Microwave Assisted Synthesis & Structure Activity Relationship of 2-Hydroxy-2-phenyl-2,3-dihydro-imidazo[1,2-a]pyrimidinium Salts and 2N-Substituted 4(5)-Phenyl-2-Amino-1H-imidazoles as Inhibitors of the Biofilm Formation by Salmonella Typhimurium and Pseudomonas aeruginosa
In the current chapter a library of 1-substituted 2-hydroxy-2-phenyl-2,3-dihydro-imidazo[1,2-a]pyrimidinium salts and 2N-substituted 4(5)-phenyl-2-amino-1H-imidazoles was synthesized via microwave assisted protocol and tested for the antagonistic effect against biofilm formation by *Salmonella* Typhimurium and *Pseudomonas aeruginosa*.

**Publications:**


2.1 Introduction

As described in chapter-1 the class of 2-aminoimidazoles has recently been given particular interest due to various biological properties of these compounds. 2-Aminoimidazole alkaloids and their metabolites, isolated from the marine sponges *Hymeniacidon* sp., have been described as potent antagonists of serotonergic\textsuperscript{1} and histaminergic\textsuperscript{2} receptors. Naamine and isonaamine alkaloids from the marine sponges *Leucetta* sp. exhibit antiviral and anticancer activity.\textsuperscript{3,4} Because of these interesting biological activities, numerous synthetic routes to 1-substituted and 1-unsubstituted 2-aminoimidazoles have been reported. Modern synthetic methods for accessing 1-unsubstituted 2-amino-1\textit{H}-imidazoles can be roughly classified as heterocyclization of substituted or protected guanidines with 1,2-dielectrophiles,\textsuperscript{5a-c} heteroaromatic nucleophilic substitution\textsuperscript{5c,6} and recyclization of 2-aminooxazoles.\textsuperscript{7} Although different substituted guanidines are readily available and can be prepared in situ (e.g. from cyanamines\textsuperscript{8}), the high basicity of guanidines together with non-regioselectivity often leads to multiple products.\textsuperscript{9} Protection by acetyl\textsuperscript{5a} and Boc-groups\textsuperscript{5c} requires, in turn, acidic deprotection conditions. Another procedure is the cyclocondensation of aldehydes and guanidine nitrate using sodium cyanide and supported aluminum oxide, which provides symmetric 2-aminoimidazoles.\textsuperscript{10}

Recently, we described two new approaches to the synthesis of substituted 2-amino-1\textit{H}-imidazoles. The first approach is based on the cleavage of imidazo[1,2-\textit{a}]pyrimidines\textsuperscript{11} with hydrazine\textsuperscript{12} In the second approach we reported microwave assisted one pot synthesis.(scheme-3)\textsuperscript{13}
2.2 Reaction scheme:

2.2.1 2-amino pyridine: (Scheme-1)

\[
\text{N}\text{N} + \text{R-NH}_2 \xrightarrow{\text{TEA, EtOH, MW}} 120 \degree \text{C}, 25 \text{ min} \xrightarrow{\text{R}} \text{N}\text{N}
\]

2.2.2 Synthesis of substituted 2-amino 1\text{H}-imidazole. (Scheme-2)

\[
\text{N}\text{N} + \text{MeCN, MW} \xrightarrow{80 \degree \text{C}, 30 \text{ min}} \text{Br} \xrightarrow{\text{MeCN, MW}} \text{N}-\text{R} \xrightarrow{64\% \text{N}_2\text{H}_4, \text{MeCN, MW}} \text{R}_1 \xrightarrow{100 \degree \text{C}, 10 \text{ min}} \text{H}\text{N}\text{N}\text{N} \text{H}_{\text{R}_2}
\]

2.2.3 One-Pot approach: (Scheme-3)

\[
\text{N}\text{N} + \text{Br} \xrightarrow{1. \text{MW, 80 \degree C, MeCN, 30 min}} \text{N}\text{N} \xrightarrow{2. \text{N}_2\text{H}_4, \text{MW 90 \degree C, MeCN, 10 min}} \text{H}\text{N}\text{N}\text{N} \text{H}_{\text{R}_2}
\]
2.3 **Proposed Mechanism:**

Regarding the mechanism of the transformation of 2-hydroxy-2,3-dihydro-1H-imidazo[1,2-\(\alpha\)]pyrimidinium salts into 2-amino-1H-imidazoles, we presume that the reaction proceeds via an unusual Dimroth-type rearrangement\(^\text{14-16}\) (Scheme-4).

**Scheme-4: Proposed Mechanism for the Dimroth-type Rearrangement of 2-Hydroxy-2,3-dihydro-1H-imidazo[1,2-\(\alpha\)]pyrimidinium Salts III-12**

In the first step, the 2-hydroxy-2,3-dihydroimidazo[1,2-\(\alpha\)]pyrimidinium salt (1) undergoes cleavage of the pyrimidine ring, resulting in the generation of pyrazole and 2-amino-5-hydroxyimidazolidine (C), which is in equilibrium with the open form (D). This can cyclize again leading to the isomeric 2-amino-5(4)-hydroxyimidazolidines (E). Both isomers (C) and (E) were detected by mass-spectrometry. Final dehydratation upon microwave irradiation, results in the rearranged 2-amino-1H-imidazoles 2. This dehydratation step, as judged by mass-spectrometry, was found to be the slowest step of the transformation. While some 2-amino-5(4)-hydroxyimidazolidines (E) lost water spontaneously at room temperature, other required higher temperature upon microwave irradiation. Therefore all reactions were run at 100 °C, preventing the sequence from stopping after the first step.
2.4 Results and discussion:

Initially careful investigation of the formation and dehydration of salt (3) resulting in the formation of salt (4) under conventional heating conditions as well as upon microwave irradiation has been studied. As a proof of concept, the condensation of 2-methylaminopyrimidine (1, R1 = Me) and α-phenacylbromide (2, R2 = Ph) was studied (Table 1). A sealed vial containing a solution of the starting compounds in acetonitrile was conventionally heated with an oil bath (Table 1, No-1-6) or irradiated with microwaves (Table 1, No-7-12) at different temperatures for 30−60 min. The formation of the 2-hydroxy salt (3) was faster under microwave irradiation and this compound was obtained in 88% yield within 30 min. Further increase of the temperature up to 120 °C using conventional heating or microwave irradiation led to a mixture of salts (3) and (4) (Table 1). Interestingly, using microwave irradiation at 120 °C for 60 min, we were able to drive the reaction completely to the formation of the imidazo[1,2-a]pyrimidinium salt (4) (Table 1, No-12).

![Chemical structure](image)

<table>
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All reactions were carried out on a 1 mmol scale of 2-methylaminopyrimidine (1, R₁ = Me) with 1.35 equiv of α-phenacylbromide (2, R₂ = Ph) in MeCN (5 mL); isolated yield after recrystallization from MeCN.

**Table-1:** Investigation of the condensation under conventional heating and microwave irradiation

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<th>R₂</th>
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<td>2</td>
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As the transformation of salts (3) into salts (4) is relatively rapid at the temperatures above 100 °C, the synthesis of salts 3 was conducted at 80 °C. Treatment of substituted 2-aminopyrimidines (1) with 15 mol % excess of α-bromoketones (2) in MeCN under microwave irradiation for 30 min generated the intermediate salts (3) which, in most cases, precipitated from the reaction mixture upon cooling (Table-2). Reaction progress was monitored by mass-spectrometry. In all cases examined, the reaction appeared to be complete after 30 min. The cleavage step was performed under microwave irradiation at 90 °C, using 7 equivalents of hydrazine hydrate. Based on the data given in (Table-2), the reaction appears to be compatible with both aryl and alkyl substitutions. All the reactions were clean, smooth, and provided the products in good and high yields. The compounds were purified by column chromatography using 5–10% MeOH in CH₂Cl₂ as the eluent. All the final 2-amino-1H-imidazoles were characterized by ¹H and ¹³C NMR spectroscopy. Their composition was also confirmed by HRMS.
<p>| | | |</p>
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</table>

*Compounds have been synthesized via One-pot protocol (Scheme-3).

All compounds are either oily or amorphous solid.

**Table-2: Microwave assisted synthesis of substituted 2-amino-1H-imidazoles.**

**2.5 Biofilm activity:**

Bacteria are able to switch between a planktonic life style and a biofilm mode of growth, in which they live as structured communities of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface. As bacteria in biofilms are more resistant to challenges from predators, antibiotics, disinfectants and host immune systems, serious problems and high costs have been associated with biofilms, both in medicine and industrial settings. According to the National Institutes of Health, more than 80% of microbial infections are related to biofilms. Especially the use of indwelling medical devices comprises a high risk for
the development of biofilm related infections. This high prevalence of biofilm related infections is particularly problematic given the fact that bacteria in biofilms can be up to 1000-fold more resistant to antibiotics. In industry, biofilms have been implicated e.g. in the contamination of installations in food industry, mild steel corrosion, decreased passage through pipelines by colonization of the interior of the pipes, and enhanced resistance of vessels by initiation of “biofouling” on the vessel hulls. The yearly economic loss caused by ‘biofouling’ in the marine industry is estimated at $ 6.5 billion.

One way to deal with this problem is the development of small molecules that are able to prevent or destroy biofilm formation. Only a few molecular scaffolds have been identified to date, among which the best-studied examples are (1) the halogenated furanones, which were originally isolated from the seaweed Delisea pulchra, (2) analogues of the homoserine lactone signalling molecules and (3) analogues of the sponge-derived marine natural alkaloids oroidin and bromoageliferin. A particularly valuable approach is the development of small molecules that specifically target the biofilm formation in a non-toxic manner, as it is expected that resistance against these compounds will emerge much slower than against classical microbiocidal compounds. As a consequence, non-toxic biofilm inhibitors have the potential to be used in a preventive treatment of a wide diversity of industrial and medical surfaces. Furthermore, the potential to co-dose biofilm inhibitors and classical antibiotics for the treatment of biofilm infections is also an attractive option.

