), 2.22–2.16 (m, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.4, 161.7, 158.4, 149.8, 145.7, 145.2, 135.9, 130.0, 128.2, 128.0, 127.0, 113.6, 105.6, 86.3, 86.2, 86.1, 70.7, 66.5, 63.9, 57.1, 55.4, 53.4, 45.9, 35.8.

Anal. Calcd for $C_{37}H_{42}N_4O_9$: C, 64.71; H, 6.16; N, 8.16. Found: C, 64.56; H, 6.12; N, 8.02.

N-Cyclohexyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3o)

Yield: 457 mg (69%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.95–11.88 (m, 1 H), 8.66 (ddd, *J* = 5.7, 5.2, 2.1 Hz, 1 H), 8.40 (s, 1 H), 7.38–7.29 (m, 2 H), 7.29–7.14 (m, 7 H), 6.90–6.79 (m, 4 H), 6.07–6.02 (m, 1 H), 5.31 (d, *J* = 3.6 Hz, 1 H), 4.11–4.04 (m, 1 H), 3.89 (ddd, *J* = 5.5, 2.9, 2.1 Hz, 1 H), 3.70 (s, 6 H), 3.18–3.10 (m, 2 H), 2.25–2.12 (m, 2 H), 1.81–1.72 (m, 2 H), 1.61 (dd, *J* = 12.2, 5.1 Hz, 2 H), 1.52–1.46 (m, 1 H), 1.36–1.12 (m, 6 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.8, 160.7, 158.4, 149.8, 145.7, 145.3, 135.9, 135.7, 130.2, 128.2, 127.0, 113.7, 105.7, 86.3, 86.2, 86.1, 70.7, 64.0, 55.4, 47.4, 36.2, 32.7, 25.6, 24.5.

Anal. Calcd for $C_{37}H_{41}N_3O_8$: C, 68.77; H, 5.62; N, 6.33. Found: C, 68.58; H, 5.52; N, 6.38.

N-Cyclypentyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3p)

Yield: 435 mg (68%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.98–11.86 (m, 1 H), 8.69–8.62 (m, 1 H), 8.39 (s, 1 H), 7.37–7.30 (m, 2 H), 7.29–7.12 (m, 7 H), 6.90–6.79 (m, 4 H), 6.08–6.02 (m, 1 H), 5.35–5.29 (m, 1 H), 4.15–4.04 (m, 2 H), 3.93–3.87 (m, 1 H), 3.70 (s, 6 H), 3.19–3.10 (m, 2 H), 2.27–2.15 (m, 2 H), 1.90–1.79 (m, 2 H), 1.58 (ddd, *J* = 21.2, 13.8, 8.1 Hz, 4 H), 1.43–1.33 (m, 2 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.7, 161.1, 158.4, 149.8, 145.6, 145.2, 135.9, 130.1, 128.2, 127.0, 113.6, 105.6, 86.3, 86.2, 85.1, 70.8, 64.0, 55.4, 50.7, 33.1, 33.0, 23.7.

Anal. Calcd for $C_{36}H_{39}N_3O_8$: C, 67.38; H, 6.13; N, 6.55. Found: C, 67.16; H, 6.05; N, 6.27.

N-Adamantyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3q)

Yield: 530 mg (75%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.91 (s, 1 H), 8.56 (s, 1 H), 8.39 (d, *J* = 3.0 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz, 2 H), 7.31–7.20 (m, 6 H), 7.20–7.16 (m, 1 H), 6.87 (d, *J* = 8.8 Hz, 4 H), 6.05 (t, *J* = 6.4 Hz, 1 H), 5.35–5.31 (m, 1 H), 4.11–4.05 (m, 1 H), 3.93–3.88 (m, 1 H), 3.71 (d, *J* = 2.6 Hz, 6 H), 3.17 (d, *J* = 4.1 Hz, 2 H), 2.29–2.23 (m, 1 H), 2.21–2.15 (m, 1 H), 1.95 (dd, *J* = 3.7 Hz, 9 H), 1.65–1.55 (m, 6 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.8, 160.4, 158.4, 149.8, 145.5, 145.2, 135.7, 130.1, 128.2, 128.0, 127.0, 113.6, 106.1, 86.26, 86.22, 86.1, 70.7, 64.0, 55.3, 51.1, 42.4, 41.6, 36.5, 36.3, 29.3, 29.2.

Anal. Calcd for $C_{41}H_{45}N_3O_8$: C, 69.57; H, 6.41; N, 5.94. Found: C, 69.53; H, 6.27; N, 5.69.

