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**Synthesis of new 1,4- and 1,5-disubstituted *N*-ethyl acetate and *N*- α -butyro- γ -lactone
alkylimidazole derivatives as *N*-acylhomoserine lactones analogues**

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Abstract – New alkyimidazoles functionalized with a homoserine lactone or an alkyloxycarbonyl moiety have been synthesized as *N*-acylhomoserine lactones (AHL) analogues. The 1,4-disubstituted imidazole derivatives were prepared by alkylation of 4(5)-alkylimidazoles with α -bromo- γ -butyrolactone or ethyl α -bromoacetate. An alternative route was preferred for the synthesis of their 1,5-disubstituted counterparts based on the use of a *N*₁-protected alkyimidazole, its alkylation to an *N*₃-imidazolyl- α -acetate and deprotection to the desired 1,5-disubstituted esters and subsequent alkylation of the acetate moiety with cyclic ethylene sulfate followed by acid catalyzed cyclization. The ability to modulate bacterial quorum sensing of all new compounds was compared to that of previously reported AHL analogues in which the amide bond is replaced by a heterocyclic group.

Keywords – Imidazole, bioisostere, AHL analogue, Quorum sensing.

Introduction

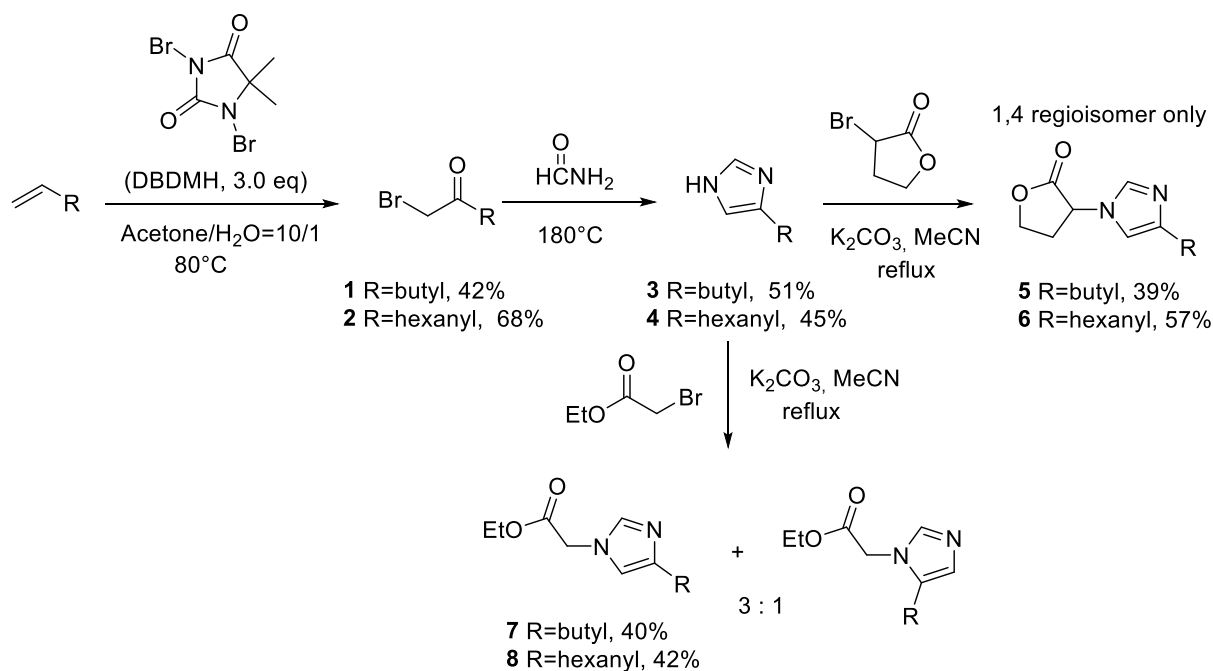
Bioisosterism is a rational approach for the design of bioactive molecules, notably for the replacement of the amide functional group [1]. In the course of our study of acylhomoserine lactones (AHLs)-regulated bacterial quorum sensing, we have previously reported several families of AHL analogues in which the amide central linkage is substituted with bioisosteres [2-5]. With respect to analogues built on a heterocyclic amide mimic, only a handful of families have been reported, including triazolic and tetrazolic ones [6-9]. However, up to date, imidazole based systems have never been studied. Herein, we report the synthesis of disubstituted *N*-ethyl acetate and *N*- α -butyro- γ -alkylimidazole derivatives using two routes leading to either the 1,4- or 1,5-disubstituted systems. While the 1,4-disubstituted derivatives were obtained by direct substitution of an alkyl imidazole using ethyl α -bromo-acetate or α -bromo- γ -lactone, the 1,5-disubstituted products were prepared by multistep sequence based on the alkylation of a *N*-trityl alkylimidazole with ethyl α -bromoacetate, deprotection and alkylation at the α -acetate position by cyclic ethylene sulfate followed by a cyclisation step in acidic conditions. This strategy that we call “late lactone formation” has never been applied for the preparation of AHL analogues. The collection of new 1,4 and 1,5-imidazolyl AHL analogues was then compared to previously reported heterocyclic systems with respect to their quorum sensing activity in *Vibrio fischeri* using an *Escherichia coli* strain NM522 equipped with the sensor plasmid pSB401.