Salmonella enterica serovar Typhimurium and Pseudomonas aeruginosa are two well studied organisms in terms of biofilm formation. Salmonella enterica is worldwide one of the most important causes of foodborne infections. Salmonella is able to form biofilms on a variety of both biotic surfaces (such as gallstones, plant surfaces, and epithelial cell layers) and abiotic surfaces (such as concrete, plastics, glass, polystyrene, …). These biofilms are an important survival strategy in all stages of infection, from transmission to chronic infection. Severe non-typhoid Salmonella infections are commonly treated with fluoroquinolones and third-generation cephalosporins. Unfortunately, there are alarming reports concerning the development of resistance against these antibiotics, underlining the urgent need of alternative anti-Salmonella strategies. Given the importance of biofilms in the spread of Salmonella, the development of Salmonella biofilm inhibitors seems a promising
approach. *P. aeruginosa* is an opportunistic pathogen implicated in a myriad of infections. Patients with compromised host defenses, such as burn patients, HIV patients and cystic fibrosis patients (80% colonization rate of *P. aeruginosa*) are particularly susceptible to *P. aeruginosa* infections. *P. aeruginosa* biofilms have been related to recurrent ear infections, chronic bacterial prostatitis and lung infections in CF patients, the latter being extremely harmful as *P. aeruginosa* colonization and chronic lung infection is the major causative agent of morbidity and mortality in CF patients. Moreover, *P. aeruginosa* can colonize as biofilms a variety of medical devices such as intravascular catheters and urinary catheters. Obviously there is an urgent need of agents that can prevent or eradicate *P. aeruginosa* biofilms on infected tissues and on medical devices.

### 2.5.1 2N-substituted 2-aminopyrimidines

Some members of the 2-aminopyrimidine class of compounds have previously been shown to possess antibacterial and antifungal activity. These molecules are the precursors of the N1-substituted diazo[1,2-a]pyrimidinium salts in our synthesis pathway (scheme-2). The availability of a broad array of 2-aminopyrimidines, substituted with n-alkyl, cyclo-alkyl and aromatic groups at the N2-position prompted us to investigate the potential of this class of compounds as biofilm inhibitors. The influence of compounds on the biofilm formation of *S. Typhimurium* was tested at 25°C. Remarkably, none of the compounds does have an effect on the biofilm formation at 400 µM, which was the highest concentration tested.

### 2.5.2 2-hydroxy-2,3-dihydro-imidazopyrimidinium salts

A broad array of 1-substituted 2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts were synthesized via previously established chemistry from our laboratory and their ability to prevent the biofilm formation of *S. Typhimurium* and *P. aeruginosa* was tested. These molecules differ in the substitution pattern of the 2-phenyl ring and in the nature of the substituent at the 1-position i.e. n-alkyl, iso-alkyl, cyclo-alkyl.

#### 2.5.2.1 n-Alkyl or iso-alkyl substituents at 1-position
In first instance, a series of 2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts with a broad variety of n-alkyl or iso-alkyl substituents at the 1-position, with lengths ranging from 1 carbon atom to 14 carbon atoms was synthesized. The 2-phenyl group of these salts is either unsubstituted, para-substituted with a chlorine atom, a nitro group, a fluorine atom, a bromine atom or a methoxy group, or 3,4-disubstituted with chlorine atoms. Each compound was assayed for the ability to inhibit S. Typhimurium ATCC14028 biofilm formation at 25 °C. As depicted in figure 1A, a clear correlation was found between the length of the alkyl substituent and the biofilm inhibitory activity. In general the activity of the molecules with a short alkyl chain was found to be very low (IC$_{50}$ > 400 µM). Within a series of molecules with the same substitution of the 2-phenyl ring, in general a gradual increase in biofilm inhibitory activity was observed by raising the length of the alkyl chain from 1 to 8 carbon atoms. The compounds with an octyl substituent show a maximal activity with IC$_{50}$ values in the range of 6-11 µM. By further raising the alkyl chain length from 8 to 14 carbon atoms, a gradual decrease in biofilm inhibitory activity was observed. For the molecules with a heptyl, octyl, nonyl and decyl side chain (which are the most active molecules), the nature of the substituent of the 2-phenyl group does not have a substantial effect on the biofilm inhibitory activity.

Next the influence of a subset of the 2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts for their ability to prevent the biofilm formation of P. aeruginosa was studied. As represented in table-4 and figure-1B, a similar structure activity relationship was found as in the case of Salmonella biofilm inhibition. Compounds with short alkyl substituents (C1-6) in general only have a slight effect on the biofilm formation (IC$_{50}$’s >80 µM), while compounds with medium length side chains (C7-C10) have IC$_{50}$ values between 20-40 µM and compounds with long side chains (C11-C14) have IC$_{50}$ values higher than 800 µM. However, it should be mentioned that some of the compounds with long side chain do reduce the biofilm formation to a certain extent, but their dose response curves reach a steady state level of 25 to 45 % biofilm inhibition starting from concentrations between 25 and 50 µM.
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IC$_{50}$: Concentration of inhibitor needed to inhibit biofilm formation by 50%.

**Table-4:** Influence of 1-alkylated 2-hydroxy-2,3-dihydro-imidazo[1,2-a]pyrimidinium salts on the biofilm formation of *S. Typhimurium* ATCC14028 and *P. aeruginosa* PA14 at 25°C.
2.5.2.2 Further Modification in the most active core structure

Since the compounds with a n-octyl chain substituted at the 1-position have the highest activity against Salmonella biofilms and also have a high activity against Pseudomonas biofilms, we decided to synthesize the additional 1-octyl-2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts with more variation in the substitution pattern of the 2-phenyl ring. As depicted in Table 5 these compounds generally inhibit biofilm formation of S. Typhimurium at low concentrations. However, no improved activity was observed in comparison with the previously described compounds (Table 2). The effect of the n-octyl substituted compounds on the biofilm formation of P. aeruginosa strongly depends on the substitution pattern of the 2-phenyl ring, as some
of the compounds have low \( IC_{50} \) values (10-40 µM), while the other compounds only have a moderate activity (\( IC_{50} = 100-400 \) µM).

![Chemical structure](image)

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<th>CODE</th>
<th>R</th>
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<th>( P. ) aeruginosa IC(_{50})</th>
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<td>4-F</td>
<td>7.6</td>
<td>nd</td>
</tr>
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<td>4-OMe</td>
<td>10.5</td>
<td>nd</td>
</tr>
<tr>
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<td>BS-177</td>
<td>3,4-diCl</td>
<td>7.1</td>
<td>nd</td>
</tr>
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**Table-5:** Influence of N1-octyl 2-hydroxy-2, 3-dihydro-imidazo[1,2-a]pyrimidinium salts on the biofilm formation of \( S. \) Typhimurium ATCC14028 and \( P. \) aeruginosa PA14 at 25°C.

### 2.5.2.3 Cyclo-alkyl substituents at 1-position

A series of 2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts with a broad variety of cyclo-alkyl substituents at the 1-position was synthesized with lengths ranging from 3 to 12 carbon atoms (Table 6). The 2-phenyl group of these salts was either unsubstantiated or para-substituted with a chlorine atom. Similarly to the structure-activity relationship delineated for the n-alkyl substituted salts, a gradual increase in the inhibitory activity against \( S. \)almonella biofilms was observed by rising the length of the cyclo-alkyl chain from 3 to 8 carbon atoms. However, in contrast to the salts with n-dodecyl chain at the 1-position, the salts with a cyclo-dodecyl chain
do have a very strong effect against *Salmonella* biofilms (IC$_{50}$ values < 6.25 µM). By analogy with (1) the effect on *Salmonella* biofilms and (2) the activity of the n-alkyl substituted salts, we found that all the cyclo-alkyl substituted salts with a short side chain do only have a slight effect on the biofilm formation of *P. aeruginosa* (IC$_{50}$’s >150 µM), while the compounds with a medium length side chain have a stronger biofilm inhibitory activity. The salts with a cyclo-dodecyl chain do drastically reduce the *Pseudomonas* biofilm formation (IC$_{50}$’s ~7 µM), in sharp contrast to the compounds with n-dodecyl side chain.

<table>
<thead>
<tr>
<th>SR</th>
<th>CODE</th>
<th>R2</th>
<th>R1</th>
<th><em>S. Typhimurium</em> IC$_{50}$</th>
<th><em>P. aeruginosa</em> IC$_{50}$</th>
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<tbody>
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<td>c-Hex</td>
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<td>3</td>
<td>BS-046</td>
<td>H</td>
<td>c-Hep</td>
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<td>c-Bu</td>
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<td>c-Pen</td>
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<td>41.9</td>
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<td>c-Doc</td>
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*Table-6:* Influence of 1-cyclo-alkyl-2-hydroxy-2,3-dihydro-imidazo[1,2-a]pyrimidinium salts on the biofilm formation of *S. Typhimurium* ATCC14028 and *P. aeruginosa* PA14 at 25°C.

### 2.5.3 2N-substituted 2-aminoimidazoles

In the present it was interesting to investigate whether introduction of n-alkyl, iso-alkyl, cyclo-alkyl or aromatic group at the 2N-position of the 4(5)-phenyl-2-amino-
1H-imidazoles could also enhance their biofilm inhibitory activity. Therefore a broad range of 2N-substituted 4(5)-phenyl-2-amino-1H-imidazoles were synthesized. An array of 4(5)-phenyl-2-aminoimidazoles 2N-substituted with either a short n- or iso-alkyl chain (C1-C5) or n-octyl chain was synthesized. As depicted in table 7, a broad diversity of (substituted) 4(5)-phenyl groups were included. The compounds with a iso-butyl substitution at the 2N-position were found to be in general more active than their 2N-unsubstituted counterparts, with respect to both the Salmonella and Pseudomonas biofilm formation.

\[
\begin{align*}
R_1 & \quad \text{N} & \quad \text{HN} & \quad \text{R}_2 \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>SR</th>
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<th>R₂</th>
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<th>P. aeruginosa IC₅₀</th>
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<td>Nd</td>
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<td>261.0</td>
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<td>C₃H₇</td>
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<tr>
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<td>4-OCH₃</td>
<td>&gt;400</td>
<td>&gt;800</td>
</tr>
<tr>
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Table-7: Influence of 2N-alkylated 2-aminoimidazoles on the biofilm formation and the planktonic growth of S. Typhimurium ATCC14028 and P. aeruginosa PA14 at 25°C.
2.6 Conclusion

In the present study, the potential of these 1-substituted 2-hydroxy-2,3-dihydro-imidazopyrimidinium salts and 2N-subsituted 2-amino-1H-imidazoles as inhibitors of the biofilm formation by *S. Typhimurium* and *P. aeruginosa* was thoroughly investigated. We found that 2-hydroxy-2,3-dihydro-imidazopyrimidinium salts with intermediate length n-alkyl chains (C7-C10) substituted at the 1-position in general prevent the biofilm formation of both species at low micromolar concentrations (IC$_{50}$ = 5-50 µM). For these molecules, the nature of the substituent of the 2-phenyl group does not have a substantial effect on the biofilm inhibitory activity. Salts with a shorter (C1-C5) or longer (C11-C14) n-alkyl chain at the 1-position were found to be much less potent. Consistent with this, we observed that salts with an intermediate length cyclo-alkyl chain are much more active against biofilm formation of both species as compared to the salts with a short cyclo-alkyl chain. However, remarkably salts with a long cyclo-dodecyl side chain were found to have even better activities than salts with an intermediate length cyclo-alkyl side chain.