N-*n*-Decyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3r)

Yield: 541 mg (76%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.89 (ddd, *J* = 11.4, 8.7, 4.2 Hz, 1 H), 8.63 (s, 1 H), 8.40 (s, 1 H), 7.31 (d, *J* = 7.1 Hz, 2 H), 7.25–7.13 (m, 6 H), 6.82 (d, *J* = 8.4 Hz, 4 H), 6.06–6.00 (m, 1 H), 5.32 (d, *J* = 3.5 Hz, 1 H), 4.11–4.03 (m, 1 H), 3.89 (d, *J* = 3.4 Hz, 1 H), 3.67 (s, 6 H), 3.17 (dd, *J* = 11.9, 7.2 Hz, 4 H), 2.23 (s, 1 H), 2.16 (d, *J* = 6.3 Hz, 1 H), 1.40 (d, *J* = 3.8 Hz, 2 H), 1.17 (s, 18 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.6, 161.6, 158.4, 149.8, 145.6, 145.2, 135.9, 135.7, 130.1, 128.2, 126.9, 113.6, 105.7, 86.3, 86.2, 86.1, 70.7, 63.9, 55.3, 38.8, 31.7, 29.5, 29.4, 29.3, 29.1, 26.8, 22.5, 14.3.

Anal. Calcd for $C_{41}H_{51}N_3O_8$: C, 68.98; H, 7.20; N, 5.89. Found: C, 68.78; H, 7.01; N, 5.71.

N-Oleyl-5-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3s)

Yield: 675 mg (82%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.94 (s, 1 H), 8.66 (t, *J* = 5.6 Hz, 1 H), 8.43 (s, 1 H), 7.34 (d, *J* = 7.9 Hz, 2 H), 7.21 (ddd, *J* = 30.6, 14.0, 7.3 Hz, 7 H), 6.89–6.81 (m, 4 H), 6.06 (t, *J* = 6.4 Hz, 1 H), 5.35–5.24 (m, 3 H), 4.08 (dt, *J* = 8.5, 4.2 Hz, 1 H), 3.91 (dd, *J* = 8.5, 4.3 Hz, 1 H), 3.70 (s, 6 H), 3.21 (dd, *J* = 12.7, 6.4 Hz, 2 H), 3.16 (d, *J* = 4.1 Hz, 2 H), 2.29–2.22 (m, 1 H), 2.22–2.14 (m, 1 H), 2.00–1.85 (m, 4 H), 1.42 (d, *J* = 5.7 Hz, 2 H), 1.20 (s, 22 H), 0.81 (t, *J* = 5.7 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 163.6, 161.6, 158.4, 149.8, 145.7, 145.2, 135.9, 135.7, 130.2, 130.0, 128.0, 127.0, 113.6, 105.7, 86.3, 86.2, 86.1, 70.7, 63.9, 55.3, 38.8, 32.3, 31.7, 29.5, 29.2, 29.1, 29.0, 27.0, 26.8, 22.5, 14.3.

Anal. Calcd for $C_{49}H_{65}N_3O_8$: C, 71.42; H, 7.95; N, 5.10. Found: C, 71.26; H, 7.79; N, 5.19.

5-(Piperidine)-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3t)

Yield: 461 mg (72%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.58 (s, 1 H), 7.66 (s, 1 H), 7.34 (d, *J* = 7.4 Hz, 2 H), 7.28 (t, *J* = 7.7 Hz, 2 H), 7.24–7.18 (m, 5 H), 6.87 (d, *J* = 8.3 Hz, 4 H), 6.11 (t, *J* = 6.7 Hz, 1 H), 5.33 (t, *J* = 4.6 Hz, 1 H), 4.22 (dt, *J* = 9.1, 4.6 Hz, 1 H), 3.90–3.87 (m, 1 H), 3.72 (d, *J* = 0.5 Hz, 6 H), 3.49–3.35 (m, 2 H), 3.28–3.06 (m, 5 H), 1.51–1.24 (m, 7 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.3, 160.7, 158.4, 150.2, 145.1, 139.7, 136.0, 130.0, 128.3, 128.0, 127.0, 113.6, 112.4, 86.2, 86.1, 85.3, 79.6, 70.9, 64.1, 55.4, 47.9, 42.4, 26.2, 25.4, 24.2.

Anal. Calcd for $C_{36}H_{39}N_3O_8$: C, 67.38; H, 6.13; N, 6.55. Found: C, 67.45; H, 6.20; N, 6.45.

5-(Pyrrolidine)-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3u)

Yield: 470 mg (75%); off-white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.62 (s, 1 H), 7.76 (s, 1 H), 7.34 (d, *J* = 7.5 Hz, 2 H), 7.27 (t, *J* = 7.7 Hz, 2 H), 7.21 (ddd, *J* = 17.7, 10.7, 6.0 Hz, 5 H), 6.89–6.83 (m, 4 H), 6.11 (t, *J* = 6.7 Hz, 1 H), 5.34 (d, *J* = 4.4 Hz, 1 H), 4.24 (dt, *J* = 9.1, 4.4 Hz, 1 H), 3.91–3.88 (m, 1 H), 3.71 (s, 6 H), 3.25–3.15 (m, 4 H), 3.09–3.05 (m, 2 H), 2.25–2.19 (m, 2 H), 1.70–1.58 (m, 4 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.2, 160.4, 158.4, 150.1, 145.1, 140.5, 135.9, 130.0, 128.3, 128.0, 127.0, 113.6, 113.2, 86.2, 86.1, 85.3, 70.9, 64.1, 55.4, 47.3, 45.9, 36.2, 25.7, 24.2.