Results and discussion

Synthesis

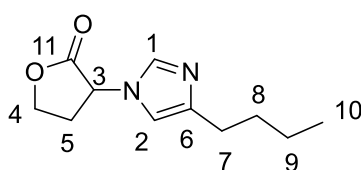
The new substituted imidazoles AHL analogues were synthesized as depicted in Scheme 1. The synthesis starts with a two steps sequence involving the formation of bromoketone **1** and

2 by treatment of alkenes with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) [10] and their cyclization with formamide producing 4(5)-butylimidazole (**3**) and 4(5)-hexanylimidazole (**4**) in moderate yield [11]. In this process, it is worthy to note that formamide should be preheated before adding the starting bromoketone, likely because additional ammonia must be produced for constructing the imidazole ring. Subsequently, the reaction of 4(5)-substituted imidazole with bromolactone was expected to afford the two isomers, 1,4- and 1,5-disubstituted imidazole, but only the 1,4-disubstituted imidazole regioisomers (**5** and **6**) were observed without any formation of the 1,5-isomer (Scheme 2). This can be ascribed to the steric hindrance of the bromolactone. Indeed, when we used the ethyl bromoacetate as alkylation reagent, both regioisomers **7** and **8** were obtained as a difficultly separable mixture of the two regioisomers in a 3:1 ratio, with the 1,4-isomer being the major product.