In the framework of the 2-aminoimidazoles, be the introduction of a butyl, pentyl or hexyl side chain at the 2N-position of the 2-aminoimidazoles results in an enhanced biofilm inhibitory activity against both species, while introduction of a shorter n-alkyl chain reduces the biofilm inhibitory activity. The effect of introduction of longer n-alkyl chains however seems to be strongly dependent on the substitution pattern of the 5-phenyl ring and the bacterial species studied.

In conclusion, the 2N-substituted 2-aminoimidazoles and 2-hydroxy-2-phenyl-2,3-dihydro-imidazopyrimidinium salts of the present study are valuable candidates in the development of therapeutics and sanitizers for the combat of biofilm formation by *S. Typhimurium, P. aeruginosa* and possibly other pathogenic bacteria.
2.7 Experimental

2.7.1 General Methods

All chemical reagents were used without further purification. Solvents for column chromatography and TLC were laboratory grade and distilled before use. For thin-layer chromatography (TLC), analytical TLC plates (Alugram SIL G/UV454 (E. M. Merk) were used. Column chromatography was performed with flash silica gel (100-200 mesh) or neutral alumina oxide (50-200 micron). \(^1\)H and \(^{13}\)C NMR spectra were recorded on a Bruker Avance 300 (300 MHz) or a Bruker AMX-400 (400 MHz) spectrometers. NMR samples were run in the indicated solvents and were referenced internally. Chemical shift values were quoted in ppm and coupling constants were quoted in Hz. Chemical shift multiplicities were reported as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad. Low-resolution mass spectra were recorded on a HEWLETT-PACKARD instrument (CI or EI) and LCQ Advantage instrument (ESI). High-resolution mass spectra (EI) were recorded on a KRATOS MS50TC instrument. Melting points were determined using Reichert-Jung Thermovar apparatus and were uncorrected.

2.7.2 Microwave Irradiation Experiments

Microwave irradiation experiments were carried out in a dedicated CEM-Discover mono-mode microwave apparatus or Milestone MicroSYNTH multi-mode microwave reactor (Laboratory Microwave Systems). Microwave apparatuses were used in the standard configuration as delivered, operating at a frequency 2.45 GHz with continuous irradiation power from 0 to 400 W. The reactions were carried out in 10, 20, 30 and 50 mL glass tubes. The temperature was measured with an IR sensor on the outer surface of the process vial or fibre optic sensor inside the process vial. After the irradiation period, the reaction vessel was cooled rapidly (2-5 min) to ambient temperature by air jet cooling.
2.8 Biological assays

2.8.1 Static peg assay for prevention of Salmonella Typhimurium and Pseudomonas aeruginosa biofilm formation

The device used for biofilm formation is a platform carrying 96 polystyrene pegs (Nunc no. 445497) that fits as a microtiter plate lid with a peg hanging into each microtiter plate well (Nunc no. 269789). Two-fold serial dilutions of the compounds in 100 µl liquid broth (Tryptic Soy Broth diluted 1/20 (TSB 1/20)) per well were prepared in the microtiter plate (2 or 3 repeats per compound). Subsequently, an overnight culture of *S. Typhimurium* ATCC14028 (grown in Luria-Bertani medium) or *P. aeruginosa* (grown in TSB) was diluted 1:100 into the respective liquid broth and 100 µl (~10^6 cells) was added to each well of the microtiter plate, resulting in a total amount of 200 µl medium per well. The pegged lid was placed on the microtiter plate and the plate was incubated for 24 h at 25°C without shaking. During this incubation period biofilms were formed on the surface of the pegs. After 24 h, the optical density at 600 nm (OD_{600}) was measured for the planktonic cells in the microtiter plate using a VERSAmax microtiter plate reader (Molecular Devices). This gives a first indication of the effect of the compounds on the planktonic growth. For quantification of biofilm formation, the pegs were washed once in 200 µl phosphate buffered saline (PBS). The remaining attached bacteria were stained for 30 min with 200 µl 0.1% (w/v) crystal violet in an isopropanol/methanol/PBS solution (v/v 1:1:18). Excess stain was rinsed off by placing the pegs in a 96-well plate filled with 200 µl distilled water per well. After the pegs were air dried (30 min), the dye bound to the adherent cells was extracted with 30% glacial acetic acid (200 µl). The OD_{570} of each well was measured using a VERSAmax microtiter plate reader (Molecular Devices). The IC_{50} value for each compound was determined from the concentration gradient by using the GraphPad software of Prism.
2.8.2 Bioscreen assay for measuring Salmonella Typhimurium and P. aeruginosa growth inhibition

The Bioscreen device (Oy Growth Curves Ab Ltd) was used for measuring the influence of the chemical compounds on the planktonic growth of Salmonella Typhimurium and P. aeruginosa. The Bioscreen is a computer controlled incubator/reader/shaker that uses 10x10 well microtiter plates and measures light absorbance of each well at a specified wave length in function of time. An overnight culture of S. Typhimurium ATCC14028 (grown up in LB medium) or P. aeruginosa (grown up in TSB) was diluted 1:200 in liquid broth (TSB 1/20). 300 µl of the diluted overnight culture was added to each well of the 10x10 well microtiter plate. Subsequently, serial dilutions of the chemical compounds were prepared in DMSO or EtOH. 3 µl of each diluted stock solution was added to the wells (containing the 300 µl bacterial culture) in 3-fold. As a control 3 µl of the appropriate solvent was also added to the plate in 3- or 4-fold. The microtiter plate was incubated in the Bioscreen device at 25°C for at least 24 h, with continuous medium shaking. The absorbance of each well was measured at 600 nm each 15 min. Excel was used to generate the growth curves for the treated wells and the untreated control wells.

The effect of each compound concentration on the planktonic growth was classified into one of the following categories:

1) The planktonic growth is not or only slightly affected, indicated by the symbol ‘-’.
2) The planktonic growth is retarded, indicated by the symbol ‘+’.
3) The planktonic growth is completely or almost completely inhibited, indicated by the symbol ‘o’.

The following criterium was used to decide between the first and the second category: If the absorbance (measured at 600 nm) of the bacterial culture treated with the compound is at least 0.5 (for Salmonella) or 0.8 (for Pseudomonas) units lower than the absorbance of the untreated culture during 4 consecutive hours, then the effect on the planktonic growth is classified in category 2.
2.9 Experimental protocol:
2.9.1 General Procedure for the Preparation of Substituted 2-Aminopyrimidines

In a 50 mL microwave vial were successively dissolved in EtOH (20 mL) 2-chloropyrimidine (3.43 g, 30 mmol), amine (39 mmol, 1.3 equiv) and triethylamine (6.2 mL, 45 mmol, 1.5 equiv). The reaction tube was sealed, and irradiated in the cavity of a Milestone MicroSYNTH microwave reactor at a ceiling temperature of 120 °C at 100 W maximum power for 25 min. After the reaction mixture was cooled with an air flow for 15 min, it was diluted with water (100 mL), extracted with DCM (2×150 mL) and dried over Na₂SO₄. The solvent was evaporated in vacuo, and the crude mixture was purified by silica gel flash chromatography using 0-5% MeOH–DCM as the eluent.

13 new substituted 2-aminopyrimidine derivatives were synthesized in similar manner. (Table-1)

Table-1 Compound synthesized

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2.9.2 General Procedure for the Preparation of Salts.

To a solution of 2-substituted aminopyrimidine (6 mmol) and α-bromoacetophenone (7.2 mmol, 1.2 equiv) in acetonitrile (12 mL) was added 4-dimethylaminopyridine (6 mg, 0.05 mmol). After being stirred at 85 °C for 5 h, the reaction mixture was diluted with acetone (20 mL) and the precipitate was filtered and washed with acetone (2×20 mL), ether (2×20 mL) and dried over P₂O₅ to give salt as a white solid. 10 new compounds were synthesized in similar manner.

2.9.3 General Procedure for the Preparation of Salts. (Microwave)

In a 50 mL microwave vial were successively dissolved 2-substituted aminopyrimidine (6 mmol) and α-bromoacetophenone (7.2 mmol, 1.2 equiv) in acetonitrile (12 mL) was added 4-dimethylaminopyridine (6 mg, 0.05 mmol). The reaction tube was sealed, and irradiated in the cavity of a Milestone MicroSYNTH microwave reactor at a ceiling temperature of 80 °C at 100 W maximum power for 30 min. After the reaction mixture was cooled with an air flow for 15 min, the reaction mixture was diluted with acetone (20 mL) and the precipitate was filtered and washed with acetone (2×20 mL), ether (2×20 mL) and dried over P₂O₅ to give salt as a white solid. 34 new compounds were synthesized in similar manner.

2.9.4 General Procedure for the Preparation of 2-Amino-1H-imidazoles.

To a suspension of salt (2 mmol) in MeCN (5 mL) hydrazine hydrate (0.7 mL, 14 mmol of a 64% solution, 7 equiv) was added, and the mixture was irradiated in the sealed Milestone MicroSYNTH microwave reactor for 10 min at a ceiling temperature of 100 °C at 150 W maximum power. After cooling down hydrazine hydrate was evaporated with toluene (3×20 mL). The resulting residue was purified by column chromatography (silica gel; MeOH–DCM 1:4 v/v with 5% of 6M NH₃ in MeOH) to afford 2-amino-1H-imidazole as an amorphous material. 12 new compounds were synthesized in similar manner.