Anal. Calcd for $C_{35}H_{37}N_3O_8$: C, 66.97; H, 5.94; N, 6.69. Found: C, 66.88; H, 5.87; N, 6.85.

5-(Morpholine)-carboxamide-5′-*O*-DMT-2′-deoxyuridine (3v)

Yield: 527 mg (82%); off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.58 (s, 1 H), 7.77–7.72 (m, 1 H), 7.35–7.16 (m, 9 H), 6.85 (d, *J* = 8.6 Hz, 4 H), 6.09 (dt, *J* = 11.2, 5.5 Hz, 1 H), 5.29 (dd, *J* = 8.3, 4.3 Hz, 1 H), 4.19 (dd, *J* = 10.9, 7.6 Hz, 1 H), 4.04–

3.94 (m, 1 H), 3.90–3.84 (m, 1 H), 3.70 (s, 6 H), 3.47–3.40 (m, 2 H), 3.20–3.03 (m, 4 H), 2.24–2.14 (m, 2 H), 1.98–1.93 (m, 1 H), 1.25–1.09 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 162.7, 160.7, 158.4, 150.2, 145.2, 140.9, 135.9, 130.0, 128.3, 128.0, 127.0, 113.6, 113.1, 111.6, 86.1, 85.4, 70.8, 66.6, 64.1, 55.4, 47.5, 42.3, 21.2, 14.5.

Anal. Calcd for $C_{35}H_{37}N_3O_9$: C, 65.31; H, 5.79; N, 6.53. Found: C, 65.09; H, 5.53; N, 6.43.

4-Chloro-5-iodo-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (4c)

Yield: 255 mg (59%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.78 (s, 1 H), 8.32 (s, 1 H), 8.05 (s, 1 H), 8.03 (s, 1 H), 7.46 (s, 1 H), 7.44 (s, 1 H), 2.35 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 152.9, 152.8, 150.4, 147.2, 133.8, 133.0, 130.8, 128.53, 118.8, 59.4, 21.6.

Anal. Calcd for $C_{13}H_9ClN_3O_2S$: C, 36.01; H, 2.09; N, 9.69; S, 7.39. Found: C, 36.25; H, 2.22; N, 9.78; S, 7.45.

***N*-Benzyl-4-(benzylamino)-7-tosyl-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxamide (4d)**

Yield: 409 mg (80%); white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (dq, *J* = 5.6, 3.5 Hz, 1 H), 9.42–9.35 (m, 1 H), 8.58 (s, 1 H), 8.22 (s, 1 H), 7.99 (d, *J* = 7.8 Hz, 2 H), 7.43 (d, *J* = 7.9 Hz, 2 H), 7.37–7.12 (m, 10 H), 4.69 (d, *J* = 5.4 Hz, 2 H), 4.45 (d, *J* = 4.4 Hz, 2 H), 2.33 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.8, 156.9, 154.65, 154.64, 150.3, 146.7, 139.5, 139.1, 134.1, 130.6, 128.86, 128.82, 128.4, 127.9, 127.6–127.1 (m), 124.8, 114.2, 102.9, 43.7, 43.1, 21.5.

Anal. Calcd for $C_{28}H_{25}N_5O_3S$: C, 65.74; H, 4.93; N, 13.69; S, 6.27. Found: C, 65.72; H, 4.96; N, 13.72; S, 6.32.

4-Chloro-*N*-(2-morpholinoethyl)benzamide (Moclobemide) (5c)[53]

The general procedure was followed employing Et_3N (2 equiv) and 2-morpholinoethan-1-amine (2 equiv).

Yield: 190 mg (94%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35–8.26 (m, 2 H), 7.55 (t, *J* = 9.7 Hz, 1 H), 7.48–7.41 (m, 2 H), 3.74–3.71 (m, 4 H), 3.50–3.46 (m, 2 H), 2.58 (ddd, *J* = 5.9, 5.3, 2.2 Hz, 2 H), 2.50 (s, 4 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 186.4, 161.5, 141.1, 132.6, 128.9, 66.9, 56.7, 53.3, 35.7.

***N*,*N*-Diethylnicotinamide (Nikethamide) (6c)**[54]

Yield: 163 mg (92%); pale yellow oil.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.61 (dd, *J* = 4.9, 1.7 Hz, 1 H), 8.56–8.53 (m, 1 H), 7.79–7.76 (m, 1 H), 7.44 (ddd, *J* = 7.8, 4.9, 0.8 Hz, 1 H), 3.43 (d, *J* = 6.6 Hz, 2 H), 3.15 (d, *J* = 6.7 Hz, 2 H), 1.13 (t, *J* = 6.3 Hz, 3 H), 1.03 (t, *J* = 6.3 Hz, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 168.1, 150.5, 147.2, 134.4, 133.4, 124.0, 43.4, 39.3, 14.5, 13.2.

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