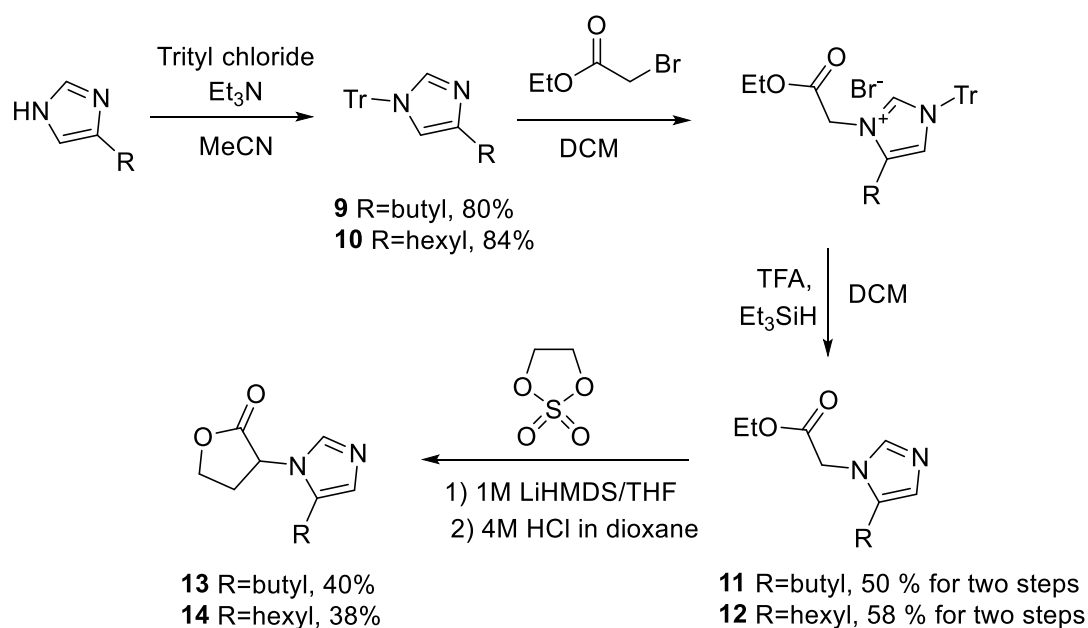


Scheme 1 Synthesis of 1,4-disubstituted imidazoles derivatives.

Compound **5** was taken for the determination of structure using NMR experiments. Two peaks at 7.43 ppm and 6.63 ppm were assigned to the protons of the imidazole nucleus. The ^{13}C NMR spectrum of compound **5** shows signals at 136.0, 113.2, and 144.3 ppm for C-1, C-2 and C-6 carbon atoms, respectively. To assume that the alkylation position of lactone moiety is at the *N*-1 imidazole position, we performed a 2D-NMR HMBC experiment in which their distant correlations between H and C atoms can be observed. In this spectrum, a three-bond correlation between C-2 and proton 3 is observed, as well as the correlation between C-1 and H-3. Being four bonds apart, there is no correlation between C-6 and H-3. So, the 1,4-disubstituted imidazole is unambiguously confirmed.

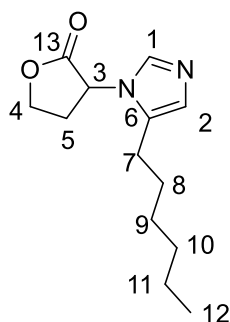


As the first approach proved to be unable to provide the 1,5-lactone product, and not efficient enough for reaching pure the 1,5-ester product, an alternative route towards the 1,5-systems was investigated (Scheme 2). It involved the ready protection of the N-1 position of 4(5)-butylimidazole or 4(5)-hexanylimidazole by a trityl group to the corresponding 1-tritylimidazole derivative **9** or **10**, which were then alkylated with bromo ethyl acetate to generate a quaternary salt. After deprotection with TFA, the targeted 1,5-disubstituted imidazole **11** and **12** were obtained in moderate yield. At this stage, for reaching the lactone 1,5-derivative, we applied a late lactone formation strategy inspired by the literature on other substrates [12, 13] but never used in the design of AHL analogues. This strategy involved the α -alkylation of acetates with a C2 building block and further cyclization for the construction of the lactone ring at the end of the sequence. After having checked that the strategy was able to handle heterocyclic motifs using several α -substituted acetates, bearing pyridine, pyrazole, unsubstituted imidazole and benzimidazole substituents (see SI), it was applied to ethyl esters **11** and **12**. α -Alkylation of these latter with cyclic sulfate using LiHMDS as the base, followed by acidic treatment with 4M HCl in dioxane produced the lactone ring in the targeted compounds **13** and **14**.



Scheme 2 Synthesis of 1,5-disubstituted imidazole derivatives via late lactone formation.