2.9.5 General procedure for the one-pot two-step microwave-assisted synthesis of 2-amino-1H-imidazoles.

In a microwave vial (10 mL) were successively dissolved in dry MeCN (3 mL) the corresponding 2-aminopyrimidine (4 mmol) and α-bromoketone (4.6 mmol). The reaction tube was sealed and irradiated in a microwave reactor at a ceiling
temperature of 80 °C and a maximum power of 50 W for 30 min. After the reaction mixture was cooled with an air flow for 15 min, hydrazine hydrate (0.9 mL, 28 mmol of a 64% solution, 7 equiv) was added, and the mixture was irradiated at a ceiling temperature of 90 °C and a maximum power of 50 W for another 10 min. After the reaction mixture was cooled, hydrazine hydrate was removed by distillation with toluene (3×20 mL). The resulting residue was purified by column chromatography (silica gel; MeOH-DCM 1:9 v/v with 0.5 % of 6N ammonia in MeOH) to afford 2-amino-1H-imidazole as amorphous solid. 10 new compounds were synthesized in similar manner.

2.10 Spectral Characterization

**N-Cyclooctylpyrimidin-2-amine (BS-024)**

\[
\begin{array}{c}
\text{N} \\
\text{C}_{12}\text{H}_{19}\text{N}_{3}
\end{array}
\]

Yield: 60%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.25 (d, J = 4.77 Hz, 2H), 6.46 (t, J = 4.8 Hz, 1H), 5.07 (br s, 1H), 4.04 (m, 1H), 1.93 (m, 1H), 1.63 (m, 12H). \(^13\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta = 161.6, 158.0 (\times 2), 110.0, 50.6, 31.7 (\times 2), 27.5 (\times 2), 25.3, 23.5 (\times 2).\) HRMS (EI): C\(_{12}\)H\(_{19}\)N\(_3\), calcd 205.2994, found: 205.2982.

**N-Cycloheptylpyrimidin-2-amine (BS-025)**

\[
\begin{array}{c}
\text{N} \\
\text{C}_{11}\text{H}_{17}\text{N}_{3}
\end{array}
\]

Yield: 64%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.26 (d, J = 4.77 Hz, 2H), 6.47 (t, J = 4.77 Hz, 1H), 5.09 (br s, 1H), 4.01 (m, 1H), 2.02 (m, 2H), 1.55 (m, 12H). \(^13\)C NMR (75.5 MHz, CDCl\(_3\)): \(\delta = 161.6, 158.0 (\times 2), 110.0, 51.6, 35.0 (\times 2), 28.2 (\times 2), 23.9 (\times 2).\) HRMS (EI): C\(_{11}\)H\(_{17}\)N\(_3\), calcd 191.2728, found: 191.2742.

**N-Heptylpyrimidin-2-amine (BS-026)**

\[
\begin{array}{c}
\text{N} \\
\text{C}_{7}\text{H}_{15}
\end{array}
\]

Yield: 87%. \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 8.27 (d, J = 4.8 Hz, 2H), 6.50 (t, J = 4.8 Hz, 1H), 5.07 (br s, 1H), 3.40 (m, 2H), 1.61 (m, 2H), 1.31 (m, 8H), 0.85 (m 3H). \(^13\)C
NMR (75.5 MHz, CDCl$_3$): $\delta =$162.5, 157.9 ($\times 2$), 110.1, 41.5, 31.8, 29.6, 29.0, 26.9, 22.6, 14.0. HRMS (EI): C$_{11}$H$_{19}$N$_3$, calcld 193.2887, found: 193.2894.

$N$-Octylpyrimidin-2-amine (BS-027)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_8\text{H}_{17}
\end{array}
\]

Yield: 86%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 8.27 (d, $J = 4.74$ Hz, 2H), 6.49 (t, $J = 4.77$ Hz, 1H), 5.11 (br s, 1H), 3.40 (m, 2H), 1.60 (m, 2H), 1.27 (m, 10H), 0.87 (m 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$162.4, 158.0 ($\times 2$), 110.1, 41.5, 31.8, 29.6, 29.3, 29.2, 26.9, 22.6, 14.1. HRMS (EI): C$_{12}$H$_{21}$N$_3$, calcld 207.3152, found: 207.3131.

$N$-Decylpyrimidin-2-amine (BS-028)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_{10}\text{H}_{21}
\end{array}
\]

Yield: 87%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 8.27 (d, $J = 4.8$ Hz, 2H), 6.50 (t, $J = 4.9$ Hz, 1H), 5.07 (br s, 1H), 3.38 (m, 2H), 1.60 (m, 2H), 1.26 (m, 14H), 0.87 (t, $J = 6.93$, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$162.4, 158.0 ($\times 2$), 110.1, 41.5, 31.8, 29.6 ($\times 2$), 29.5, 29.3 ($\times 2$), 26.9, 22.6, 14.1. HRMS (EI): C$_{14}$H$_{25}$N$_3$, calcld 235.3684, found: 235.3670.

$N$-Cyclobutylpyrimidin-2-amine (BS-030)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_8\text{H}_8
\end{array}
\]

Yield: 61%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 8.27 (m, 2H), 6.51 (t, $J = 4.77$ Hz, 1H), 5.29 (br s, 1H), 4.46 (m, 1H), 2.42 (m, 2H), 1.89 (m, 2H), 1.76 (m, 2H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$161.6, 158.0 ($\times 2$), 110.4, 46.3, 31.5 ($\times 2$), 15.0. HRMS (EI): C$_8$H$_{11}$N$_3$, calcld 149.1930, found: 149.1917.

$N$-Nonylpyrimidin-2-amine (BS-033)

\[
\begin{array}{c}
\text{N} \\
\text{N} \\
\text{N} \\
\text{C}_9\text{H}_{21}
\end{array}
\]

Yield: 86%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta =$ 8.27 (d, $J = 4.71$ Hz, 2H), 6.50 (t, $J = 4.77$ Hz, 1H), 5.07 (br s, 1H), 3.40 (m, 2H), 1.61 (m, 2H), 1.26 (m, 12H), 0.87 (t, $J = 6.9$, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$162.5, 158.0 ($\times 2$), 110.1, 41.5, 31.8, 29.6,
29.5, 29.4, 29.2, 27.0, 22.6, 14.1. HRMS (EI): C_{13}H_{23}N_{3}, calcd 221.3418, found: 221.3400.

**N–Undecylpyrimidin-2-amine (BS-034)**

![Undecylpyrimidin-2-amine](image)

Yield: 88%. ¹H NMR (300 MHz, CDCl₃): δ = 8.27 (d, J = 4.62 Hz, 2H), 6.50 (t, J = 4.77 Hz, 1H), 5.07 (br s, 1H), 3.40 (m, 2H), 1.60 (m, 2H), 1.25 (m, 16H), 0.87 (t, J = 6.87, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ = 162.5, 158.0 (×2), 110.2, 41.5, 31.9, 29.6 (×4), 29.3 (×2), 26.9, 22.6, 14.1. HRMS (EI): C_{15}H_{27}N_{3}, calcd 249.3950, found: 249.3938.

**N–Dodecylpyrimidin-2-amine (BS-035)**

![Dodecylpyrimidin-2-amine](image)

Yield: 89%. ¹H NMR (300 MHz, CDCl₃): δ = 8.27 (d, J = 4.41 Hz, 2H), 6.50 (t, J = 4.74 Hz, 1H), 5.07 (br s, 1H), 3.40 (m, 2H), 1.61 (m, 2H), 1.25 (m, 18H), 0.88 (t, J = 6.84, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ = 162.4, 158.0 (×2), 110.2, 41.5, 31.9, 29.6 (×5), 29.3 (×2), 26.9, 22.6, 14.1. HRMS (EI): C_{16}H_{29}N_{3}, calcd 263.4216, found: 263.4202.

**N–Tridecylpyrimidin-2-amine (BS-036)**

![Tridecylpyrimidin-2-amine](image)

Yield: 88%. ¹H NMR (300 MHz, CDCl₃): δ = 8.27 (d, J = 4.77 Hz, 2H), 6.50 (t, J = 4.8 Hz, 1H), 5.07 (br s, 1H), 3.38 (m, 2H), 1.60 (m, 2H), 1.25 (m, 20H), 0.88 (t, J = 6.9, 3H). ¹³C NMR (75.5 MHz, CDCl₃): δ = 162.4, 158.0 (×2), 110.1, 41.5, 31.9, 29.6 (×6), 29.3 (×2), 27.0, 22.7, 14.1. HRMS (EI): C_{17}H_{31}N_{3}, calcd 277.4481, found: 277.4491.

**N–Tetradecylpyrimidin-2-amine (BS-037)**

![Tetradecylpyrimidin-2-amine](image)
Yield: 88%. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 8.27 (d, $J=4.77$ Hz, 2H), 6.50 (t, $J=4.8$ Hz, 1H), 5.07 (br s, 1H), 3.38 (m, 2H), 1.60 (m, 2H), 1.25 (m, 22H), 0.88 (t, $J=6.9$, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 162.4, 158.0 ($\times$2), 110.2, 41.5, 31.9, 29.6 ($\times$7), 29.3 ($\times$2), 26.9, 22.7, 14.1. HRMS (EI): C$_{19}$H$_{33}$N$_3$, calcd 291.4747, found: 291.4723.

1-Heptyl-2-hydroxy-2-phenyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide amine (BS-049)

Yield: 75 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.85 (m, 1H), 7.80 (s, 1H), 7.77 (m, 2H), 7.49 (m, 3H), 7.31 (m, 1H), 4.82 (s, 2H), 3.17 (m, 2H), 1.36 (m, 2H), 1.09 (m, 8H), 0.80 (t, $J=6.84$ Hz, 3H).

2-Hydroxy-1-octyl-2-phenyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-052)

Yield: 73 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.86 (m, 1H), 7.80 (s, 1H), 7.75 (m, 2H), 7.47 (m, 3H), 7.31 (t, $J=5.49$ Hz, 1H), 4.83 (s, 2H), 3.17 (m, 2H), 1.36 (m, 2H), 1.09 (m, 10H), 0.83 (t, $J=6.72$ Hz, 3H).

1-Decyl-2-hydroxy-2-phenyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-055)
Yield: 78 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.03$ (d, $J = 4.62$ Hz, 1H), 8.87 (d, $J = 6.18$ Hz, 1H), 7.81 (s, 1H), 7.74 (m, 2H), 7.47 (m, 3H), 7.31 (m, 1H), 4.83 (s, 2H). 3.17 (m, 2H), 1.09 (m, 16H), 0.85 (t, $J = 6.51$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$167.5, 154.5, 148.2, 138.2, 129.2, 128.3 ($\times$2), 126.9 ($\times$2), 111.1, 90.6, 62.6, 40.7, 31.2, 28.7, 28.6, 28.5, 28.2, 27.3, 25.8, 22.0, 13.9.

1-Hexyl-2-hydroxy-2-phenyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-058)

Yield: 80 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.03$ (m, 1H), 8.87 (m, 1H), 7.81 (s, 1H), 7.74 (m, 2H), 7.47 (m, 3H), 7.31 (m 1H), 4.83 (s, 2H). 3.17 (m, 2H), 1.34 (m, 2H), 1.09 (m, 6H), 0.78 (t, $J = 6.48$ Hz, 3H).

2-Hydroxy-1-nonyl-2-phenyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-061)

Yield: 75 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.03$ (m, 1H), 8.87 (m, 1H), 7.80 (s, 1H), 7.74 (m, 2H), 7.47 (m, 3H), 7.31 (t, $J = 6.21$ Hz, 1H), 4.83 (s, 2H). 3.17 (m, 2H), 1.09 (m, 14H), 0.84 (t, $J = 6.63$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta =$167.5, 154.5, 148.2, 138.2, 129.2, 128.3 ($\times$2), 126.9 ($\times$2), 111.1, 90.6, 62.6, 40.7, 31.1, 28.5, 28.4, 28.2, 27.3, 25.8, 22.0, 13.9.

2-Hydroxy-2-phenyl-1-undecyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-064)
Yield: 80 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (d of d, $J$ = 1.89, 4.68 Hz, 1H), 8.87 (d, $J$ = 6.06 Hz, 1H), 7.80 (s, 1H), 7.75 (m, 2H), 7.47 (m, 3H), 7.31 (m 1H), 4.83 (s, 2H). 3.17 (m, 2H), 1.09 (m, 18H), 0.85 (t, $J$ = 6.42 Hz, 3H).

1-Dodecyl-2-hydroxy-2-phenyl-2,3-dihydro-1$^H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-067)

Yield: 78 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.87 (m, 1H), 7.81 (s, 1H), 7.74 (m, 2H), 7.46 (m, 3H), 7.31 (m, 1H), 4.84 (s, 2H). 3.17 (m, 2H), 1.22 (m, 20H), 0.85 (t, $J$ = 6.24 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.5, 154.5, 148.2, 138.2, 129.2, 128.3 (×2), 126.9 (×2), 111.1, 90.6, 62.6, 40.7, 31.2, 28.9 (×2), 28.8, 28.6 (×2), 28.2, 27.3, 25.8, 22.0, 13.9.

2-Hydroxy-2-phenyl-1-tridecyl-2,3-dihydro-1$^H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-070)

Yield: 79 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.87 (m, 1H), 7.80 (s, 1H), 7.76 (m, 2H), 7.46 (m, 3H), 7.31 (m 1H), 4.83 (s, 2H). 3.17 (m, 2H), 1.22 (m, 22H), 0.85 (m, 3H).

2-Hydroxy-2-phenyl-1-tetradecyl-2,3-dihydro-1$^H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-073)
Yield: 72 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (d, $J$ = 4.65 Hz, 1H), 8.87 (d, $J$ = 6.27 Hz, 1H), 7.81 (s, 1H), 7.77 (m, 2H), 7.46 (m, 3H), 7.32 (m 1H), 4.84 (s, 2H), 3.17 (m, 2H), 1.23 (m, 24H), 0.85 (m, 3H).

1-Cyclobutyl-2-hydroxy-2-phenyl-2,3-dihydro-$1H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-079)

Yield: 77 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.83 (m, 1H), 7.86 (s, 1H), 7.65(m, 2H), 7.46(m, 3H), 7.34 (m 1H), 4.76 (s, 2H), 3.90 (m, 1H), 2.76 (m, 2H), 1.88 (m, 2H), 1.69 (m, 2H).

2-Hydroxy-1-pentyl-2-phenyl-2,3-dihydro-$1H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-083)

Yield: 74 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (m, 1H), 8.86 (m, 1H), 7.82 (s, 1H), 7.77 (m, 2H), 7.47 (m, 3H), 7.31 (m 1H), 4.83 (s, 2H), 3.17 (m, 2H), 1.36, (m, 2H), 1.09 (m, 4H), 0.73 (t, $J$ = 6.72 Hz, 3H).

2-(4-Chlorophenyl)-1-cycloheptyl-2-hydroxy-2,3-dihydro-$1H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-088)
Yield: 90 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.00$ (d of d, $J = 1.92$, 4.65 Hz, 1H), 8.85 (m, 1H), 7.92 (s, 1H), 7.79 (d, $J = 8.64$ Hz, 2H), 7.56 (d, $J = 8.58$ Hz, 2H), 7.28 (m, 1H), 4.74 (m, 2H). 3.10 (m, 1H), 2.19 (m, 2H), 1.40 (m, 10H).

2-(4-Chlorophenyl)-1-heptyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-089)

Yield: 91 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.04$ (d, $J = 4.65$ Hz, 1H), 8.87 (d, $J = 5.85$ Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.61$ Hz, 2H), 7.55 (d, $J = 8.58$ Hz, 2H), 7.32 (m, 1H), 4.82 (s, 2H). 3.17 (m, 2H), 1.09 (m, 10H), 0.81 (t, $J = 7.17$ Hz, 3H).

2-(4-Chlorophenyl)-2-hydroxy-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-090)

Yield: 71 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.05$ (d, $J = 6.51$ Hz, 1H), 8.90 (d, $J = 6.24$ Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.61$ Hz, 2H), 7.55 (d, $J = 8.58$ Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.09 (m, 12H), 0.83 (t, $J = 6.75$ Hz, 3H).

2-(4-Chlorophenyl)-1-decyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-091)

Yield: 86 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.04$ (d, $J = 3.33$ Hz, 1H), 8.86 (d, $J = 6.0$ Hz, 1H), 7.89 (s, 1H), 7.81 (d, $J = 8.37$ Hz, 2H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.09 (m, 16H), 0.85 (t, $J = 6.51$ Hz, 3H). $^{13}$C NMR
(75.5 MHz, CDCl\textsubscript{3}): δ = 167.7, 154.6, 148.2, 137.3, 134.1, 129.0 (×2), 126.3 (×2), 111.1, 90.2, 62.5, 40.7, 31.2, 28.8, 28.6 (×2), 28.2, 27.2, 25.8, 22.0, 13.9.

2-(4-Chlorophenyl)-1-hexyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-092)

Yield: 83 %. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ = 9.04 (d, J = 4.47 Hz, 1H), 8.87 (d, J = 6.3 Hz, 1H), 7.90 (s, 1H), 7.78 (d, J = 8.55 Hz, 2H), 7.56 (m, 2H), 7.33 (t, J = 5.0 Hz, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.05 (m, 8H), 0.79 (t, J = 6.30 Hz, 3H).

2-(4-Chlorophenyl)-2-hydroxy-1-nonyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-093)

Yield: 82 %. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ = 9.03 (d of d, J = 1.86, 4.62 Hz, 1H), 8.86 (m, 1H), 7.89 (s, 1H), 7.78 (d, J = 8.64 Hz, 2H), 7.55 (d, J = 8.58 Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.09 (m, 14H), 0.84 (t, J = 6.63 Hz, 3H).

2-(4-Chlorophenyl)-2-hydroxy-1-undecyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-094)
Yield: 83 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (d, $J = 4.56$ Hz, 1H), 8.87 (d, $J$ = 6.3 Hz, 1H), 7.89 (s, 1H), 7.78 (d, $J = 8.49$ Hz, 2H), 7.55 (d, $J = 8.49$ Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.22 (m, 18H), 0.85 (t, $J = 6. 3$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.5, 154.6, 148.2, 137.3, 134.1, 129.0 ($\times$2), 128.3 ($\times$2), 111.1, 90.2, 62.5, 40.7, 31.2, 28.9, 28.8, 28.6 ($\times$2), 28.2, 27.2, 25.8, 22.0, 13.9.

2-(4-Chlorophenyl)-1-dodecyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-095)

Yield: 90 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (d of d, $J = 1.83$, 4.59 Hz, 1H), 8.87 (d, $J = 6.06$ Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.64$ Hz, 2H), 7.55 (d, $J = 8.61$ Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.22 (m, 20H), 0.85 (t, $J = 6. 33$ Hz, 3H).

2-(4-Chlorophenyl)-2-hydroxy-1-tridecyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-096)

Yield: 95 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.03 (d of d, $J = 1.83$, 4.65 Hz, 1H), 8.87 (d of d, $J = 1.77$, 6.27 Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.61$ Hz, 2H), 7.55 (d, $J$ = 8.61 Hz, 2H), 7.32 (m, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.23 (m, 22H), 0.85 (t, $J$ = 6. 33 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.5, 154.6, 148.2, 137.2, 134.1, 129.0 ($\times$2), 128.3 ($\times$2), 111.2, 90.2, 62.5, 40.7, 31.2, 28.9 ($\times$3), 28.8, 28.6 ($\times$2), 28.2, 27.2, 25.8, 22.0, 13.9.

2-(4-Chlorophenyl)-2-hydroxy-1-tetradecyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-097)
Yield: 90 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.03$ (d, $J = 4.56$ Hz, 1H), 8.87 (d, $J = 6.12$ Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.55$ Hz, 2H), 7.55 (d, $J = 8.55$ Hz, 2H), 7.32 (t, $J = 4.95$ Hz, 1H), 4.82 (m, 2H). 3.17 (m, 2H), 1.23 (m, 24H), 0.85 (t, $J = 6.09$ Hz, 3H).