The 1,5-disubstituted imidazole **14** was taken as an example to explain how their structure was determined. The typical signals of the protons of the imidazole nucleus appear at 7.49 ppm and 6.62 ppm. The ^{13}C NMR spectrum of compound **14** shows signals at 135.3, 125.7 and 132.3 ppm for carbons C-1, C-2 and C-6, respectively. The HMBC experiment permitted to identify their distant protons-carbons correlations. In the 2D-NMR spectra, the three-bond correlation between C-1 and proton 3 is observed, as well as the correlation between C-6 and proton 3 confirming the 1,5-disubstituted imidazole structure.



Biological evaluation

For the purpose of comparison, the series of synthetic imidazole derivatives were evaluated for their ability to modulate quorum sensing exactly through the same QS assay as in our previous work on tetrazole and triazole AHL analogues [6], using a QS-regulated bioluminescence assay in the NM522 E. coli strain [14]. The agonistic activity is measured by the ability to activate the bioluminescence whereas the agonistic activity is evaluated for the ability of compounds to decrease the bioluminescence induced by 200 nM 3-oxo-hexanoyl-L-homoserine lactone (OHHL). The results are reported in Table 1.

Table 1 IC₅₀ values for compounds **5-8, 11-14**.

Compounds	IC ₅₀ (μM)
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1,4-imidazole-C4-lactone (5)	inactive
1,4-imidazole-C6-lactone (6)	inactive
1,4-imidazole-C4-acetate (7)	>200 ^a
1,4-imidazole-C6-acetate (8)	87 ± 7
1,5-imidazole-C4-acetate (11)	>200 ^a
1,5-imidazole-C6-acetate (12)	>200 ^a
1,5-imidazole-C4-lactone (13)	190 ± 9
1,5-imidazole-C6-lactone (14)	110 ± 20

^a compounds **7**, **11**, **12**, showed 27%, 22%, 36%, inhibition at 200 μM.

Six compounds (**7**, **8**, **11-14**) were found to be moderately active as antagonists with IC₅₀ values ranging from 87 to 190 μM, while only the 1,4 imidazoles **5** and **6** being totally deprived of any activity. Compared to our previously reported bioisostere analogues of AHLs, activities slightly weaker but within the same range as for tetrazoles (IC₅₀ = 74-80 μM) and triazoles (IC₅₀ 51-94 μM) [6].

Conclusions

To summarize, two routes were used for the synthesis of AHLs analogues involving the replacement of the amide function with an imidazole nucleus. 1,4-Disubstituted derivatives were accessed by substitution of α-bromo-γ-butyrolactone or ethyl α-bromoacetate with 4(5)-alkylimidazole while 1,5-disubstituted derivatives were prepared using an alternative lactone construction method, based on the alkylation of intermediate α-substituted esters with ethylene sulfate and subsequent cyclisation, applied for the first time to the design of AHLs analogues. Activity of these new compounds as QS modulators is within the same range as our previously reported heterocyclic AHL analogues.

Experimental section

Synthesis

All commercial materials were used without further purification. Flash chromatography was carried out using Macherey-Nagel Kieselgel 60 M silica. Analytical thin layer chromatography was performed using aluminum-backed plates coated with Macherey-Nagel Kieselgel 60 XtraSIL G/UV254. Compounds were visualized under UV light (at 254 nm) or stained using KMnO₄. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AVL300 or a Bruker AV400 or a Bruker AV500 spectrometer, operating respectively at 300 MHz, 400 MHz and 500 MHz for the proton (¹H) NMR and 75 MHz, 100 MHz and 125 MHz for the carbon (¹³C) NMR. Chemical shifts were reported in parts per million (ppm) in the scale relative to residual solvent signals. Coupling constants are measured in Hertz (Hz). High-resolution mass spectra (HRMS) and low-resolution mass spectra were performed by the Centre Commun de Spectrométrie de Masse (CCSM), University of Lyon 1, Lyon, France.