2-(4-Chlorophenyl)-1-cyclohexyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-098)

Yield: 84 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.01$ (d of d, $J = 1.86$, 4.68 Hz, 1H), 8.84 (d of d, $J = 1.83$, 6.39 Hz, 1H), 7.96 (s, 1H), 7.78 (d, $J = 8.64$ Hz, 2H), 7.56 (d, $J = 8.58$ Hz, 2H), 7.30 (m, 1H), 4.72 (m, 2H). 3.02 (m, 1H), 2.13 (m, 2H), 0.75 (m, 8H).

2-(4-Chlorophenyl)-2-hydroxy-1-pentyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-099)

Yield: 78 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.04$ (d of d, $J = 1.8$, 4.56 Hz, 1H), 8.87 (d of d, $J = 1.65$, 6.27 Hz, 1H), 7.90 (s, 1H), 7.78 (d, $J = 8.64$ Hz, 2H), 7.56 (d, $J = 8.61$ Hz, 2H), 7.32 (m, 1H), 4.81 (m, 2H). 3.17 (m, 2H), 1.10 (m, 6H), 0.75 (t, $J = 6.81$ Hz, 3H).

2-(4-Chlorophenyl)-1-cyclobutyl-2-hydroxy-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium (BS-100)
Yield: 81 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.06$ (d, $J = 4.11$ Hz, 1H), 8.84 (d, $J = 6.21$ Hz, 1H), 7.95 (s, 1H), 7.69 (d, $J = 8.58$ Hz, 2H), 7.55 (d, $J = 8.55$ Hz, 2H), 7.35 (t, $J = 5.22$ Hz, 1H), 4.64 (m, 2H), 3.89 (m, 1H), 2.73 (m, 2H), 1.91 (m, 2H), 1.66 (m, 2H).

2-Hydroxy-2-(4-methoxyphenyl)-1-octyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-175)

Yield: 77 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.02$ (m, 1H), 8.84 (d, $J = 6.3$ Hz, 1H), 7.71 (s, 1H), 7.65 (d, $J = 8.79$ Hz, 2H), 7.30 (m, 2H), 7.01 (d, $J = 8.79$ Hz, 1H), 4.79 (s, 2H), 3.79 (s, 3H), 3.17 (m, 2H), 1.10 (m, 12H), 0.83 (t, $J = 6.66$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.4$, 159.7, 154.4, 148.2, 129.8, 128.4 ($\times$2), 113.5 ($\times$2), 111.0, 90.5, 62.5, 55.2, 40.5, 31.0, 28.2 ($\times$2), 27.3, 25.8, 22.0, 13.8.

2-(4-Fluorophenyl)-2-hydroxy-1-octyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-176)

Yield: 68 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.03$ (d of d, $J = 1.92$, 4.71 Hz, 1H), 8.84 (d of d, $J = 1.65$, 6.3 Hz, 1H), 7.86 (s, 1H), 7.82 (m, 2H), 7.33 (m, 3H), 4.82 (s, 2H), 3.17 (m, 2H), 1.10 (m, 12H), 0.83 (t, $J = 6.72$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.4$, 164.1, 160.8, 154.5, 134.5 ($\times$2), 129.5 (d), 115.3 (d), 111.2, 90.2, 62.5, 40.6, 31.0, 28.2 ($\times$2), 27.3, 25.8, 21.9, 13.8.
2-(3,4-Dichlorophenyl)-2-hydroxy-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-177)

Yield: 82 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.05 (d of d, $J$ = 1.86, 4.62 Hz, 1H), 8.88 (d of d, $J$ = 1.74, 6.27 Hz, 1H), 8.07 (s, 1H), 8.02 (s, 1H), 7.78 (s, 2H), 7.33 (m, 1H), 4.83 (m, 2H), 3.23 (m, 2H), 1.11 (m, 12H), 0.83 (t, $J$ = 6.75 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.4, 154.6, 148.0, 139.4, 132.1, 131.2, 130.4, 129.4, 127.3, 111.3, 89.6, 62.3, 40.6, 31.0, 28.2 (×2), 27.2, 25.7, 21.9, 13.8.

2-(3-Bromophenyl)-2-hydroxy-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-178)

Yield: 53 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.04 (d of d, $J$ = 1.86, 4.68 Hz, 1H), 8.87 (d of d, $J$ = 1.62, 6.27 Hz, 1H), 8.01 (s, 1H), 7.93 (s, 1H), 7.77 (d, $J$ = 7.86 Hz, 1H), 7.66 (d, $J$ = 8.4 Hz, 1H), 7.46 (t, $J$ = 7.92 Hz, 1H) 7.33 (m, 1H), 4.82 (m, 2H), 3.22 (m, 2H), 1.36 (m, 2H), 1.11 (m, 10H), 0.83 (t, $J$ = 6.72 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.4, 154.6, 148.1, 140.9, 132.1, 131.2, 130.4, 129.4, 126.0, 121.7, 111.2, 89.8, 62.5, 40.6, 31.0, 28.2 (×2), 27.2, 25.7, 21.9, 13.8.

2-Hydroxy-2-(naphthalen-1-yl)-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-179)
Yield: 82 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.08$ (d, $J = 4.11$ Hz, 1H), 9.00 (d, $J = 5.25$ Hz, 1H), 8.38 (s, 1H), 8.02 (m, 4H), 7.86 (d, $J = 7.61$ Hz, 1H), 7.60 (m, 2H), 7.38 (t, $J = 5.64$ Hz, 1H), 4.99 (s, 2H), 3.26 (m, 2H), 1.39 (m, 2H), 1.00 (m, 10H), 0.76 (t, $J = 6.6$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.4$, 154.7, 148.3, 135.4, 132.9, 132.1, 128.4, 128.1, 127.5, 127.0, 126.6 ($\times 2$), 124.2, 111.2, 90.8, 62.5, 40.7, 30.9, 28.2 ($\times 2$), 27.3, 25.8, 21.9, 13.8.

2-Hydroxy-2-(4-nitrophenyl)-1-octyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-180)

Yield: 75 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.06$ (m, 1H), 8.89 (m, 1H), 8.37 (d, $J = 8.7$ Hz, 2H), 8.12 (s, 1H), 8.05 (d, $J = 8.76$ Hz, 2H), 7.36 (m, 1H), 4.86 (m, 2H), 3.22 (m, 2H), 1.39 (m, 2H), 1.09 (m 10H), 0.81 (t, $J = 6.66$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.5$, 154.7, 148.2, 147.9, 145.2, 128.7 ($\times 2$), 123.0 ($\times 2$), 111.4, 90.0, 62.3, 40.8, 30.9, 28.2 ($\times 2$), 27.2, 25.7, 21.9, 13.8.

2-Hydroxy-2-(4’-nitrobiphenyl-4-yl)-1-octyl-2,3-dihydro-1$H$-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-185)
2-Hydroxy-2-(4-(methylsulfonyl)phenyl)-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-186)

 Yield: 48 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.06$ (d of d, $J = 1.65$, 4.47 Hz, 1H), 8.94 (d of d, $J = 1.56$, 6.21 Hz, 1H), 8.08 (s, 1H), 8.05 (s, 4H), 7.36 (m, 1H), 4.87 (m, 2H). 3.27 (s, 3H), 3.24 (m, 2H), 1.40 (m, 2H), 1.11 (m, 10H), 0.82 (t, $J = 6.66$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.4$, 154.7, 148.2, 143.7 ($\times$2), 141.6, 128.1 ($\times$2), 127.0, 111.4, 90.3, 62.5, 43.3, 40.9, 31.0, 28.2 ($\times$2), 27.4, 25.9, 21.9, 13.8.

2-Hydroxy-2-(4-(methylthio)phenyl)-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-187)

 Yield: 48 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 9.06$ (d of d, $J = 1.65$, 4.47 Hz, 1H), 8.94 (d of d, $J = 1.56$, 6.21 Hz, 1H), 8.08 (s, 1H), 8.05 (s, 4H), 7.36 (m, 1H), 4.87 (m, 2H). 3.27 (s, 3H), 3.24 (m, 2H), 1.40 (m, 2H), 1.11 (m, 10H), 0.82 (t, $J = 6.66$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 167.4$, 154.7, 148.2, 143.7 ($\times$2), 141.6, 128.1 ($\times$2), 127.0, 111.4, 90.3, 62.5, 43.3, 40.9, 31.0, 28.2 ($\times$2), 27.4, 25.9, 21.9, 13.8.

2-Hydroxy-2-(4-(methylsulfonyl)phenyl)-1-octyl-2,3-dihydro-1H-imidazo[1,2-a]pyrimidin-4-ium bromide (BS-186)
Yield: 49 %. $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 9.02 (m, 1H), 8.85 (m, 1H), 7.78 (s, 1H), 7.66 (d, $J$ = 8.52 Hz, 2H), 7.33 (m, 3H), 4.79 (m, 2H), 3.33 (s, 3H), 3.22 (m, 2H), 1.39 (m, 2H), 1.10 (m, 10H), 0.83 (t, $J$ = 6.66 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 167.4, 154.7, 148.2, 143.7 ($\times$2), 141.6, 128.1 ($\times$2), 127.0, 111.4, 90.3, 62.5, 43.3, 40.9, 31.0, 28.2 ($\times$2), 27.4, 25.9, 21.9, 13.8.

5-(2,4-Dimethoxyphenyl)-N-methyl-1H-imidazol-2-amine (BS-136)

Yield: 48 %. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 10.63 (br, 1H), 7.43 (d, $J$ = 3.0 Hz, 1H), 7.07 (s, 1H), 6.90 (d, $J$ = 8.8 Hz, 1H), 6.63 (d of d, $J$ = 3.1, 3.1 Hz, 1H), 5.73 (q, $J$ = 5.1 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 2.77 (d, $J$ = 5.1 Hz, 3H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ = 153.1, 151.0, 149.5, 129.3, 123.4, 114.8, 111.8, 111.2, 110.1, 55.5, 55.2, 29.8. HRMS (EI) C$_{12}$H$_{15}$N$_3$O$_2$, calcd: 233.1164, found: 233.1173.

N-((Benzol[d][1,3]dioxol-6-yl)-5-(naphthalene-3-yl)-1H-imidazol-2-amine (BS-137)

Yield: 72 %. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ = 10.61 (br, 1H), 8.06 (s, 1H), 7.83-7.79 (m, 4H), 7.44-7.37 (m, 2H), 7.19 (s, 1H), 6.99 (s, 1H), 6.87-6.86 (m, 2H), 6.32 (t, $J$ = 6.4 Hz, 1H), 5.96 (s, 2H), 4.34 (d, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta$ = 151.2, 147.0, 145.8, 134.6, 133.5, 131.3, 127.5 ($\times$2), 127.4, 127.3, 126.0, 125.6, 124.6, 123.2, 120.4, 108.0 ($\times$2), 107.8, 100.6 ($\times$2), 46.1. HRMS (EI) C$_{21}$H$_{18}$N$_3$O$_2$, calcd: 343.1321, found: 343.1340.

5-(3,4-Dichlorophenyl)-N-propyl-1H-imidazol-2-amine (BS-140)
Yield : 70 %. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta = 10.55$ (br, 1H), 7.82 (s, 1H), 7.58 (s, 1H), 7.50 (d, $J = 8.2$ Hz, 1H), 7.22 (s, 1H), 5.83 (t, $J = 6.0$ Hz, 1H), 3.10 (q, $J = 8.2$ Hz, 2H), 1.54 (m, 2H), 0.90 (t, $J = 7.35$ Hz, 3H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) $\delta =$151.6, 130.9 (x 2), 130.3 (x 2), 126.3, 124.6, 123.4, 104.2, 44.7, 22.6, 11.4. HRMS EI C$_{12}$H$_{13}$Cl$_2$N$_3$, calcd 269.0487, found : 269.0480.

$N$-Cyclohexyl-5-(4-(methylsulfonyl)phenyl)-1H-imidazol-2-amine (BS-141)

Yield : 43 %. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta = 10.54$ (br, 1H), 7.83-7.76 (m, 4H), 7.31 (s, 1H), 5.75 (d, $J = 8.4$ Hz, 1H), 3.16 (s, 3H), 2.49 (s, 1H), 1.90 (s, 2H), 1.70 (m, 2H), 1.20 (m, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) $\delta =$151.1, 140.1, 136.1, 127.2(x 4), 123.4 (x 2), 104.2, 51.1, 43.7, 33.0(x 2), 25.4, 24.6(x 2). HRMS EI C$_{16}$H$_{21}$N$_3$O$_2$S, calcd 319.1354, found : 319.1337.

5-(4-Chlorophenyl)-N-octyl-1H-imidazol-2-amine (BS-143)

Yield : 43%. $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta = 10.43$ (br, 1H), 7.63 (d, $J = 8.3$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.09 (s, 1H), 5.71 (t, $J = 4.9$ Hz, 1H), 3.12 (m, 2H), 1.48-1.51 (m, 2H), 1.25 (m, 10H), 0.85 (t, $J = 4.2$ Hz, 3H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$) $\delta =$151.5, 128.8 (x 2), 128.1 (x 3), 124.9 (x 2), 100.7, 42.9, 31.2, 29.4, 28.8, 28.7, 26.4, 22.0, 13.9. HRMS EI C$_{17}$H$_{24}$ClN$_3$, calcd 305.1659, found : 305.1646.

5-(4-Chlorophenyl)-N-pentyl-1H-imidazol-2-amine (BS-146)
Yield: 57 %. \(^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta = 10.44 \text{ (br, 1H), 7.65 \text{ (d, } J = 7.3 \text{ Hz, 2H), 7.31 \text{ (d, } J = 8.3 \text{ Hz, 2H), 7.09 \text{ (s, 1H), 5.71 \text{ (t, } J = 5.1 \text{ Hz, 1H), 3.12 \text{ (m, 2H), 1.51 \text{ (t, } J = 1.7 \text{ Hz, 2H), 1.30 \text{ (m, 4H), 0.88 \text{ (t, } J = 6.7 \text{ Hz, 3H).}}\)\(^{13}\text{C NMR (75.5 MHz, DMSO-}d_6\text{)} \delta = 151.5, 128.9 \text{ (x 2), 128.1 \text{ (x 3), 124.9 \text{ (x 2), 104.1, 42.8, 29.1, 28.6, 21.9, 13.9.}}\)\(^{\text{HRMS EI C}_{14}\text{H}_{18}\text{ClN}_{3}, \text{ calcd 263.1189, found: 263.1180.}}\)\)

\(5\)-(4-Fluorophenyl)-N-hexyl-1\text{H-imidazol-2-amine (BS-147)}\)

Yield: 61 %. \(^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta = 10.38 \text{ (br, 1H), 7.62 \text{ (m, 2H), 7.09 \text{ (t, } J = 8.8 \text{ Hz, 2H), 6.99 \text{ (s, 1H), 5.66 \text{ (m, 1H), 3.13-3.10 \text{ (m, 2H), 1.51 \text{ (m, 2H), 1.28 \text{ (m, 6H), 0.87 \text{ (t, } J = 6.4 \text{ Hz, 3H).}}\)\(^{13}\text{C NMR (75.5 MHz, DMSO-}d_6\text{)} \delta = 161.6, 158.5, 151.4, 125.0, 124.9, 115.0, 114.7, 104.1 \text{ (x 2), 42.9, 31.0, 29.4, 26.1, 22.1, 13.8.}, \text{HRMS EI C}_{15}\text{H}_{20}\text{FN}_{3}, \text{ calcd 261.1641, found: 261.1631.}}\)\)

\(N\)-(4-Methoxyphenethyl)-5-(3-bromophenyl)-1\text{H-imidazol-2-amine(BS-148)}\)

Yield: 44 %. \(^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta = 10.56 \text{ (br, 1H), 7.82 \text{ (s, 1H), 7.65 \text{ (d, } J = 6.5 \text{ Hz, 2H), 7.24-7.16 \text{ (m, 5H), 6.88 \text{ (d, } J = 8.4 \text{ Hz, 2H), 5.77 \text{ (m, 1H), 3.72 \text{ (s, 3H), 3.35 \text{ (s, 2H), 2.77 \text{ (t, } J = 7.6 \text{ Hz, 2H).}}\)\(^{13}\text{C NMR (75.5 MHz, DMSO-}d_6\text{)} \delta = 157.5, 151.3, 131.6 \text{ (x 2), 130.3, 129.6 \text{ (x 3), 127.3, 125.7, 122.1, 121.9, 113.6 \text{ (x 3), 54.9, 44.8, 34.6., HRMS EI C}_{18}\text{H}_{18}\text{BrN}_{3}\text{O, calcd 371.0633, found: 371.0658.}}\)\)

\(N\)-Cyclooctyl-5-(4-(methylsulfonyl)phenyl)-1\text{H-imidazol-2-amine (BS-154)}\)

Yield: 53 %. \(^1\text{H NMR (300 MHz, DMSO-}d_6\text{)} \delta = 10.49 \text{ (br, 1H), 7.86 \text{ (d, } J = 8.5 \text{ Hz, 2H), 7.79 \text{ (d, } J = 8.5 \text{ Hz, 2H), 7.31 \text{ (d, } J = 1.5 \text{ Hz, 1H), 5.74 \text{ (d, } J = 8.4 \text{ Hz, 1H), 3.64}}\)
(s, 1H), 3.16 (s, 3H), 1.80 (m, 2H), 1.53 (m, 12H). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ = 151.5, 138.8, 136.2, 127.7 (x 3), 124.0 (x 2), 105.1, 53.7, 44.6, 32.3 (x 2), 27.2 (x 2), 25.2, 23.4 (x 2). HRMS El C$_{18}$H$_{25}$N$_3$O$_2$S, calcd 344.1667, found : 344.1644.

**4-(2-(2-Methoxyethylamino)-1H-imidazole-5-yl)benzonitrile (BS-139)**

Yield 85 %. $^1$H NMR (300 MHz, DMSO-d$_6$) δ = 10.6 (br, 1H), 7.7 (m 4H), 7.3 (s 1H), 5.8 (s 1H), 3.5 (t 2H), 3.4 (m 2H), 3.2 (s 3H). $^{13}$C NMR (300 MHz, DMSO-d$_6$) δ = 151.3, 140.1, 134.2, 132.2 (x 2), 123.8, 119.5, 110.8, 106.4, 104.1, 70.9, 57.9, 54.8, 43.3. HRMS El C$_{13}$H$_{14}$N$_4$O, calcd 242.1168, found : 242.1167.

**5-(4-Methoxyphenyl)-N-octyl-1H-imidazol-2-amine (BS-258)**

Yield : 78 %. $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 10.91 (br s, 1H), 7.51 (d, $J$ = 8.57 Hz, 2H), 6.95 (s, 1H), 6.87 (d, $J$ = 8.75 Hz, 2H), 6.05 (m, 1H), 3.74 (s, 3H), 3.16 (m, 2H), 1.51 (m, 2H), 1.28 (m, 10H), 0.85 (t, $J$ = 6.75 Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 149.2, 131.1, 129.5, 129.3 (x 2), 128.8 (x 2), 128.2, 123.4, 43.1, 31.6, 29.5, 29.0, 28.9, 26.4, 22.2, 14.0. HRMS (EI): C$_{18}$H$_{27}$N$_3$O, calcd 301.2154, found: 301.2142.

**5-(4-Fluorophenyl)-N-octyl-1H-imidazol-2-amine (BS-259)**

Yield : 69% . $^1$H NMR (300 MHz, DMSO-d$_6$): δ = 10.44 (br s, 1H), 7.61 (t, $J$ = 5.85 Hz, 2H), 7.08 (t, $J$ = 8.78 Hz, 2H), 6.99 (s, 1H), 5.67 (t, $J$ = 6.03 Hz, 1H), 3.10 (m, 2H), 1.51 (m, 2H), 1.25 (m, 10H), 0.83 (m, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ = 163.8, 160.5, 148.7, 130.2, 128.4, 127.0, 122.9, 115.5, 104.7, 43.0, 31.6, 29.5, 29.0, 28.9, 26.4, 22.5, 14.0. HRMS (EI): C$_{17}$H$_{24}$FN$_3$, calcd 289.1954, found: 289.1964.