General procedure for the synthesis of 4(5)-substituted imidazoles: to a mixture of alkene (1.0 eq) in acetone/water (10/1) was added DBDMH (3.0 eq) at rt. The mixture was refluxed at 80°C for 6h. After completion of the reaction, saturated NaHCO₃ was added to neutralize HBr, and acetone was evaporated. The residue was diluted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄, concentrated and purified by flash chromatography to yield the α -bromoketone as a colorless oil. Formamide (5mL) was preheated at 180°C under N₂ until the solution turned yellow. Then the α -bromoketone (3mmol) was added dropwise and the reaction mixture was stirred at 180°C for 2h. After cooling to rt, the mixture was diluted with toluene and washed with aq. NaOH (3M). The organic extract was dried over anhydrous

Na₂SO₄, concentrated and purified by flash chromatography to give 4(5)-substituted imidazoles.

4(5)-butyl-1H-imidazole (3). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **3** (51 %) as a yellow oil. ¹H NMR (300 MHz, Chloroform-*d*) δ 10.73 (s, 1H, NH), 7.55 (d, *J* = 1.1 Hz, 1H, Imidazole), 6.77 (d, *J* = 1.0 Hz, 1H, Imidazole), 2.61 (t, *J* = 7.2 Hz, 2H, CH₂), 1.62 (m, 2H, CH₂), 1.41 – 1.27 (m, 2H, CH₂), 0.90 (t, *J* = 7.3 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 136.7 (Imidazole), 134.3 (Imidazole), 117.9 (Imidazole), 31.6 (CH₂), 26.2 (CH₂), 22.3 (CH₂), 13.8 (CH₃).

4(5)-hexyl-1H-imidazole (4). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **4** (45 %) as a yellow oil. ¹H NMR (300 MHz, Chloroform-*d*) δ 10.32 (s, 1H, NH), 7.51 (s, 1H, Imidazole), 6.74 (s, 1H, Imidazole), 2.57 (t, *J* = 7.7 Hz, 2H, CH₂), 1.59 (m, 2H, CH₂), 1.38 – 1.14 (m, 6H, 3×CH₂), 0.84 (t, *J* = 6.5 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 136.6 (Imidazole), 134.2 (Imidazole), 117.9 (Imidazole), 31.6 (CH₂), 29.4 (CH₂), 29.0 (CH₂), 26.5 (CH₂), 22.6 (CH₂), 14.0 (CH₃).

General procedure for imidazole alkylation: to a mixture of imidazole derivatives (1 mmol) and K₂CO₃ (2 mmol) in MeCN (4 mL) was added α-bromo-γ-butyrolactone (1.4 mmol) or ethyl bromoacetate (1.2 mmol). The mixture was stirred under reflux for 2h. After cooling to rt, the solid was filtered and washed with EtOAc. The solution phase was collected and concentrated. The residue was purified by flash chromatography to give the desired product.

3-(4-butyl-1H-imidazol-1-yl)dihydrofuran-2(3H)-one (5). Following the general procedure, flash chromatography of the crude product (1:1 EtOAc-Acetone) afforded **5** (39 %) as a yellow oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.43 (s, 1H, CH=N-Imidazole), 6.62 (s, 1H, CH=C-Imidazole), 4.92 (dd, *J* = 11.3, 8.7 Hz, 1H, CH-lactone), 4.51 – 4.40 (td, *J* = 9.2, 1.9 Hz, 1H, OCHH-lactone), 4.28 (ddd, *J* = 10.6, 9.4, 6.1 Hz, 1H, OCHH-lactone), 2.76 (m, 1H, CHH-lactone), 2.55 – 2.41 (m, 3H, CHH-lactone, CH₂), 1.61 – 1.47 (m, 2H, CH₂), 1.29 (h, *J*

= 7.4 Hz, 2H, CH₂), 0.84 (t, *J* = 7.3 Hz, 3H, CH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 172.4 (CO), 144.3 (C-N, Imidazole), 136.0 (CH=N, Imidazole), 113.2 (CH=C, Imidazole), 65.4 (OCH₂-lactone), 54.7 (CH-lactone), 31.3 (CH₂), 30.5 (CH₂-lactone), 28.1 (CH₂), 22.4 (CH₂), 13.9 (CH₃). ESI-HRMS(M+H)⁺: 209.1285; found: 209.1284.

3-(4-hexyl-1*H*-imidazol-1-yl)dihydrofuran-2(3*H*)-one (6). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **6** (57 %) as a yellow syrup. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.54 (s, 1H, CH=N-Imidazole), 6.69 (s, 1H, CH=C-Imidazole), 4.95 (dd, *J* = 11.2, 8.7 Hz, 1H, CH-lactone), 4.58 – 4.51 (td, *J* = 9.2, 2.0 Hz, 1H, OCHH-lactone), 4.38 (ddd, *J* = 10.5, 9.4, 6.2 Hz, 1H, OCHH-lactone), 2.85 (m, 1H, CHH-lactone), 2.65 – 2.50 (m, 3H, CHH-lactone, CH₂), 1.62 (m, 2H, CH₂), 1.38 – 1.23 (m, 6H, 3×CH₂), 0.88 – 0.81 (t, *J* = 6.8 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 172.0 (CO), 144.5 (C-N, Imidazole), 135.9 (CH=N, Imidazole), 113.2 (CH=C, Imidazole), 65.3 (OCH₂-lactone), 54.7 (CH-lactone), 31.7 (CH₂), 30.7 (CH₂-lactone), 29.2 (CH₂), 29.1 (CH₂), 28.4 (CH₂), 22.6 (CH₂), 14.1 (CH₃). ESI-HRMS(M+H)⁺: 237.1598; found: 237.1596.

Ethyl 2-(4-butyl-1*H*-imidazol-1-yl)acetate (7). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **7** (40 %) as a syrup. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.35 (s, 1H, Imidazole), 6.58 (s, 1H, Imidazole), 4.55 (s, 2H, CH₂), 4.17 (q, *J* = 7.1 Hz, 2H, OCH₂), 2.50 (t, *J* = 7.3 Hz, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.39 – 1.27 (m, 2H, CH₂), 1.22 (t, *J* = 7.1 Hz, 3H, CH₃), 0.85 (t, *J* = 7.3 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 167.6 (CO), 143.7 (Imidazole), 137.0 (Imidazole), 115.8 (Imidazole), 62.0 (OCH₂), 48.1 (CH₂), 31.4 (CH₂), 28.0 (CH₂), 22.4 (CH₂), 14.1 (CH₃), 13.9 (CH₃). ESI-HRMS(M+H)⁺: 211.1441; found: 211.1445.

Ethyl 2-(4-hexyl-1*H*-imidazol-1-yl)acetate (8). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **8** (42 %) as a syrup. ¹H NMR (300 MHz, Chloroform-*d*) δ 7.38 (s, 1H, Imidazole), 6.63 (s, 1H, Imidazole), 4.59 (s,

2H, CH₂), 4.21 (q, $J = 7.2$ Hz, 2H, OCH₂), 2.54 (t, $J = 7.3$ Hz, 2H, CH₂), 1.62 (m, 2H, CH₂), 1.41 – 1.21 (m, 9H, 3×CH₂, CH₃), 0.86 (t, $J = 7.5$ Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 167.6 (CO), 143.8 (Imidazole), 137.0 (Imidazole), 115.7 (Imidazole), 62.0 (OCH₂), 48.0 (CH₂), 31.7 (CH₂), 29.2 (CH₂), 29.1 (CH₂), 28.4 (CH₂), 22.6 (CH₂), 14.1 (2×CH₃). ESI-HRMS(M+H)⁺: 239.1754; found: 239.1746.