**5-(3,4-Dichlorophenyl)-N-octyl-1H-imidazol-2-amine (BS-260)**
Yield : 72 %.

\[ ^1H \text{NMR (300 MHz, DMSO-d}_6\text{): } \delta = 10.52 \text{ (br s, 1H), 7.82 (s, 1H),} \]

7.58 (m, 1H), 7.50 (d, \( J = 8.13 \) Hz, 1H), 7.22 (s, 1H), 5.78 (m, 1H), 3.11 (m, 2H), 1.51 (m, 2H), 1.28 (m, 10H), 0.85 (t, \( J = 6.94 \) Hz, 3H).

\[ ^{13}C \text{NMR (75.5 MHz, CDCl}_3\text{): } \delta =149.6, 132.8, 131.1, 131.0, 129.5, 127.1, 127.0, 124.2, 43.3, 31.6, 29.5, 29.0, 28.9, 26.4, 22.5, 14.0. \]

HRMS (EI): C\(_{17}\)H\(_{23}\)Cl\(_2\)N\(_3\), calcd 339.1269, found: 339.1279.

5-(3-Bromophenyl)-N-octyl-1H-imidazol-2-amine (BS-261)

C\(_8\)H\(_{17}\)

Yield : 79 %.

\[ ^1H \text{NMR (300 MHz, DMSO-d}_6\text{): } \delta = 10.49 \text{ (br s, 1H), 7.79 (s, 1H),} \]

7.59 (s, 1H), 7.22 (m, 1H), 7.14 (s, 1H), 5.73 (t, \( J = 5.66 \) Hz, 1H), 3.11 (m, 2H), 1.51 (m, 2H), 1.25 (m, 10H), 0.84 (t, \( J = 6.69 \) Hz, 3H).

\[ ^{13}C \text{NMR (75.5 MHz, CDCl}_3\text{): } \delta =149.2, 133.0, 130.8, 130.1 \text{ (×2), 128.0, 126.5, 123.8, 122.6, 43.2, 31.6, 29.5, 29.0,} \]

28.9, 26.4, 22.5, 14.0. HRMS (EI): C\(_{17}\)H\(_{24}\)BrN\(_3\), calcd 349.1154, found: 249.1138.

5-(Naphthalen-1-yl)-N-octyl-1H-imidazol-2-amine (BS-262)

C\(_8\)H\(_{17}\)

Yield : 68 %.

\[ ^1H \text{NMR (300 MHz, DMSO-d}_6\text{): } \delta = 10.53 \text{ (br s, 1H), 8.05 (s, 1H),} \]

7.80 (m, 3H), 7.39 (m, 3H), 7.17 (s, 1H), 5.73 (m, 1H), 3.16 (m, 2H), 1.54 (m, 2H), 1.26 (m, 10H), 0.83 (t, \( J = 6.86 \) Hz, 3H).

\[ ^{13}C \text{NMR (75.5 MHz, CDCl}_3\text{): } \delta =149.1, 133.4, 132.4, 129.5, 128.3, 128.2, 127.9, 127.7, 126.6, 126.4 \text{ (×2), 126.0, 123.0, 43.3,} \]

31.6, 29.5, 29.0, 28.9, 26.4, 22.5, 14.0. HRMS (EI): C\(_{21}\)H\(_{24}\)BrN\(_3\), calcd 349.1154, found: 249.1138.

5-(4-Nitrophenyl)-N-octyl-1H-imidazol-2-amine (BS-263)

C\(_8\)H\(_{17}\)

Yield : 66 %.

\[ ^1H \text{NMR (300 MHz, DMSO-d}_6\text{): } \delta = 10.74 \text{ (br s, 1H), 8.12 (d, } \text{J = 8.92 Hz, 2H),} \]

7.84 (d, \( J = 8.92 \) Hz, 2H), 7.43 (s,1H), 5.91 (t, \( J = 5.54 \) Hz, 1H), 3.16 (m, 2H), 1.52 (m, 2H), 1.25 (m, 10H), 0.85 (t, \( J = 6.75 \) Hz, 3H).

\[ ^{13}C \text{NMR (75.5 MHz, CDCl}_3\text{): } \delta =163.8, 160.5, 148.7, 130.2, 128.4, 127.0, 122.9, 115.5, 104.7, 43.0, 31.6, 29.5, 29.0, 28.9, 26.4, 22.5, 14.0. \]

HRMS (EI): C\(_{17}\)H\(_{24}\)N\(_4\)O\(_2\), calcd 316.1899, found:.316.1909.
5-(4’-Nitrobiphenyl-4-yl)-N-octyl-1H-imidazol-2-amine (BS-264)

Yield: 75%. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.53$ (br s, 1H), 8.27 (d, $J = 8.71$ Hz, 2H), 7.96 (d, $J = 8.71$ Hz, 2H), 7.75 (s, 4H), 7.18 (s, 1H), 5.76 (t, $J = 5.88$ Hz, 1H), 3.16 (m, 2H), 1.53 (m, 2H), 1.26 (m, 10H), 0.86 (t, $J = 6.75$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 163.8$, 160.5, 148.7, 130.2, 128.4, 127.0, 122.9, 115.5, 104.7, 43.0, 31.6, 29.5, 29.0, 28.9, 26.4, 22.5, 14.0. HRMS (EI): C$_{23}$H$_{28}$N$_4$O$_2$, calcd 392.2212, found: 392.2201.

5-(4-(Methylsulfonyl)phenyl)-N-octyl-1H-imidazol-2-amine (BS-265)

Yield: 54%. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.62$ (br s, 1H), 7.84 (d, $J = 8.55$ Hz, 2H), 7.76 (d, $J = 8.35$ Hz, 2H), 7.32 (s, 1H), 5.83 (t, $J = 5.97$ Hz, 1H), 3.16 (m, 5H), 1.52 (m, 2H), 1.25 (m, 10H), 0.85 (t, $J = 6.56$ Hz, 3H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 150.7$, 138.1, 136.6, 127.9 (×2), 127.6, 127.4 (×2), 126.0, 44.5, 43.6, 31.6, 29.6, 29.0, 28.9, 26.5, 22.5, 14.0. HRMS (EI): C$_{18}$H$_{27}$N$_3$O$_2$S, calcd 349.4909, found: 349.4918.

$N$-Isobutyl-5-(4-nitrophenyl)-1H-imidazol-2-amine (BS-292)

Yield: 70%. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.69$ (br s, 1H), 8.12 (d, $J = 9.02$ Hz, 2H), 7.84 (d, $J = 8.50$ Hz, 2H), 7.42 (s, 1H), 5.99 (t, $J = 5.93$ Hz, 1H), 2.99 (t, $J = 6.44$ Hz, 2H), 1.83 (m, 1H), 0.89 (d, $J = 6.70$ Hz, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta = 152.2$ (×2), 143.8, 141.6, 123.9 (×2), 123.3, 104.1 (×2), 50.4, 27.9, 20.1 (×2). HRMS (EI): C$_{13}$H$_{16}$N$_4$O$_2$, calcd 260.1273, found: 260.1287.

$N$-Isobutyl-5-phenyl-1H-imidazol-2-amine (BS-293)
Yield : 71 %. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.52$ (br s, 1H), 7.59 (d, $J = 7.47$ Hz, 2H), 7.28 (t, $J = 7.47$ Hz, 2H), 7.09 (t, $J = 7.25$ Hz, 1H), 7.04 (s, 1H), 5.92 (t, $J = 5.71$ Hz, 1H), 2.98 (t, $J = 6.37$ Hz, 2H), 1.82 (m, 1H), 0.89 (d, $J = 6.59$ Hz, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta =$151.2, 134.0, 133.1, 128.2 (×2), 125.1, 123.4(×2), 104.1, 50.5, 27.9, 20.1 (×2). HRMS (EI): C$_{13}$H$_{17}$N$_3$, calcd 215.1422, found:215.1411.

5-(4-Bromophenyl)-N-isobutyl-1$H$-imidazol-2-amine (BS-294)

![Structure of BS-294](image)

Yield : 69 %. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.46$ (br s, 1H), 7.55 (d, $J = 8.25$ Hz, 2H), 7.42 (d, $J = 8.25$ Hz, 2H), 7.08 (s, 1H), 5.80 (t, $J = 5.75$ Hz, 1H), 2.97 (t, $J = 6.25$ Hz, 2H), 1.82 (m, 1H), 0.89 (d, $J = 6.50$ Hz, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta =$151.6, 134.1, 133.0 (×3), 125.3 (×2), 117.2, 104.1, 50.6, 27.9, 20.1 (×2). HRMS (EI): C$_{13}$H$_{16}$BrN$_3$, calcd 293.0528, found:293.0529.

5-(4-Chlorophenyl)-N-isobutyl-1$H$-imidazol-2-amine (BS-295)

![Structure of BS-295](image)

Yield : 73 %. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta = 10.46$ (br s, 1H), 7.60 (d, $J = 8.35$ Hz, 2H), 7.29 (d, $J = 8.35$ Hz, 2H), 7.07 (s, 1H), 5.81 (t, $J = 5.96$ Hz, 1H), 2.97 (t, $J = 6.20$ Hz, 2H), 1.82 (m, 1H), 0.89 (d, $J = 6.68$ Hz, 6H). $^{13}$C NMR (75.5 MHz, DMSO-$d_6$): $\delta =$151.5, 133.6, 133.2, 128.9, 128.0 (×2), 124.9 (×2), 104.1, 50.5, 27.9, 20.1 (×2). HRMS (EI): C$_{13}$H$_{16}$ClN$_3$, calcd 249.1033, found:249.1047.
2.11 Representative NMR spectra

2.11.1 $^1$H and $^{13}$C NMR spectra of bs-026

![NMR spectra of bs-026](image)
2.11.2 $^1$H and $^{13}$C NMR spectra of bs-091
2.11.3 $^1$H and $^{13}$C NMR spectra of bs-143
2.12 References