General procedure for the synthesis of 1,5-disubstituted imidazoles via late lactone formation: to a solution of 4(5)-butylimidazole or 4(5)-hexylimidazole (1 mmol) in DCM (5 mL) were added triethylamine (2.5 mmol) and trityl chloride (1.2 mmol). The mixture was stirred at rt for 1h. After the reaction, the mixture was diluted with DCM and washed with saturated NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄, concentrated and purified by flash chromatography (EtOAc/Pentane 1:1) to give 4-butyl-1-trityl-1*H*-imidazole **9** or 4-hexyl-1-trityl-1*H*-imidazole **10**.

To a solution of compound **9** or **10** (0.5 mmol) in DCM (3 mL) was added ethyl bromoacetate (0.6 mmol) and the reaction mixture was stirred under N₂ at 40°C overnight. Then the solvent was evaporated and the resulting product was precipitated from cold Et₂O. The residue solid was dissolved in DCM (2 mL). 20%(v/v) TFA and triethylsilane (0.5 mmol) were added dropwise. The mixture was stirred at rt for 1h. After the reaction, saturated NaHCO₃ was added to neutralize the excess TFA. The mixture was firstly extracted with DCM and followed by extraction with EtOAc. The organic phase was dried over anhydrous Na₂SO₄, concentrated and purified by flash chromatography (EtOAc/Acetone 2:1) to give compound **11** or **12** as a colorless oil.

To a solution of ethyl ester (0.5 mmol) in 4 mL THF was added LiHMDS (1M in THF, 0.6 mL, 0.6 mmol) dropwise at -78°C. After the reaction mixture was stirred for 40 min at -78°C, the solution of ethylene sulfate (75 mg, 0.6 mmol) in 2mL THF was slowly added. The mixture was warmed to rt for 1 day. After evaporation of the solvent, dioxane (2 mL) and 4M

HCl in dioxane (1 mL) were added. The reaction mixture was stirred overnight at 80°C. After the reaction, the mixture was diluted with DCM and washed with saturated NaHCO₃. The organic phase was dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography to give the final product **13** or **14**.

Ethyl 2-(5-butyl-1H-imidazol-1-yl)acetate (11): ¹H NMR (300 MHz, Chloroform-*d*) δ 7.39 (s, 1H, Imidazole), 6.76 (s, 1H, Imidazole), 4.55 (s, 2H, CH₂), 4.19 (q, *J* = 7.1 Hz, 2H, OCH₂), 2.41 (t, *J* = 7.3 Hz, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.49 – 1.29 (m, 2H, CH₂), 1.24 (t, *J* = 7.1 Hz, 3H, CH₃), 0.90 (t, *J* = 7.3 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 167.6 (CO), 137.6 (Imidazole), 132.1 (Imidazole), 126.1 (Imidazole), 62.0 (OCH₂), 45.9 (CH₂), 30.1 (CH₂), 23.4 (CH₂), 22.3 (CH₂), 14.1 (CH₃), 13.8 (CH₃). ESI-HRMS(M+H)⁺: 211.1441; found: 211.1434.

Ethyl 2-(5-hexyl-1H-imidazol-1-yl)acetate (12): ¹H NMR (300 MHz, Chloroform-*d*) δ 7.43 (s, 1H, Imidazole), 6.79 (s, 1H, Imidazole), 4.58 (s, 2H, CH₂), 4.30 – 4.07 (q, *J* = 7.1 Hz, 2H, OCH₂), 2.44 (t, *J* = 7.7 Hz, 2H, CH₂), 1.59 (m, 2H, CH₂), 1.46 – 1.15 (m, 9H, 3×CH₂, CH₃), 0.88 (t, *J* = 6.9 Hz, 3H, CH₃). ¹³C NMR (75 MHz, Chloroform-*d*) δ 167.6 (CO), 137.6 (Imidazole), 132.2 (Imidazole), 126.1 (Imidazole), 62.0 (OCH₂), 46.0 (CH₂), 31.5 (CH₂), 29.0 (CH₂), 28.0 (CH₂), 23.7 (CH₂), 22.5 (CH₂), 14.1 (CH₃), 14.0 (CH₃). ESI-HRMS(M+H)⁺: 239.1754; found: 239.1753.

3-(5-butyl-1H-imidazol-1-yl)dihydrofuran-2(3H)-one (13). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **13** (40 %) as a colorless oil. ¹H NMR (400 MHz, Chloroform-*d*) δ 7.52 (s, 1H, Imidazole), 6.85 (s, 1H, Imidazole), 4.92 (dd, *J* = 11.4, 8.8 Hz, 1H, CH-lactone), 4.66 – 4.54 (m, 1H, OCHH-lactone), 4.42 (ddd, *J* = 10.5, 9.5, 6.2 Hz, 1H, OCHH-lactone), 2.85 (m, 1H, CHH-lactone), 2.66 – 2.44 (m, 3H, CHH-lactone, CH₂), 1.66 (m, 2H, CH₂), 1.43 (m, 2H, CH₂), 0.95 (t, *J* = 7.4 Hz, 3H, CH₃). ¹³C NMR (101 MHz, Chloroform-*d*) δ 171.9 (CO), 134.9 (Imidazole),

132.4 (Imidazole), 126.3 (Imidazole), 65.2 (OCH₂), 53.0 (CH-lactone), 30.8 (CH₂), 30.1 (CH₂), 23.9 (CH₂), 22.4 (CH₂), 13.8 (CH₃). ESI-HRMS(M+H)⁺: 209.1285; found: 209.1286.

3-(5-hexyl-1*H*-imidazol-1-yl)dihydrofuran-2(3*H*)-one (14). Following the general procedure, flash chromatography of the crude product (2:1 EtOAc-Acetone) afforded **14** (38 %) as a white solid. ¹H NMR (400 MHz, Acetone-*d*₆) δ 7.49 (s, 1H, Imidazole), 6.62 (s, 1H, Imidazole), 5.27 (dd, *J* = 11.8, 8.9 Hz, 1H, CH-lactone), 4.49 (td, *J* = 8.9, 1.5 Hz, 1H, OCHH-lactone), 4.37 (ddd, *J* = 10.8, 9.0, 6.1 Hz, 1H, OCHH-lactone), 2.85 (m, 1H, CHH-lactone), 2.71 – 2.57 (m, 1H, CHH-lactone), 2.49 (m, 2H, CH₂), 1.56 (m, 2H, CH₂), 1.30 (m, 2H, CH₂), 1.26 – 1.10 (m, 4H, 2×CH₂), 0.79 (t, *J* = 6.0 Hz, 3H, CH₃). ¹³C NMR (101 MHz, Acetone-*d*₆) δ 173.0 (CO), 135.3 (Imidazole), 132.3 (Imidazole), 125.7 (Imidazole), 65.3 (OCH₂), 52.7 (CH-lactone), 31.4 (CH₂), 30.4 (CH₂), 28.9 (CH₂), 28.2 (CH₂), 23.6 (CH₂), 22.4 (CH₂), 13.4 (CH₃). ESI-HRMS(M+H)⁺: 237.1598; found: 237.1598. m.p. 60°C.

Biological evaluation

Escherichia coli strain NM522 equipped with the sensor plasmid pSB401 was grown in Luria broth (50 mL) at 30°C. After 18 h, this bacterial culture was diluted 10 times and 100 μL per well (96 wells plates) were added. For agonistic activity, compounds were tested at increasing concentrations in DMSO (max 2 % in a total volume of 200 μL of LB). For antagonistic activity, compounds were tested at increasing concentrations in DMSO (max 2 % in a total volume of 200 μL) in competition with OHHL (200 nM). Bioluminescence was measured with a Tecan spark luminometer.

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Availability of data

Data are available in the results and experimental sections of this article, and, for the lactone formation scope and NMR data and spectra of all new compounds, in the supplementary material.

Conflicts of interest

There is no conflict to declare.

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